Synthesis of Substituted Azetidines
and Spirocyclic Diazetidines

by

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

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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:


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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Ac₂O</td>
<td>Acetic anhydride</td>
</tr>
<tr>
<td>Aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxy carbonyl</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
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<tr>
<td>Calcd.</td>
<td>Calculated</td>
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<tr>
<td>COSY</td>
<td>Correlated Spectroscopy</td>
</tr>
<tr>
<td>δ</td>
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</tr>
<tr>
<td>d</td>
<td>Day(s) or doublet</td>
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<tr>
<td>dd</td>
<td>Doublet of doublets</td>
</tr>
<tr>
<td>ddd</td>
<td>Doublet of doublet of doublets</td>
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<td>DABCO</td>
<td>1,4-Diazabicyclo[2.2.2]octane</td>
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<tr>
<td>DCC</td>
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</tr>
<tr>
<td>de</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
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<tr>
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<td>DIBAL</td>
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<td>DMDO</td>
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<tr>
<td>DMEDA</td>
<td>N,N’-Dimethylethlenediamine</td>
</tr>
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<td>Abbreviation</td>
<td>Full Form</td>
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</tr>
<tr>
<td>DMF</td>
<td>N,N’-Dimethylformamide</td>
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<td>Dimethyl sulfoxide</td>
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<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
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<td>Electron withdrawing group</td>
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<td>Fourier Transform-Infrared</td>
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<td>GC</td>
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<tr>
<td>h</td>
<td>Hour(s)</td>
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<td>HMBC</td>
<td>Heteronuclear Multiple Bond Correlation</td>
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<tr>
<td>HOMO</td>
<td>Highest Occupied Molecular Orbital</td>
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<tr>
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<td>Heteronuclear Single Quantum Coherence</td>
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<tr>
<td>HPLC</td>
<td>High-Performance Liquid Chromatography</td>
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<td>HSAB</td>
<td>Hard-Soft Acids and Bases</td>
</tr>
<tr>
<td>¹Pr</td>
<td>Isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared Radiation</td>
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<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>LC-MS</td>
<td>Liquid Chromatography-Mass Spectrometry</td>
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<td>LDA</td>
<td>Lithium diisopropylamide</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
</tr>
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<td>m.p.</td>
<td>Melting point</td>
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<tr>
<td>M</td>
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<td>Multiplet</td>
</tr>
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</tr>
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<tr>
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<td>Acetonitrile</td>
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<tr>
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<td>Methanol</td>
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<td>MS</td>
<td>Mass Spectrometry</td>
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<td>µW</td>
<td>Microwave</td>
</tr>
<tr>
<td>m/z</td>
<td>Mass/charge ratio</td>
</tr>
<tr>
<td>NHC</td>
<td>N-Heterocyclic carbene</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser Effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser Effect Spectroscopy</td>
</tr>
<tr>
<td>Nosyl</td>
<td>Nitrobenzenesulfonyl</td>
</tr>
<tr>
<td>P</td>
<td>Pressure</td>
</tr>
<tr>
<td>p-</td>
<td>para-</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium Chlorochromate</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>PE</td>
<td>Photoelectron</td>
</tr>
<tr>
<td>pg</td>
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<tr>
<td>pKa</td>
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<td>Triphenylphosphine</td>
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<td>ppm</td>
<td>Parts per million</td>
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<td>PTC</td>
<td>Phase Transfer Catalyst</td>
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<td>Quartet</td>
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<tr>
<td>quint</td>
<td>Quintet</td>
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<td>RAMP</td>
<td>(R)-1-Amino-2-methoxymethylpyrrolidine</td>
</tr>
<tr>
<td>Rₜ</td>
<td>Retention factor</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
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<tr>
<td>SAMP</td>
<td>(S)-1-Amino-2-methoxymethylpyrrolidine</td>
</tr>
<tr>
<td>T</td>
<td>Temperature</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TDS</td>
<td>Thexyldimethylsilyl</td>
</tr>
<tr>
<td>TCNE</td>
<td>Tetracyanoethylene</td>
</tr>
<tr>
<td>TEBAC</td>
<td>Benzyltriethylammonium chloride</td>
</tr>
<tr>
<td>Tf</td>
<td>Trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>Tetrahydropyran</td>
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<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
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<td>------------------------------</td>
</tr>
<tr>
<td>TMEDA</td>
<td>Tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>$t_R$</td>
<td>Retention time</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
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<tr>
<td>TSA</td>
<td>Toluene sulfonic acid</td>
</tr>
<tr>
<td>wt</td>
<td>Weight</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
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</table>
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).\(^3\)

\[\text{Scheme 1.1. Gabriel's synthesis of azetidine 2.}\]

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).\(^4\)

\[\text{Scheme 1.2. Catalytic hydrogenation for the synthesis of 2 by Yasamura et al.}\]
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.\textsuperscript{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).

\begin{center}
\textbf{Scheme 1.3. Synthesis of 2 by Wadsworth.}\textsuperscript{5}
\end{center}

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 ($\phi$) of 33.1° (Figure 1.1). Compared to cyclobutane, the dihedral angles are comparable ($\phi \approx 35°$ for cyclobutane), but with a higher barrier to ring inversion of 1.26 kcal mol\textsuperscript{-1}.\textsuperscript{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.\textsuperscript{5–8}
Chapter 1: Asymmetric Synthesis of 2-Substituted Azetidin-3-ones

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. 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. 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. The azetidine subunit is a key structural requirement for the uptake of iron from the soil. More recently, the alkaloid Calydarphinone has been isolated from the Daphniphyllum plant species, and bears an azetidine moiety amidst its complex polycyclic skeleton.
Chapter 1: Asymmetric Synthesis of 2-Substituted Azetidin-3-ones

Figure 1.2. Natural products containing an azetidine core.

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. 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. Medicinal chemists at Pfizer have identified CE-178,253 9 as a CB1 antagonist, which is currently in clinical development for the treatment of metabolic disorders including obesity. 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. Novel benzodioxane 11 is patented for the inhibition of leukotriene hydrolase, with application in the treatment of cardiovascular diseases.
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.\textsuperscript{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.\textsuperscript{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. 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.

![Scheme 1.4. Asymmetric cyclopropanation using azetidine chiral bidentate ligand 14.](image)

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. 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.](image)
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. 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).

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. For example, alkylation of primary amines by bistriflate 23 formed 1,3-disubstituted azetidine 24 in 92% yield (Scheme 1.7).
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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).

![Scheme 1.9](image)

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

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. 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). 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.

![Scheme 1.10](image)

Scheme 1.10. Ring-opening of aziridine 33 to form 2-substituted azetidine 35.

Other methods for the synthesis of azetidines have been developed, including the metal-catalysed cyclisation reactions published by Ohno and co-workers. 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.\(^{34}\)

![Scheme 1.11. Palladium-catalysed cyclisation of allene 36 to cis-azetidine 37.\(^{33}\)](image)

More recently, Jamison and co-workers used Nickel catalysis for the synthesis of enantiomerically pure azetidines starting from aziridines.\(^{35}\) Initial cross coupling with \(\text{NiCl}_2\) 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).

![Scheme 1.12. Nickel-catalysed cross coupling to form azetidine 40.\(^{35}\)](image)

### 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).
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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).

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).
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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 1H 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.

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. 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).

![Scheme 1.19. Photodimerisation of N-acetyl-2-azetine 59.](image)

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. Spectroscopic evidence confirmed the endo stereochemistry.

![Scheme 1.20. Diels-Alder reaction of 59 with reactive dienes.](image)
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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 diastereoccontrol 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

\[
\begin{array}{c}
\text{Method A: MeCN, 80 °C} \\
\text{Method B: [Ag(fod)], EtOAc, 30 °C}
\end{array}
\]

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 LiAlH₄, diborane, Raney nickel and alanes.46,47

Testa and co-workers developed the initial reduction of azetidin-2-ones using LiAlH₄, 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).

\[
\begin{array}{c}
\text{Scheme 1.22. Reduction of azetidin-2-ones using LiAlH₄.48}
\end{array}
\]
Azetidin-2-one reduction by diborane was first introduced by Wells et al in the early 1970s.\footnote{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).

\begin{formula}
\begin{align*}
71 \quad \xrightarrow{i) \ B_2H_6, \ \text{THF, reflux, 16 h}} & \quad \xrightarrow{\text{ii) 3N HCl, rt, 2 h}} \quad 72 \\
\text{R = NH}_2, 67\% \\
\text{R = N}_3, 65\%
\end{align*}
\end{formula}

\textbf{Scheme 1.23.} Reduction of azetidin-2-ones using diborane in THF.\footnote{49}

Ojima and co-workers have pioneered the use of DIBAL-H and chloroalanes (AlH$_2$Cl and AlHCl$_2$) for this reduction, the latter of which is highly selective for a wide variety of substrates.\footnote{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).\footnote{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.

\begin{formula}
\begin{align*}
75 \quad \xrightarrow{\text{DIBAL-H, THF reflux, 2 h}} & \quad 76a \quad (73\%) \\
& \quad 76b \quad (16\%)
\end{align*}
\end{formula}

\textbf{Scheme 1.24.} Reduction of azetidin-2-one 75 using DIBAL-H.\footnote{50}
Switching to the chloroalanes led solely to compound 76a in 94% yield, when either monochloroalane or dichloroalane were used (Scheme 1.25).\textsuperscript{50}

\[ 75 \xrightarrow{\text{AlH}_2\text{Cl or AlHCl}_2, \text{Et}_2\text{O, reflux, 1 h}} 76a \]

**Scheme 1.25.** Chloroalanes as reducing agents for azetidin-2-one reduction.\textsuperscript{50}

The generality and efficiency of this process was later demonstrated through direct reduction of bis-\(\beta\)-lactam 77 with chlorohydroalane, forming bisazetidine 78 in 85% yield (Scheme 1.26).\textsuperscript{51}

\[ 77 \xrightarrow{\text{AlH}_2\text{Cl, Et}_2\text{O, reflux, 6 h}} 78 \]

**Scheme 1.26.** Bis-\(\beta\)-lactam reduction of 77 using chlorohydroalane.\textsuperscript{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.\textsuperscript{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.
More recently, the same group developed a metal-catalysed chemoselective approach using hydrosilanes as the reducing agent.\textsuperscript{53} In the presence of zinc catalyst, β-lactam \textbf{81} was successfully reduced to give enantiopure azetidine \textbf{82} with no erosion of stereoselectivity (Scheme 1.28). This method tolerates the presence of other reducible functional groups such as azides and cyanohydrins.

\textbf{Scheme 1.28.} Chemoselective reduction of \textbf{81} using hydrosilanes.\textsuperscript{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) \textbf{83} and azetidin-3-ones \textbf{84} have received much attention as well (Figure 1.4).

\textbf{Figure 1.4.} Structure of azetidine \textbf{2}, azetidin-2-one \textbf{83} and azetidin-3-one \textbf{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

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 actomyosin 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
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 aminohalo ketones 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.
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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. The Jones reagent generated ketone 97 in 40% yield, with poor stability of the compound at low temperatures (Scheme 1.30).

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

![Scheme 1.29](image)

Scheme 1.29. Oxidative ring contraction to tetrasubstituted azetidin-3-one 94.

![Scheme 1.30](image)

Scheme 1.30. Oxidation of azetidin-3-ols to form ketone 97.
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A convenient method was reported by the De Kimpe group, starting from imine 98, synthesised from butane-2,3-dione in several steps. 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).

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

### 1.5.2 Synthesis by Ring Closure

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

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

The extent of cyclisation for monocyclic azetidin-3-ones is dependent on the nucleophilicity of the acid employed, as reported by Pusino et al. 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).
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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
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. 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.

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. 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).
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Scheme 1.37. Synthesis of 116 under Horner-Wadsworth-Emmons conditions.\textsuperscript{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 \textit{et al} developed an organocatalytic direct cross-aldol reaction to access such compounds, avoiding the need for preformed enol or “enolate-like” intermediates.\textsuperscript{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).
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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.
Chapter 1: Asymmetric Synthesis of 2-Substituted Azetidin-3-ones

Scheme 1.39. Stereocontrolled synthesis of 121 using N-H insertion by Seebach and co-workers.\textsuperscript{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).\textsuperscript{73}

Scheme 1.40. Synthesis of polyoximic acid 125 using chiral diazoketones.\textsuperscript{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.\textsuperscript{74,75}
Silver catalysts have also been employed under Wolff rearrangement conditions to form the corresponding 2-substituted azetidin-3-ones (Scheme 1.42). 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.

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.
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In 2010, Zhang and co-workers pioneered the introduction of gold-catalysed carbenes accessible by the oxidation of alkynes. The group extended this work to form enantiomerically enriched azetidin-3-ones by gold-catalysed oxidative cyclisation of chiral N-propagylsulfonamides. Using Ellman’s method, enantiomerically enriched tert-butylsulfinamide 134 was readily formed by stereocontrolled ethynylation. Oxidation with mCPBA 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.](image)

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). A number of reviews have been published outlining the broad utility of this chemistry.
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![Scheme 1.44. Generalised use of SAMP hydrazone 137.](image)

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).

![Scheme 1.45. Asymmetric synthesis of 2-substituted cyclobutane 141.](image)

This work was recently extended to include 2-substituted oxetan-3-ones in our group. 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.
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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. 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.

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 diastereoocontrol 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.

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).
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, $[\alpha]^2_{D} +23.4$ ($c 0.12$, 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.
Chapter 1: Asymmetric Synthesis of 2-Substituted Azetidin-3-ones

Asymmetric Synthesis of 2-Substituted Azetidin-3-ones

Table 1.1. Optimisation of conditions for lithiation of 151. *Isolated yield of 151 and 154 after column chromatography. ^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 1H 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. Geden et al demonstrated the facile cleavage of the SAMP auxiliary from oxetan-3-ones using mild hydrolysis conditions (Scheme 1.46). 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.
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.
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Scheme 1.52. One pot synthesis of (5)-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 tBuLi 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.
Chapter 1: Asymmetric Synthesis of 2-Substituted Azetidin-3-ones

The use of $N,N$-dimethyl hydrazones to form azaenolates has been well documented. 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).

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) 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.
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Table 1.2. Optimisation of yield and enantioselectivity for (S)-159. *Each reaction was repeated twice and the highest yield reported. †Remainder of the mass balance revealed unknown products. ‡Enantioselectivity determined by chiral GC analysis. Each chiral GC was repeated twice and the highest enantioselectivity reported. §1.1 equiv. 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.
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![Reaction Scheme](151)

\[
\text{i) } \text{BuLi (1.1 equiv), THF, } -78 \ ^\circ \text{C, 2 h}
\text{ii) electrophile RX (1.2 equiv), } -78 \ ^\circ \text{C, 2 h } \rightarrow \text{ rt, 18 h}
\text{iii) } (\text{CO}_2\text{H})_2, \text{ H}_2\text{O, rt, 20 h}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Product X</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_2)=CHCH(_2)Br</td>
<td>159</td>
<td>67</td>
<td>81(^a)</td>
</tr>
<tr>
<td>2</td>
<td>CH(_2)=CHCH(_2)Br(^b)</td>
<td>159</td>
<td>55</td>
<td>81(^a)</td>
</tr>
<tr>
<td>3</td>
<td>(CH(_3))(_2)C=CHCH(_2)Br</td>
<td>165</td>
<td>53</td>
<td>81(^a)</td>
</tr>
<tr>
<td>4</td>
<td>PhCH=CHCH(_2)Br</td>
<td>166</td>
<td>74</td>
<td>77(^c)</td>
</tr>
<tr>
<td>5</td>
<td>CH(_3)I</td>
<td>167</td>
<td>41</td>
<td>51(^a)</td>
</tr>
<tr>
<td>6</td>
<td>CH(_3)CH(_2)CH(_2)I</td>
<td>168</td>
<td>50</td>
<td>79(^a)</td>
</tr>
<tr>
<td>7</td>
<td>(CH(_3))(_2)CHI</td>
<td>169</td>
<td>52</td>
<td>85(^a)</td>
</tr>
<tr>
<td>8</td>
<td>(CH(_3))(_2)CO</td>
<td>170</td>
<td>59</td>
<td>78(^c)</td>
</tr>
<tr>
<td>9</td>
<td>PhCHO</td>
<td>171</td>
<td>71</td>
<td>31, 17(^c),(^d)</td>
</tr>
</tbody>
</table>

\(^{a}\) Isolated yield
\(^{b}\) Prepared in 20% yield only
\(^{c}\) Isolated yield
\(^{d}\) Isolated yield
Table 1.3. Stereoselective synthesis of azetidin-3-ones. *Enantioselectivity determined by chiral GC analysis. **(R)-151 was used. ***Enantioselectivity determined by chiral HPLC analysis. **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 Ac₂O/Et₃N failed to enable separation of the peaks.

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

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).

### Scheme 1.59. Attempted synthesis of 176.

```
\[
\begin{array}{c}
\text{N-Boc} \hspace{1cm} \text{OMe} \\
\text{151} \hspace{1cm} \text{OBn}
\end{array}
\]

\text{i) } ^{6}\text{BuLi, THF, }-78 \, ^{\circ}\text{C, 2 h} \\
\text{ii) I} \\
\text{OBn} \hspace{1cm} -78 \, ^{\circ}\text{C, 2 h } \rightarrow \text{rt, 18 h} \\
\text{iii) (CO}_2\text{H})_2, \text{H}_2\text{O, rt, 20 h} \\
\text{N-Boc} \hspace{1cm} \text{OBn}
\]

\text{176}
```

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

```
\[
\begin{array}{c}
\text{N-Boc} \hspace{1cm} \text{CO}_2\text{Et}
\end{array}
\]

\text{150} + \text{\begin{array}{c}
\text{N-Boc} \hspace{1cm} \text{CO}_2\text{Et}
\end{array}}

\text{177} \hspace{1cm} \text{I}_2, \text{MeCN} \text{ reflux, 18 h}

\text{178}
```
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).
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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).

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

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.](image)

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).
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.

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

![Chemical structure](image)

**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
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-CH₂ 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. Hydrazine (S)-151 was treated with ²BuLi and quenched with allyl bromide, then further subjected to ²BuLi 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 ¹H NMR, and an additional quaternary centre in the ¹³C 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 hydrazine prior to hydrolysis proved unproductive.
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).

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 1BuLi.

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 C2-symmetric ketone 191 after hydrolysis (Scheme 1.71).
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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 $9.34^\circ$, 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. 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).

![Figure 1.8. Proposed lithium coordination of hydrazone alkylation.](image)

Two sites for lithium chelation are possible. The lithium atom can either be antiperiplanar to the C=C bond forming the Z\_C\_N conformer (A/B), or the lithium and the C=C are orientated to the same side, adopting the E\_C\_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\_N conformation (A) is preferred out of the isomers, due to steric restrictions disfavouring the other configurations.
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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).

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).
At tempted 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 ⁴BuLi 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 ¹H 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 '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.⁹° Reaction of ketone 196 with amino compounds afforded
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spirowcycles, 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.](image)

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).

![Scheme 1.76. Nickel-catalysed ring expansion of cyclobutanone 199 to give 2-cyclohexenone 200.](image)

Since this discovery, Aïssa and co-workers have extended Murakami’s work on cyclobutanones by demonstrating this transformation on strained heterocycles. 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.
Chapter 1: Asymmetric Synthesis of 2-Substituted Azetidin-3-ones

Scheme 1.77. Nickel-catalysed ring expansion of azetidin-3-one by Aïssa and co-workers.\textsuperscript{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).\textsuperscript{98} Simultaneously, Ishida\textit{ et al.} reported the synthesis of enantiopure dehydropiperidinones from α-amino acids in a similar fashion.\textsuperscript{99}

Scheme 1.78. Regioselective ring-opening of α-substituted azetidin-3-one 202.\textsuperscript{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.
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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.
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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. Initial hydrazone synthesis and screening of conditions identified optimised metalation conditions for the SAMP hydrazone of N-Boc-azetidin-3-one, using sBuLi 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 tBuLi 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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure110.png}
\caption{Variants of Ender’s auxiliary.}
\end{figure}
Another alternative would be to explore alkylation using Ellman’s auxiliary on azetidines to improve the selectivity. 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 Spiroyclic 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.

![Figure 2.1. Structure of azetidine 208 and 1,2-diazetidine 209.](image)

In particular, the pyridazine nucleus containing two adjacent nitrogen atoms within a six-membered ring is a privileged substructure in medicinal chemistry. An important member of this group is the saturated hexahydropyridazine nucleus, with a number of molecules including actinoramide A,103 cilazapril,104 and 1-azafagomine105 possessing prominent bioactivity (Figure 2.2).

![Figure 2.2. Bioactive compounds containing the hexahydropyridazine nucleus.](image)
Since introduction of a spirocenter into other saturated nitrogen heterocycles has proved valuable,\textsuperscript{106–108} we reasoned that rigidification of the hexahydropyridazine nucleus might have considerable merit to access spirocyclic 1,2-diazetidines (Figure 2.3).

![Diagram of 1,2-diazetidine, spirocyclic 1,2-diazetidine, and hexahydropyridazine](image)

**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.\textsuperscript{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.\textsuperscript{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).
Chapter 2: Synthesis of Spirocyclic 1,2-Diazetidines

More recently, the Cravatt group have discovered a class of aza-β-lactam inhibitors through a series of high-throughput assays.\textsuperscript{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).

![Figure 2.4. Structure of 210 for the differentiation of Friend leukaemia cells.\textsuperscript{110}](image)

![Figure 2.5. Compounds for the selective inhibition of PME-1.\textsuperscript{112}](image)

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 \(\text{tert}\)-butyl groups on 213d. Moreover, the ring tended to flatten as the size of the alkyl substituent increases.

\[
\begin{align*}
R^1 & \quad R^1 & \quad R = \text{Me} & \quad 213a (32\%) \\
\text{Et} & \quad 213b (28\%) \\
\text{\textsuperscript{1}Pr} & \quad 213c (60\%) \\
\text{\textsuperscript{1}Bu} & \quad 213d (2.3\%)
\end{align*}
\]

\textbf{Figure 2.6.} Structural orientation of the simplest 1,2-dialkyl-1,2-diazetidines 213a-213d.\textsuperscript{113}

Independently, Rademacher and Nelson used photoelectron spectroscopy (PE) to probe conformations of 213a.\textsuperscript{114,115} These studies by Rademacher revealed a dihedral angle (\(\phi\)) 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 \(\phi = 24.3°\) when the methyl substituents in 213a are in an equatorial position.\textsuperscript{116}

\[
\begin{align*}
\text{Me} & \quad \text{Me} & \quad 213a
\end{align*}
\]

\textbf{Figure 2.7.} Dihedral angle of 213a estimated by Rademacher.\textsuperscript{114}
Chapter 2: Synthesis of Spiroyclic 1,2-Diazetidines

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.\textsuperscript{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,\textsuperscript{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,\textsuperscript{119} and later adapted by Kauer and Schneider.\textsuperscript{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).

![Scheme 2.1. Thermal [2+2] cycloaddition to form 1,2-diazetidine 215.\textsuperscript{120}](image)

Hoffman and Hauser reported the thermal reaction of azodicarbonyl compounds with olefins, leading to 1,2-diazetidines through a [2+2] cycloaddition reaction.\textsuperscript{121} They discounted dihydrooxadiazine formation resulting from a [2+4] cycloaddition product, which was further supported by spectroscopic analysis conducted by Gustorf.\textsuperscript{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).\textsuperscript{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.\textsuperscript{125}
Chapter 2: Synthesis of Spirocyclic 1,2-Diazetidines

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

Warrener and Nunn demonstrated an alternative route to access dimethyl 1,2-diazetine-1,2-dicarboxylate 222, as shown in Scheme 2.3.\textsuperscript{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.\textsuperscript{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).\textsuperscript{127}

\begin{center}
\textbf{Scheme 2.4.} Thermal [2+2] cycloaddition to form bicyclic 1,2-diazetidine 225.\textsuperscript{127}
\end{center}

Xu and co-workers have since reported an effective divergent amine-catalysed [2+2] annulation of allenolates 226 with azodicarboxylate 227 as a route to access 3-alkylidene-1,2-diazetidines 228 (Scheme 2.5).\textsuperscript{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).

\begin{center}
\textbf{Scheme 2.5.} [2+2] Annulation to generate 3-alkylidene-1,2-diazetidines 228.\textsuperscript{128}
\end{center}

The proposed mechanism involves nucleophilic attack of the amine catalyst on the β-carbon of allenolate 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).
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

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).
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).\textsuperscript{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 and 1,2-dibromoethane in hot xylene (Scheme 2.10).\textsuperscript{113}

![Scheme 2.10. Synthesis of simple 1,2-dialkyl-1,2-diazetidines 213a-213d.\textsuperscript{113}

Brown et al reported the synthesis of simple 1,2-diazetidines by nucleophilic ring closure.\textsuperscript{132} Competing reactions were observed leading to formation of both diazetidine and oxadiazine, as the ambidentate carbamate nucleophile facilitates ring closure through either the nitrogen or the oxygen atom in (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.\textsuperscript{133} When substrate 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 was the sole product from the reaction with sulfonamide, as cyclisation could only proceed through the nitrogen atom, whilst converting to the iodide substrate led to a large improvement in reaction yield. These observations corrected earlier findings made by Miao.\textsuperscript{134}
Chapter 2: Synthesis of Spirocyclic 1,2-Diazetidines

Scheme 2.11. Nucleophilic ring closure to provide 1,2-diazetidines using the HSAB principle.\textsuperscript{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 \textbf{240} with aryl halides for the synthesis of \textit{trans}-1,2-diazetidines \textbf{241} in up to 77\% yield (Scheme 2.12).\textsuperscript{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 \textbf{241} from allenolate \textbf{240}.\textsuperscript{135}

Brown \textit{et al} demonstrated the efficient two step synthesis of 3-methylene-1,2-diazetidine \textbf{244} using Cu(I)-catalysed \textit{4-exo-trig} ring cyclisation from 2-halo-2-propenyl hydrazine \textbf{243}, as illustrated in Scheme 2.13.\textsuperscript{136} The hydrazine precursor \textbf{243} was accessed through a variation on the Mitsunobu reaction in yields of up to 92\%, with the subsequent cyclisation producing diazetidine \textbf{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.\textsuperscript{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.\textsuperscript{136}
Iacobini et al demonstrated highly chemo- and enantioselective hydrogenation of the exocyclic double bond in 244 using rhodium catalysis (Scheme 2.15). 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.

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. 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).
Chapter 2: Synthesis of Spirocyclic 1,2-Diazetidines

### Scheme 2.16
Synthetic route to 3-substituted 1,2-diazetidines 252 and further functionalisation.

#### 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 feature provides three-dimensionality to the compound, allowing access to compounds which deviate away from planarity.\(^{139,140}\)

![Figure 2.8](image-url) 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. 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. Structural rigidity arising from spirocycles is attractive in drug design, as this further reduces the conformational entropy penalty associated with binding a protein target.

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).

As previously stated, spirocyclic heterocycles are emerging as valuable tools in medicinal chemistry, with those containing a four-membered ring being of prominent interest. 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 containing a strained four-membered heterocyclic component are known (Figure 2.10).
Methodologies developed to synthesise spirocyclic heterocycles include alkylation reactions, transition-metal based reactions, cycloadditions, rearrangements and ring closure reactions. A recent review by Carreira and co-workers highlighted the synthetic procedures available for accessing four-membered ring containing spirocycles.

2.4 Research Aims

Hexahydropyridazaines 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\(_\text{N}2\) 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 \(258\).

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 Spiro cyclic 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-\(\text{tert}\)-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 ¹H 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.
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 LiBH₄ in THF. Encouraged by this, 269 was subjected to these reaction conditions, with an additional 2 equivalents of LiBH₄ 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 Et₂O resulted in an 85% yield of the required product, indicating a strong solvent dependency of the reaction. When a mixture of Et₂O-MeOH was used, this reduced the rate of the reaction, with only 18% of 270 isolated, suggesting the instability of LiBH₄ in MeOH. With this in mind, diethyl ether was chosen as the solvent for the reduction step.

### Table 2.1. Optimisation of formation of 269.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Lithiation time (h)</th>
<th>Quench time</th>
<th>269 (%)</th>
<th>269a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂O</td>
<td>1</td>
<td>40 min then 1 h to rt</td>
<td>51</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>1</td>
<td>40 min then 1 h to rt</td>
<td>67</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>2</td>
<td>1 h then 1 h to rt</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>1</td>
<td>2 h then 1 h to rt</td>
<td>83</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>1</td>
<td>2 h then 18 h to rt⁶</td>
<td>66</td>
<td>7</td>
</tr>
</tbody>
</table>

*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. Dry ice/acetone bath was not removed and the reaction warmed slowly to room temperature for 18 hours.

![Scheme 2.19](image)
Similarly, starting from 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).

**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.

**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.

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).
Chapter 2: Synthesis of Spirocyclic 1,2-Diazetidines

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂, PPh₃, imidazole, CH₂Cl₂, 0 °C → rt, 18 h</td>
<td>275, 79%</td>
</tr>
<tr>
<td>2</td>
<td>PPh₃, imidazole, CH₂Cl₂, 0 °C → rt, 18 h</td>
<td>270, 94%</td>
</tr>
<tr>
<td>3</td>
<td>SOCl₂, CHCl₃, 0 °C → reflux, 18 h¹⁴⁵</td>
<td>275, 58%</td>
</tr>
<tr>
<td>4</td>
<td>CsI, BF₃·Et₂O, MeCN, rt, 20 h¹⁴⁶</td>
<td>270, 16%</td>
</tr>
<tr>
<td>5</td>
<td>salt 277, imidazole, toluene, 80 °C¹⁴⁷</td>
<td>270, 92%</td>
</tr>
<tr>
<td>6</td>
<td>salt 277, imidazole, toluene, 100 °C, 1 h, µW</td>
<td>274, 0%</td>
</tr>
</tbody>
</table>

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.\(^{148}\)

![Scheme 2.24. Direct cyclisation from mesylate 278.](image)

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\(_2\)SN=NSO\(_2\)Ar 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).

![Scheme 2.25. Attempted synthesis of 281/282.](image)
Additionally, attempts to benzylate the free NH using caesium carbonate\(^{149}\) or sodium hydride\(^{150}\) as base were unsuccessful (Scheme 2.26).

![Scheme 2.26. Attempted benzylation of 269.](image)

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.

![Scheme 2.27. Revised synthetic route to 279.](image)

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).

![Reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cs₂CO₃ (4 eq), MeCN, rt, 2 d&lt;sup&gt;132&lt;/sup&gt;</td>
<td>269</td>
</tr>
<tr>
<td>2</td>
<td>LiOH, THF/H₂O, rt, 2 d&lt;sup&gt;151&lt;/sup&gt;</td>
<td>269</td>
</tr>
<tr>
<td>3</td>
<td>MeMgBr, Et₂O, 0 °C → rt, 2 d&lt;sup&gt;152&lt;/sup&gt;</td>
<td>269</td>
</tr>
<tr>
<td>4</td>
<td>NaOMe, MeOH, reflux, 2 d&lt;sup&gt;153&lt;/sup&gt;</td>
<td>285, 60%</td>
</tr>
<tr>
<td>5</td>
<td>K₂CO₃, MeOH/H₂O, rt 2 d</td>
<td>269:285, 3.57:1</td>
</tr>
<tr>
<td>6</td>
<td>K₂CO₃, MeOH/H₂O, 70 °C, 1 h, µW</td>
<td>269:285, 3.45:1</td>
</tr>
</tbody>
</table>

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.
Chapter 2: Synthesis of Spirocyclic 1,2-Diazetidines

Table 2.4. Investigation of the direct cyclisation of 286. *Unknown products formed with good mass balance recovery. †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 $\beta$-lactam synthesis using this strategy. Facile hydrolysis of ester 269 to 288 was achieved using sodium hydroxide in moderate yield. 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).
Chapter 2: Synthesis of Spirocyclic 1,2-Diazetidines

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).  

Table 2.5. Lactamisation studies of 288. †Unknown products formed with good mass balance recovery.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₂POCl, Et₃N, MeCN, rt, 2 d&lt;sup&gt;158&lt;/sup&gt;</td>
<td>0%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Ph₂POCl, Et₃N, MeCN, reflux, 20 h&lt;sup&gt;158&lt;/sup&gt;</td>
<td>0%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>DCC, CH₂Cl₂, rt, 2 d</td>
<td>288, 79%</td>
</tr>
<tr>
<td>4</td>
<td>CCl₄, PPh₃, Et₃N, MeCN, reflux, 20 h&lt;sup&gt;159&lt;/sup&gt;</td>
<td>0%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>NBS, PPh₃, Et₃N, MeCN, rt, 20 h&lt;sup&gt;159&lt;/sup&gt;</td>
<td>0%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>POCl₃, Et₃N, CH₂Cl₂, 0 °C → rt, 20 h&lt;sup&gt;160&lt;/sup&gt;</td>
<td>0%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Mukaiyama reagent, Et₃N, CH₂Cl₂, rt, 3 d&lt;sup&gt;161&lt;/sup&gt;</td>
<td>288, 89%</td>
</tr>
</tbody>
</table>
Chapter 2: Synthesis of Spirocyclic 1,2-Diazetidines

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),\textsuperscript{136} as had Pd-catalysed Heck couplings (Scheme 2.13).\textsuperscript{137} In unpublished work, the successful epoxidation of 289 using DMDO provided spirocycle 290 in excellent yield (Scheme 2.29).\textsuperscript{163} This product was rather unstable, decomposing rapidly even when stored under nitrogen.

Greg Iacobini and Mike Brown had attempted the cyclopropanation of 3-methylene-1,2-diazetidines.\textsuperscript{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.
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).

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

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).

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

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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-diaza[2.3]hexanes and 1,2-diaza[3.3]heptanes could be developed.

Following the chemistry developed in the group, \textsuperscript{136} methylene diazetidine \textsuperscript{299} was synthesised from iodo alcohol \textsuperscript{297} according to the reported method (Scheme 2.33).

![Scheme 2.33. Formation of methylene diazetidine \textsuperscript{299} from alcohol \textsuperscript{297}.](image)

As the formation of iodo alcohol \textsuperscript{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 \textsuperscript{299} (Scheme 2.34).

![Scheme 2.34. Formation of 3-methylene-1,2-diazetidine \textsuperscript{299} from 2-bromoallyl alcohol \textsuperscript{242}.](image)
Chapter 2: Synthesis of Spirocyclic 1,2-Diazetidines

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. 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.

![Scheme 2.35. Bromination and subsequent reduction to form alcohols 302 and 304](image)

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.
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.

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).
Formation of \( N \)-allylhydrazine was performed according to the procedure of Mundal \textit{et al.} \footnote{Mundal et al.} Alkylation of \( 311 \) occurred in good yields albeit slowly to provide \( 312 \). Deprotection of the phthalimide group is known to occur using methylhydrazine hydrate. \footnote{Methylhydrazine hydrate is toxic and limited in availability.} However, due to the toxicity and limited availability of this material, we decided to switch to the use of hydrazine hydrate. \footnote{Hydrazine hydrate is less toxic but still requires careful handling.} The reaction proceeded smoothly to give \( 308 \) without the need for further purification (Scheme 2.39).

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).
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.\textsuperscript{136}
Chapter 2: Synthesis of Spirocyclic 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 ¹H NMR or mass spectrometry analysis (Scheme 2.42).

![Scheme 2.42](image)

**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).

![Scheme 2.43](image)

**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.
Chapter 2: Synthesis of Spirocyclic 1,2-Diazetidines

**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. 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, with subsequent formation of diazetidine 321 occurring in moderate yield (Scheme 2.44).
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.\textsuperscript{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.\textsuperscript{173} A recent review on fluorinated carbenes highlights the extensive use of these reactive species for a wide range of reactions, including cyclopropanation reactions.\textsuperscript{174} Due to stabilisation from $\pi$-donation of the fluorine atoms to the carbon, coupled with the negative inductive effect, the resulting difluorocarbene is highly reactive towards electron rich substrates.\textsuperscript{175}

Several methods have been developed for synthesising difluorocarbenes, with the simplest route from chlorodifluoromethane developed by Buddrus and co-workers.\textsuperscript{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.\textsuperscript{177}
Alternative routes have been developed, most commonly involving trifluoromethyl reagents.\textsuperscript{178,179} Waldman and co-workers generated difluorocarbene from trimethyl(trifluoromethyl)tin at elevated temperatures, which subsequently reacted with alkenes to form difluorocyclopropanes in high yields.\textsuperscript{180} More recently, Wang \textit{et al} have used the Ruppert-Prakash reagent TMSCF\textsubscript{3} as a difluorocarbene source under sodium iodide activation for the synthesis of \textit{gem}-difluorocyclopropanes in high yields (Scheme 2.45).\textsuperscript{181}

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme2.45.png}
\end{center}

\textbf{Scheme 2.45.} Difluorocyclopropanation of 322 using the Ruppert-Prakash reagent.\textsuperscript{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.

\begin{center}
\includegraphics[width=0.7\textwidth]{Scheme2.46.png}
\end{center}

\textbf{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.](image)

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.

![Figure 2.14. NOE enhancements of (Z)-326.](image)
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).

![Scheme 2.47](image)

**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. These carbenes are typically generated from chloroform in an α-elimination process, with loss of hydrogen chloride (Scheme 2.48).

![Scheme 2.48](image)

**Scheme 2.48.** Formation of dichlorocarbene from chloroform.

Due to the rapid hydrolysis of the intermediate anion, early reports indicated the requirement for these reactions to be conducted under anhydrous conditions. 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). Many examples including enantioselective variants have since been reported.
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%).

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.
Chapter 2: Synthesis of Spirocyclic 1,2-Diazetidines

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 tetrakisubstituted 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).
Chapter 2: Synthesis of Spirocyclic 1,2-Diazetidines

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazetidine</th>
<th>Time (min)</th>
<th>Product(s) of 4MR and 5MR</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>299</td>
<td>180</td>
<td><img src="image" alt="Product 331" /> <img src="image" alt="Product 332" /></td>
<td>48 : 41</td>
</tr>
<tr>
<td>2</td>
<td>316</td>
<td>75</td>
<td><img src="image" alt="Product 333" /> <img src="image" alt="Product 334" /></td>
<td>57 : 9</td>
</tr>
<tr>
<td>3</td>
<td>317</td>
<td>15</td>
<td><img src="image" alt="Product 335" /> <img src="image" alt="Product 336" /></td>
<td>42 : 9</td>
</tr>
<tr>
<td>4</td>
<td>315</td>
<td>120</td>
<td><img src="image" alt="Product 337" /> <img src="image" alt="Product 338" /></td>
<td>0 : 42</td>
</tr>
<tr>
<td>5</td>
<td>244</td>
<td>360</td>
<td><img src="image" alt="Product 339" /> <img src="image" alt="Product 340" /></td>
<td>64 : 0</td>
</tr>
<tr>
<td>6</td>
<td>321</td>
<td>360</td>
<td><img src="image" alt="Product 341" /> <img src="image" alt="Product 342" /></td>
<td>0 : 12</td>
</tr>
</tbody>
</table>
Table 2.6. Dichlorocyclopropanations of 3-methylene-1,2-diazetidines. *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.

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Scheme 2.51. Subjecting 324 and 331 to dichlorocyclopropagation 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.](image)

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,\textsuperscript{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.](image)

Earlier studies have suggested that hydrolysis occurs rapidly with dibromocarbenes under PTC conditions.\textsuperscript{177} Nagarajan et al reported the use of potassium fluoride and alkali can be more effective in these reactions.\textsuperscript{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.\textsuperscript{189} Our work on Rh(I) catalysed asymmetric hydrogenations\textsuperscript{157} 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.\textsuperscript{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).\textsuperscript{190,191}

![Scheme 2.55. Synthesis of 353 using rhodium carbene chemistry.\textsuperscript{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.\textsuperscript{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 \textsuperscript{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.
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. Diazocompound 355 was prepared from diethyl malonate in quantitative yield using a modified procedure.\textsuperscript{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]\textsuperscript{+}) 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).

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, 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. 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).

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na, MeOH, Et₂O, 0 °C → rt, 18 h₁⁹³</td>
<td>0%*</td>
</tr>
<tr>
<td>2</td>
<td>Li, 'BuOH, Et₂O, rt → 70 °C, 18 h₁⁹⁴</td>
<td>0%*</td>
</tr>
<tr>
<td>3</td>
<td>H₂, Pd/C, MeOH, rt, 16 h</td>
<td>331, 92%</td>
</tr>
</tbody>
</table>

Table 2.7. Dechlorination studies on 331. *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).

![Scheme 2.58. Attempted deprotection of the Boc protecting groups of 331.](image)

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).

![Scheme 2.59. Deprotection of the tert-butyloxy carbonyl group in 327.](image)

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$_2$O 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.](image)

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).
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.

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.
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.

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).

![Scheme 2.64. Attempted removal of Cbz group of 362.](image)

### 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).

![Scheme 2.65. Proposed synthetic route to accessing variants of 367 using Diels-Alder cycloaddition.](image)

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).
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).

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. 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 fluorenlymethyloxycarbonyl (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™ 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<sub>254</sub>), 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 calibration, and are given in cm<sup>-1</sup>. 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.

\((S)-3-(2-(\text{Methoxymethyl})-N-(\text{azetidine-3-ylidene})\text{pyrrolidin-1-amine})-1-\text{tert-butylcarboxylate (} (S)-151)\)

\((S)-(-)-1\)-Amino-2-(methoxymethyl)pyrrolidine (537 \(\mu\)L, 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 \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2929, 2867, 1703, 1457, 1365, 1087, 940, 859, 767; \(\delta_H\) (400 MHz, CDCl\(_3\)) 4.76−4.68 (1H, m, NCHH), 4.64−4.52 (3H, m, NCHH, NCH\(_2\)), 3.50 (1H, dd, \(J = 8.0, 4.0\) Hz, CHOH\(_3\)), 3.44−3.39 (2H, m, CHOH\(_3\)), 3.38 (3H, s, CH\(_2\)OH\(_3\)), 3.33−3.26 (1H, m, NCHH), 2.79 (1H, q, \(J = 8.0\) Hz, NCH\(_2\)), 1.98−1.84 (3H, m, CH\(_3\), CH\(_2\)), 1.78−1.69 (1H, m, CHH), 1.46 (9H, s, C(CH\(_3\))\(_3\)); \(\delta_C\) (100 MHz, CDCl\(_3\)) 156.2 (COO), 135.9 (C=\(N\)), 80.1 (C(CH\(_3\))\(_3\)), 74.9 (CH\(_2\)OH\(_3\)), 65.2 (NCH), 61.4 (NCH\(_2\)), 60.4 (NCH\(_2\)), 59.3 (CH\(_2\)OH\(_3\)), 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\(_3\)O\(_3\) [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 (SiO₂, 3:1, hexane: EtOAc) provided (R)-151 (540 mg, 95%) as a pale yellow oil. R_f = 0.24 (3:1, hexane: EtOAc); [α]_D^{29} = –21.2 (c 0.11, CHCl₃); IR \( \nu_{\text{max}} \) (film)/cm⁻¹ 2979, 2930, 2888, 2835, 1687, 1460, 1364, 1105, 941, 858, 767; \( \delta_H \) (400 MHz, CDCl₃) 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, CH\_\_HOCH\_\_3), 3.45–3.35 (2H, m, CH\_\_H\_\_OCH\_\_3, NCH), 3.38 (3H, s, CH\_\_2OC\_\_H\_\_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, CH\_\_H, CH\_\_2), 1.79–1.69 (1H, m, CHH), 1.46 (9H, s, C(CH₃)₃); \( \delta_C \) (125 MHz, CDCl₃) 156.2 (COO), 135.9 (C=N), 80.1 (C(CH₃)₃), 74.9 (CH₂OCH₃), 65.1 (NCH), 61.4 (2 x NCH₂), 59.3 (CH₂OCH₃), 52.5 (NCH₂), 28.3 (C(CH₃)₃), 25.9 (CH₂), 22.7 (CH₂); MS (ESI⁺) m/z 284 (MH⁺); HRMS calcd. for C₁₄H₂₆N₃O₃ [M+H]⁺ 284.1969, found 284.1964.

(S)-3-(2-(Methoxymethyl)-N-(2-ally lazetidine-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 H₂O (10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. Purification by column chromatography (SiO₂, 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 \( \nu_{\text{max}} \) (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, NCHCH_2CH=CH_2), 4.48–4.40 (1H, m, NCHH), 4.37 (1H, dd, J = 13.6, 3.4 Hz, NCHH), 3.52 (1H, dd, J = 9.1, 4.1 Hz, CHHOCH_3), 3.46–3.25 (3H, m, CHHOCH_3, NCHCH_2, NCHHCH_2), 3.37 (3H, s, CH_2OCH_3), 2.81–2.60 (1H, m, NCHH), 2.06–1.83 (3H, m, NCHH, NCH_2), 1.71–1.63 (1H, m, NCHH), 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 (NCHCH_2CH=CH_2), 65.3 (NCHCH_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-benzazetidine-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. "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 ν_{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, NCHCH_2Ar), 4.29–4.17 (1H, m, NCHH), 3.76–3.63 (1H, m, NCHH), 3.50 (1H, dd, J = 8.5, 3.6 Hz, CHHOCH_3), 3.46–3.40 (2H, m, CHHOCH_3, NCH), 3.43 (3H, s, CH_2OCH_3), 3.34–3.31 (1H, m, NCHH), 3.23–3.14 (1H, m, CHHAr), 3.03 (1H, dd, J = 14.0, 3.2
Hz, CHHAr), 2.73 (1H, q, J = 8.3 Hz, NCHH), 1.97–1.87 (2H, m, CH2), 1.78–1.68 (2H, m, CH2), 1.46 (9H, s, C(CH3)3); δc (150 MHz, CDCl3) 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(CH3)3), 75.4 (NCH2), 74.9 (NCH2CH2Ar), 74.2 (CH2OCH3), 66.2 (NCH), 59.2 (CH2OCH3), 52.6 (CH2), 36.5 (C(CH3)3), 29.5 (C(CH3)3), 26.6 (CH2), 23.2 (CH2); MS (ESI) m/z 374 (MH+); HRMS calcd. for C21H32N3O3 [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 H2O (10 mL) and brine (10 mL). The organic layer was dried over MgSO4, filtered, and concentrated in vacuo. Purification by column chromatography (SiO2, 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. Rf = 0.27 (3:1, hexane: EtOAc); IR νmax (film)/cm⁻¹ 2926, 2874, 1701, 1477, 1450, 1390, 1365, 1127, 1016, 966, 745, 694; δH (400 MHz, CDCl3) major isomer, 7.38–7.15 (5H, m, Ar H), 6.48 (1H, d, J = 15.7 Hz, CH=CHAr), 6.25–6.14 (1H, m, CH=CHAr), 5.08–4.97 (1H, m, NCH2CH2), 4.60–4.33 (2H, m, NCH2), 3.56–3.49 (1H, m, CHHOCH3), 3.47–3.31 (2H, m, CHHOCH3, NCH2OCH2CH2), 3.37 (3H, s, CH2OCH3), 3.29–3.21 (1H, m, NCH2CH2), 2.89–2.73 (1H, m, NCHHCH2), 2.73–2.61 (2H, m, CH2CH=CHAr), 2.06–1.96 (1H, m, CHH), 1.95–1.81 (2H, m, CH2), 1.77–1.61 (1H, m, CHH), 1.46 (9H, s, C(CH3)3); δc (100 MHz, CDCl3) 155.8 (COO), 142.7 (C=N), 137.6 (C, Ar), 133.7 (CH=CHAr), 128.5 (CH, Ar), 127.2 (CH, Ar), 126.2 (CH, Ar), 124.5 (CH=CHAr), 80.0 (C(CH3)3), 74.8 (CH2OCH3), 72.8 (NCH2CH2CH=CH), 65.1
(NCHCH₂OCH₃), 60.4 (NCH₂), 59.2 (CH₂OCH₃), 52.7 (NCH₂CH₂), 36.1 (CH₂CH=CHAr), 28.4 (C(CH₃)₃), 25.9 (CH₂), 23.1 (CH₂); MS (ESI⁺) m/z 422 (MNa⁺); HRMS calcd. for C₂₃H₃₃N₃NaO₃ [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 tert-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 H₂O (10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. Purification by column chromatography (SiO₂, 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. Rf = 0.23 (3:1, hexane: EtOAc); IR νmax (film)/cm⁻¹ 2929, 2876, 1703, 1479, 1455, 1387, 1364, 1111, 1020, 746; δH (400 MHz, CDCl₃) major isomer, 4.88–4.78 (1H, m, NCH₃), 4.68–4.53 (2H, m, NCH₂), 3.50–3.43 (1H, m, CHHOCH₃), 3.41–3.33 (2H, m, CHHOCH₃, NCHCH₂), 3.36 (3H, s, CH₂OCH₃), 3.30–3.23 (1H, m, NCHH), 2.75 (1H, q, J = 8.0 Hz, NCHH), 1.93–1.83 (3H, m, CHH, CH₂), 1.77–1.67 (1H, m, CHH), 1.44 (9H, s, C(CH₃)₃), 1.44–1.41 (3H, m, NCHCH₃); δC (100 MHz, CDCl₃) 156.0 (COO), 79.8 (C(CH₃)₃), 74.9 (CH₂OCH₃), 69.3 (NCHCH₃), 64.9 (NCH), 59.3 (CH₂OCH₃), 52.6 (NCH₂), 28.4 (C(CH₃)₃), 26.0 (CH₂), 22.8 (CH₂), 18.9 (NCHCH₃), C=N not observed, azetidine NCH₂ not observed; MS (ESI⁺) m/z 298 (MH⁺), 320 (MNa⁺); HRMS calcd. for C₁₅H₂₇N₃NaO₃ [M+Na]⁺ 320.1945, found 320.1943.
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 NaHCO₃ solution (25 mL), dried over MgSO₄, filtered, and concentrated in vacuo. Purification by column chromatography (SiO₂, 7:1, hexane:EtOAc) provided (S)-159 (30 mg, 75%) as a pale yellow oil. R_f = 0.32 (7:1, hexane:EtOAc); [α]D²⁵ +55.4 (c 0.11, CHCl₃); IR ʋ max (film)/cm⁻¹: 3082, 2979, 2928, 1822, 1704, 1479, 1458, 1392, 1365, 1177, 1124, 923, 772; δH (400 MHz, CDCl₃) 5.91−5.73 (1H, m, CH₂CCH=CH₂), 5.24−5.12 (2H, m, CH₂CH=CH₂), 5.01−4.87 (1H, m, NC(CH₃)₂), 4.67 (1H, d, J = 16.6 Hz, NCH), 4.47 (1H, dd, J = 16.6, 2.2 Hz, NCHH), 2.72−2.61 (1H, m, NCHCHH), 2.61−2.51 (1H, m, NCHCHH), 1.49 (9H, s, C(CH₃)₃), broadening of peaks observed; δC (125 MHz, CDCl₃) 199.9 (C=O), 155.9 (COO), 131.6 (CH₂CH=CH₂), 119.3 (CH₂CH=CH₂), 82.2 (NCHCH₂), 80.8 (C(CH₃)₃), 69.1 (NCH₂), 34.1 (NCHCH₂), 28.3 (C(CH₃)₃); MS (ESI⁺) m/z 234 (MNa⁺); HRMS calcd. for C₁₁H₁₇NNaO₃ [M+Na]+ 234.1101, found 234.1093; 81% ee (determined by chiral GC analysis on a Chrompact cyclodextrin-β-236M-19 50m x 0.25mm x 0.25µm column, T = 110 °C, P = 15 psi, H₂ carrier gas, tR 63.35 min and tR 64.55 min).

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

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 NaHCO₃ solution (25 mL), dried
over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography provided the product.

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

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\text{(S)-151 (113 mg, 0.40 mmol), } \text{\textsuperscript{t}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\textsubscript{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]^{25}_D +52.7 (c 0.11, CHCl₃).
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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, H₂ carrier gas, t<sub>R</sub> 63.35 min and t<sub>R</sub> 64.55 min).

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

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\text{(R)-151 (113 mg, 0.40 mmol), } \text{\textsuperscript{t}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\textsubscript{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]^{30}_D −47.4 (c 0.12, CHCl₃); IR \nu_{\text{max}} (film)/cm\textsuperscript{−1} 3079, 2976, 2925, 1821, 1700, 1456, 1432, 1391, 1365, 1175, 1119, 921, 769; \delta_H (400 MHz, CDCl₃) 5.88−5.75 (1H, m, CH₂C=CH₂), 5.22−5.14 (2H, m, CH₂CH=CH₂), 4.98−4.91 (1H, m, NCHCH₂), 4.66 (1H, d, J = 16.6 Hz, NCHH), 4.48 (1H, dd, J = 16.6, 4.3 Hz, NCHH₂), 2.71−2.61 (1H, m, NCHCH₂H), 2.61−2.51 (1H, m, NCHCHH), 1.49 (9H, s, C(CH₃)₃), broadening of peaks observed; \delta_C (125 MHz, CDCl₃) 199.9 (C=O), 155.9 (COO), 131.6 (CH₂CH=CH₂), 119.4 (CH₂CH=CH₂), 82.2 (NCHCH₂), 80.8 (C(CH₃)₃), 69.1 (NCH₂), 34.1 (NCHCH₂), 28.3 (C(CH₃)₃); MS (ESI⁺) m/z 234 (MNa⁺); HRMS calcd. for C₁₁H₁₇NaO₃ [M+Na⁺] 234.1101, found 234.1102; 81% ee (determined by chiral GC analysis on a
Chapter 3: Experimental

Chrompac cyclodextrin-β-236M-19 50m x 0.25mm x 0.25µm column, T = 110 °C, P = 15 psi, H₂ carrier gas, tᵣ 41.37 min and tᵣ 42.52 min).

(S)-2-((3-Methylbut-2-en-1-yl)-3-oxoazetidine)-1-tert-butylicarboxylate (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 (SiO₂, 7:1, hexane: EtOAc) provided 165 (51 mg, 53%) as a pale yellow oil. Rᵣ = 0.39 (7:1, hexane: EtOAc); [α]²⁵D +30.3 (c 0.13, CHCl₃); IR ʋmax (film)/cm⁻¹ 2977, 2927, 1821, 1365, 1176, 1129, 856, 772; δH (400 MHz, CDCl₃) 5.18 (1H, t, J = 7.2 Hz, CH₂C≡C(CH₃₂), 4.94−4.86 (1H, m, NCH₂), 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, NCHC₃), 1.72 (3H, s, C(CH₃)(CH₃)), 1.63 (3H, s, C(CH₃)(CH₃)), 1.49 (9H, s, C(CH₃)₃), broadening of peaks observed; δC (125 MHz, CDCl₃) 200.6 (C=O), 155.9 (COO), 136.3 (CH=C(CH₃)₂), 116.9 (CH=C(CH₃)₂), 82.8 (NCHCH₂), 80.6 (C(CH₃)₃), 68.9 (NCH₂), 28.6 (NCHCH₂), 28.3 (C(CH₃)₃), 25.9 (C(CH₃)(CH₃)), 17.9 (C(CH₃)(CH₃)); MS (ES⁺) m/z 262 (MNa⁺); HRMS calcd. for C₁₃H₂₁NNaO₃ [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, tᵣ 68.27 min and tᵣ 69.17 min).

(S)-2-(Phenylallyl-3-oxoazetidine)-1-tert-butylicarboxylate (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 (SiO₂, 7:1, hexane: EtOAc) provided 166 (85 mg, 74%) as a pale yellow oil. Rᵣ = 0.36 (7:1, hexane: EtOAc); [α]¹⁹D +71.3 (c 0.12, CHCl₃); IR ʋmax (film)/cm⁻¹ 2976, 2929, 1822, 1699,
1494, 1391, 1365, 1129, 966, 743, 693; δH (400 MHz, CDCl₃) 7.40–7.19 (5H, m, Ar H), 6.51 (1H, d, J = 15.8 Hz, CH=CHAr), 6.24–6.13 (1H, m, CH=CHAr), 5.05–4.97 (1H, m, NCH₂CH₂), 4.67 (1H, d, J = 16.6 Hz, NCHH), 4.48 (1H, dd, J = 16.6, 4.3 Hz, NCHH), 2.88–2.66 (2H, m, NCHC₂H₂), 1.48 (9H, s, C(CH₃)₃);

δC (125 MHz, CDCl₃) 199.9 (C=O), 155.9 (COO), 136.9 (C, Ar), 134.4 (CH₂CH=CH), 128.6 (CH, Ar), 127.5 (CH, Ar), 126.3 (CH, Ar), 122.8 (CH₂CH=CH), 82.4 (NCH₂), 80.9 (C(CH₃)₃), 69.2 (NCH₂), 33.4 (NCH₂), 28.3 (C(CH₃)₃); MS (ESI⁺) m/z 310 (MNa⁺); HRMS calcd. for C₁₇H₂₁NNaO₃ [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, tR 34.35 min and tR 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 (SiO₂, 7:1, hexane:EtOAc) provided 167 (30 mg, 41%) as a colourless oil. RỊ = 0.25 (7:1, hexane:EtOAc); [α]D²⁶ +15.4 (c 0.23, CHCl₃); IR νmax (film)/cm⁻¹ 2959, 2925, 2856, 1828, 1709, 1458, 1389, 1367, 1180, 1144, 1126, 772; δH (400 MHz, CDCl₃) 4.98–4.88 (1H, m, NCH₂CH₂), 4.70 (1H, d, J = 16.6 Hz, NCHH), 4.57 (1H, dd, J = 16.6, 4.3 Hz, NCHH), 1.49 (9H, s, C(CH₃)₃), 1.45 (3H, d, J = 7.0 Hz, NCH₂CH₂), broadening of peaks observed; δC (125 MHz, CDCl₃) 199.8 (C=O), 155.0 (COO), 79.7 (C(CH₃)₃), 77.6 (NCH₂), 67.4 (NCH₂), 27.3 (C(CH₃)₃), 14.4 (NCH₂CH₂); GCMS (EI⁺) m/z 185 (M⁺); 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, tR 5.25 min and tR 5.53 min).
(S)-2-(Propyl-3-oxoazetidine)-1-tert-butylcarboxylate (168)

(S)-151 (113 mg, 0.40 mmol), 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 (SiO₂, 7:1, hexane: EtOAc) provided 168 (43 mg, 50%) as a pale yellow oil. Rᵢ = 0.41 (7:1, hexane: EtOAc); [α]²⁰ [D] +54.8 (c 0.10, CHCl₃); IR vₘₐₓ (film)/cm⁻¹ 2964, 2934, 2875, 1819, 1701, 1458, 1389, 1365, 1138, 1119, 774; δH (400 MHz, CDCl₃) 4.93–4.86 (1H, m, NCH₂CH₂), 4.68 (1H, d, J = 16.7 Hz, NCHH), 4.51 (1H, dd, J = 16.7, 4.3 Hz, NCH₂H), 1.87–1.77 (2H, m, NCH₂CH₂), 1.60–1.37 (2H, m, CH₂CH₂CH₃), 1.49 (9H, s, C(CH₃)₃), 0.95 (3H, t, J = 7.3 Hz, CH₂CH₂CH₃); δC (125 MHz, CDCl₃) 201.1 (C=O), 156.3 (COO), 82.9 (NCH₂CH₂), 80.7 (C(CH₃)₃), 68.9 (NCH₂), 32.4 (NCH₂CH₂), 28.3 (C(CH₃)₃), 18.1 (CH₂CH₂CH₃), 13.9 (CH₂CH₂CH₃); MS (ESI⁺) m/z 236 (MNa⁺); HRMS calcld. for C₁₁H₁₉NNaO₃ [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, tᵣ 9.64 min and tᵣ 10.00 min).

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

(S)-151 (113 mg, 0.40 mmol), butyllithium (2.45 M solution in hexanes, 180 µL, 0.44 mmol), anhydrous THF (4 mL) and 2-iodopropane (47 µL, 0.48 mmol) were reacted according to General Method A. Work-up, followed by purification by column chromatography (SiO₂, 7:1, hexane: EtOAc) provided 169 (44 mg, 52%) as a colourless oil. Rᵢ = 0.40 (7:1, hexane: EtOAc); [α]²⁰ [D] +85.2 (c 0.26, CHCl₃); IR vₘₐₓ (film)/cm⁻¹ 2966, 2934, 2875, 1819, 1701, 1478, 1389, 1365, 1138, 1119, 774; δH (400 MHz, CDCl₃) 4.76–4.71 (1H, m, NCH₂CH(CH₃)₂), 4.65 (1H, d, J = 16.7 Hz, NCHH), 4.44 (1H, dd, J = 16.7, 4.3 Hz, NCH₂H), 2.17 (1H, octet, J = 6.7 Hz, NCH₂CH(CH₃)₂), 1.49 (9H, s, C(CH₃)₃), 1.04 (3H, d, J = 6.8 Hz, CH(CH₃)(CH₃)), 1.03 (3H, d, J = 6.7 Hz, CH(CH₃)(CH₃)); δC (125 MHz, CDCl₃) 201.0 (C=O), 156.3 (COO), 88.4 (NCH₂CH(CH₃)₂), 80.8 (C(CH₃)₃), 69.4 (NCH₂), 30.0 (CH(CH₃)₂), 28.3 (C(CH₃)₃), 18.2 (CH(CH₃)(CH₃)),
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 $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3459, 2955, 2912, 2872, 2850, 1826, 1391, 1114, 1095, 717; $\delta$H (400 MHz, CDCl$_3$) 4.90−4.84 (1H, m, NC$_\text{H}$), 4.70 (1H, d, $J$ = 16.6 Hz, NC$_\text{H}$H), 4.51 (1H, dd, $J$ = 16.6, 3.9 Hz, NCH$_2$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); $\delta$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$_3$)$_2$OH), 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 diasteromers. $R_f = 0.29$ (4:1, hexane: EtOAc); IR $v_{\text{max}}$ (film)/cm$^{-1}$ 3414, 2978, 2927, 1824, 1455, 1393, 1367, 1171, 1145, 1119, 768, 733; $\delta_{\text{H}}$ (500 MHz, CDCl$_3$) 7.38–7.29 (12.5H, m, Ar H.), 5.27–5.18 (1H, m, NCHCH), 5.17–5.12 (1.5H, m, NCHCH), 5.10–5.03 (2.5H, m, NCHCH, NCHCH), 4.65 (2H, d, $J = 16.5$ Hz, NCHH, NCHH), 4.52 (1H, br s, COH), 4.47 (3H, dd, $J = 16.5$, 3.5 Hz, NCHH, NCHH), 1.50 (9H, s, C(CH$_3$)$_3$), 1.44 (13.5H, s, C(CH$_3$)$_3$), OH not observed; $\delta_{\text{C}}$ (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 (C\text{H}, Ar), 126.8 (CH, Ar), 126.5 (CH, Ar), 87.8 (NCHCH), 87.7 (NCHCH), 82.0 (C(CH$_3$)$_3$), 81.8 (C(CH$_3$)$_3$), 73.4 (C(CH$_3$)$_3$), 28.3 (C(CH$_3$)$_3$); 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 φ 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-oxazetidine)-1-tert-butylcarboxylate (172)
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<sub>R</sub> 20.62 min and t<sub>R</sub> 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<sub>2</sub>, 2:1, hexane: EtOAc) provided 173 (11 mg, 9%) as a yellow oil. R<sub>f</sub> = 0.67 (2:1, hexane: EtOAc); [α]<sup>D</sup> +93.9 (c 0.14, CHCl<sub>3</sub>); IR ν<sub>max</sub> (film)/cm<sup>−1</sup> 2976, 2924, 1822, 1613, 1587, 1514, 1457, 1391, 1365, 1176, 1126, 834; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 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<sub>H</sub>CH<sub>2</sub>), 4.52 (1H, d, J = 16.6 Hz, NCHCH<sub>2</sub>), 4.03 (1H, dd, J = 16.5, 4.3 Hz, NCHH), 3.79 (3H, s, OC<sub>H</sub>3), 3.15 (1H, dd, J = 14.4, 6.3 Hz, NCHCHH), 3.05 (1H, dd, J = 14.4, 3.8 Hz, NCHCHH), 1.49 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), broadening of peaks observed; δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 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 (NCHCH<sub>2</sub>), 80.7 (C(CH<sub>3</sub>)<sub>3</sub>), 69.0 (NCH<sub>2</sub>), 55.2 (OCH<sub>3</sub>), 34.8 (NCHCH<sub>2</sub>), 28.4 (C(CH<sub>3</sub>)<sub>3</sub>); MS (ES<sup>+</sup>) m/z 314 (MNa<sup>+</sup>); HRMS calcd. for C<sub>16</sub>H<sub>21</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup> 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<sub>R</sub> 51.28 min and t<sub>R</sub> 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<sub>2</sub>, 1:1, hexane: EtOAc) provided 161 (784 mg, 92%) as a pale yellow oil. R<sub>f</sub> = 0.53 (1:1, hexane: EtOAc); IR ν<sub>max</sub> (film)/cm<sup>−1</sup> 2974, 2864,
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1700, 1452, 1388, 1365, 1124, 1016, 940, 859, 765; δH (400 MHz, CDCl3) 4.71 (2H, t, J = 2.7 Hz, NCH2), 4.57 (2H, t, J = 2.7 Hz, NCH2), 2.70 (6H, s, N(CH3)2), 1.46 (9H, s, C(CH3)3); δC (125 MHz, CDCl3) 156.1 (C=O), 138.4 (C=N), 80.2 (C(CH3)3), 61.6 (NCH2), 61.0 (NCH2), 45.8 (N(CH3)2), 28.3 (C(CH3)3); MS (ESI+) m/z 236 (MNa+); HRMS calcd. for C10H19N3NaO2 [M+Na]+ 236.1369, found 236.1365.

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

(S)-(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 (SiO2, 3:1, hexane: EtOAc) provided 162 (1.76 g, 100%) as an orange oil. Rf = 0.37 (3:1, hexane: EtOAc); [α]D25 +33.5 (c 0.11, CHCl3); IR νmax (film)/cm⁻¹ 2926, 2875, 2825, 1686, 1599, 1451, 1115, 1091, 950, 742, 700; δH (400 MHz, CDCl3) 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, NCH2), 3.92 (2H, s, NCH2), 3.54–3.48 (1H, m, CHHOCH3), 3.41–3.28 (2H, m, CHHOCH3, NCHCH2), 3.36 (3H, s, CH2OCH3), 3.23–3.15 (1H, m, NCHHCH2), 2.68 (1H, q, J = 8.3 Hz, NCHHCH2), 1.96–1.85 (1H, m, CHH), 1.85–1.75 (2H, m, CHH), 1.73–1.62 (1H, m, CHH); δC (125 MHz, CDCl3) 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 (CH2OCH3), 65.3 (NCHCH2), 64.9 (NCH2), 64.5 (NCH2), 59.3 (CH2OCH3), 53.0 (NCH2CH2), 26.0 (CH2), 22.6 (CH3); MS (ESI+) m/z 350 (MH+); HRMS calcd. for C22H28N3O [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 "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 NaHCO₃ solution (25 mL), dried over MgSO₄, filtered, and concentrated in vacuo. Purification by column chromatography (SiO₂, 7:1, hexane: EtOAc) provided 163 (22 mg, 20%) as a pale yellow oil. Rf = 0.53 (7:1, hexane: EtOAc); [α]D²⁴ +6.50 (c 0.10, CHCl₃); IR νmax (film)/cm⁻¹ 3063, 2932, 2819, 1804, 1599, 1453, 1429, 920, 743, 698; δH (400 MHz, CDCl₃) 7.90 – 6.95 (10H, m, Ar H), 5.74 – 5.52 (1H, m, CH₂CH=CH₂), 5.01 – 4.75 (2H, m, CH₂CH=CH₂), 4.53 (1H, s, NCH), 4.18 – 3.90 (2H, m, NCHH, NCH₂CH₂), 3.61 (1H, d, J = 16.2 Hz, NCHH), 1.96 – 1.80 (2H, m, NCHCH₂); δC (125 MHz, CDCl₃) 204.4 (C=O), 142.5 (C, Ar), 142.3 (C, Ar), 133.3 (CH₂CH=CH₂), 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 (CH₂CH=CH₂), 84.7 (NCHCH₂), 77.9 (NCH), 72.9 (NCH₂), 35.0 (NCH₂CH₂); MS (ESI⁺) m/z 278 (MH⁺); HRMS calcd. for C₁₉H₂₀NO [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, tR 10.44 min and tR 11.01 min).

N,N-Dimethyl-N’-azetidine-3-ylidinehydrazine-1-benzhydryl (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 (SiO₂, 2:1, hexane: EtOAc) provided 164 (524
mg, 78%) as a yellow solid. M. p. 114–116 °C; Rf = 0.37 (2:1, hexane: EtOAc); IR νmax (neat)/cm⁻¹ 3025, 2850, 2782, 1688, 1596, 1450, 947, 743, 702; δH (400 MHz, CDCl₃) 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, NC₃H), 4.03 (2H, s, NC₃H₂), 3.91 (2H, s, NC₃H₂), 2.61 (6H, s, N(C₃H₃)₂); δC (125 MHz, CDCl₃) 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 (NCH₂), 64.4 (NCH₂), 46.3 (N(CH₃)₂); MS (ESI⁺) m/z 280 (MH⁺); HRMS calcd. for C₁₈H₂₂N₃ [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 H₂O (10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. Purification by column chromatography (SiO₂, 1:1, hexane: EtOAc) provided 160 (33 mg, 36%) as a white solid. M. p. 107–111 °C; Rf = 0.73 (1:1, hexane: EtOAc); IR νmax (neat)/cm⁻¹ 3326, 2961, 1651, 1422, 1389, 1365, 1164, 1136, 1064, 938, 768; δH (400 MHz, CDCl₃) 4.02 (2H, d, J = 9.5 Hz, NCH₂), 3.66 (2H, d, J = 9.5 Hz, NCH₂), 2.54 (1H, br s, OH), 1.44 (9H, s, OC(CH₃)₃), 0.96 (9H, s, CC(CH₃)₃); δC (125 MHz, CDCl₃) 156.4 (COO), 79.6 (OC(CH₃)₃), 76.0 (COH), 58.9 (NCH₂), 58.0 (NCH₂), 34.9 (CC(CH₃)₃), 28.4 (OC(CH₃)₃), 23.8 (CC(CH₃)₃); MS (ESI⁺) m/z 252 (MNa⁺); HRMS calcd. for C₁₂H₂₃NNaO₃ [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 CH₃CN (5 mL) was added L-tryptophan ethyl ester (140 mg, 0.60 mmol) and I₂ (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 Na₂S₂O₃ solution (10 mL), saturated aqueous NaHCO₃ solution (10 mL) and brine (10 mL). The organic layers were dried over Na₂SO₄, filtered, and the solvent removed in vacuo. Purification by column chromatography (SiO₂, 6:4, petrol: EtOAc) provided 178 (184 mg, 95%) as a light pink crystalline solid. M. p. 83–85 °C; Rᵣ = 0.29 (6:4, petrol: EtOAc); [α]D¹⁹ –25.7 (c 0.10, CHCl₃); IR ʋₘₐₓ (neat)/cm⁻¹ 3298, 2978, 2934, 2878, 1733, 1684, 1394, 1367, 1125, 1112, 741; δH (400 MHz, CDCl₃) 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, NCHH), 4.26 (2H, q, J = 7.1 Hz, CO₂CH₂CH₃), 4.16 (1H, d, J = 9.5 Hz, NCHH), 4.07 (2H, s, NCH₃), 3.77 (1H, dd, J = 9.8, 4.5 Hz, NHCH), 3.13 (1H, dd, J = 15.3, 4.6 Hz, NHCH₂CH₂H), 2.88 (1H, dd, J = 15.3, 9.9 Hz, NHCH₂CH₃), 2.75–2.42 (1H, br s, NHpip), 1.50 (9H, s, C(CH₃)₃), 1.33 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃); δC (125 MHz, CDCl₃) 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(CH₃)₃), 64.6 (NCH₂), 61.4 (CO₂CH₂CH₃), 60.4 (NCH₂), 54.0 (NCHCH₂), 51.3 (NHC), 28.4 (C(CH₃)₃), 25.4 (NCHCH₂), 14.2 (CO₂CH₂CH₃); MS (ESI⁺) m/z 386 (MH⁺), 406 (MNa⁺); HRMS calcd. for C₂₁H₂₈N₃O₄ [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 CH₃CN (5 mL) was added L-tryptophan ethyl ester (140 mg, 0.60 mmol) and I₂ (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 Na₂S₂O₃ solution (10 mL), saturated aqueous NaHCO₃ solution (10 mL) and brine (10 mL). The organic layers were dried over Na₂SO₄, filtered, and the solvent removed in vacuo to give the title compounds as a 7.9:1 mixture of diastereomers as determined by ¹H NMR spectroscopy. Purification by flash column chromatography (SiO₂, 8:2, petrol: EtOAc) provided the separable diastereomers, to afford less polar, major diastereomer (2R,3S,3’S)-179a (147 mg, 69%) as an off-white solid. M. p. 80–83 °C; Rf = 0.38 (8:2, petrol: EtOAc); [α]D²⁹ = −78.5 (c 0.11 CHCl₃); IR νmax (neat)/cm⁻¹ 3321, 3301, 2976, 2931, 1735, 1680, 1475, 1452, 1393, 1367, 1173, 1136, 916, 766, 741; δH (500 MHz, CDCl₃) 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, CH₂C=CH₂), 5.11 (1H, dd, J = 17.3, 1.4 Hz, CH₂C=CH₂), 5.05 (1H, dd, J = 10.4, 0.9 Hz, CH₂C=CH₂), 4.76–4.68 (1H, m, NC₃H₃), 4.28 (2H, q, J = 7.2 Hz, CO₂C₃H₇), 4.02 (1H, d, J = 8.6 Hz, NCH), 3.96 (1H, d, J = 8.6 Hz, NCH), 3.73–3.66 (1H, m, NHCH₂CH₃), 3.09 (1H, dd, J = 15.2, 4.3 Hz, NHCHCH₂), 2.90–2.84 (2H, m, CH₂C=CH₂), 2.75 (1H, dd, J = 11.2, 4.1 Hz, NHCHCH₂), 2.64 (1H, br d, J = 6.7 Hz, NHpip), 1.51 (9H, s, C(CH₃)₃), 1.35 (3H, t, J = 7.2 Hz, CO₂C₃H₇); δC (125 MHz, CDCl₃) 172.8 (COO), 156.5 (NCOO), 136.4 (C, Ar), 134.7 (C, Ar), 134.2 (CH₂C=CH₂), 126.7 (C, Ar), 122.4 (CH, Ar), 119.8 (CH, Ar), 118.3 (CH, Ar), 117.9 (CH₂C=CH₂), 111.2 (CH, Ar), 108.9 (C, Ar), 80.3 (C(CH₃)₃), 68.7 (NCH₂CH₃), 62.4 (NCH₂), 61.3 (OCH₂CH₃), 54.1 (NHC), 53.7 (NHCH₂CH₃), 33.0 (CH₂C=CH₂), 28.5 (C(CH₃)₃), 25.7 (NHCH₂CH₃), 14.2 (OCH₂CH₃); MS (ESI⁺) m/z 426 (MH⁺); HRMS calcd. for C₂₃H₃₂N₃O₄ [M+H]⁺
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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; Rf = 0.25 (8:2, petrol: EtOAc); [α]D20 +5.37 (c 0.12, CHCl3); IR νmax (neat)/cm−1 3367, 2966, 2928, 1721, 1475, 1447, 1390, 1368, 1168, 1128, 910, 777, 747; δH (400 MHz, CDCl3) 8.91–8.84 (1H, br s, NHindole), 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, CH2CH=CH2), 5.07 (1H, d, J = 17.3 Hz, CH2CH=CHH), 5.07 (1H, d, J = 10.2 Hz, CH2CH=CHH), 4.45–4.37 (1H, m, NCHCH2), 4.31–4.20 (3H, m, CO2CH2CH3), 3.99 (1H, d, J = 9.3 Hz, NCHH), 3.80 (1H, dd, J = 10.3, 4.1 Hz, NHCHCH2), 3.09 (1H, dd, J = 15.1, 4.1 Hz, NHCHCHH), 2.85–2.72 (3H, m, NHCHCHH, CH2CH=CH2), 1.53 (9H, s, C(CH3)3), 1.33 (3H, t, J = 7.1 Hz, CO2CH2CH3), NHpip not observed; δC (125 MHz, CDCl3) 172.8 (COO), 156.0 (NCOO), 136.5 (C, Ar), 135.1 (C, Ar), 134.5 (CH2CH=CH2), 126.5 (C, Ar), 122.3 (CH, Ar), 119.7 (CH, Ar), 118.3 (CH, Ar), 117.6 (CH2CH=CH2), 111.3 (CH, Ar), 108.6 (C, Ar), 80.5 (C(CH3)3), 72.2 (NCHCH2), 61.3 (OCH2CH3), 60.7 (NCH3), 54.5 (NHCHCH2), 54.4 (NHC), 32.9 (CH2CH=CH2), 28.6 (C(CH3)3), 25.3 (NCHCHCH2), 14.3 (OCH2CH3); MS (ESI+) m/z 426 (MH+); HRMS calcd. for C24H32N3O4 [M+H]+ 426.2387, found 426.2388.

L-Tryptophan methyl ester (182)³⁰

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 NaHCO3 solution (25 mL), and extracted with EtOAc (3 x 25 mL). The organic extracts were combined, dried over Na2SO4, filtered, and concentrated in vacuo to give 182 (534 mg, 100%) as an off-white solid. δH (500 MHz, CDCl3) 8.14 (1H, br s, NHindole), 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, NHCH), 3.84 (1H, dd, J = 7.7, 4.9 Hz, NH2CHCH2), 3.72 (3H, s, CO2CH3), 3.29 (1H, dd, J = 14.4, 4.8 Hz, NH2CHCHH), 3.06 (1H, dd, J = 14.4, 7.7
Hz, NH₂CHCHH), 1.61 (2H, br s, NH₂); δC (125 MHz, CDCl₃) 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 (NH₂CHCH₂), 52.0 (CO₂CH₃), 30.8 (NHCHCH₂); MS (ESI⁺) m/z 219 (MH⁺), 241 (MNa⁺); HRMS calcd. for C₁₂H₁₅N₂O₂ [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 CH₃CN (6 mL) was added L-tryptophan methyl ester (142 mg, 0.65 mmol) and I₂ (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 Na₂S₂O₃ solution (10 mL), saturated aqueous NaHCO₃ solution (10 mL) and brine (10 mL). The organic layers were dried over Na₂SO₄, 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 (SiO₂, 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; Rf = 0.46 (7:3, petrol: EtOAc); [α]D²⁶ =44.0 (c 0.10, CHCl₃); IR νmax (neat)/cm⁻¹ 3347, 2975, 2939, 2848, 1734, 1677, 1500, 1456, 1380, 1366, 1144, 1133, 747, 736; δH (300 MHz, CDCl₃) 8.40–8.25 (1H, br s, NHₙido), 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, NCHC(CH₃)₂OH), 4.09 (1H, d, J = 8.6 Hz, NCHH), 3.98 (1H, d, J = 8.7 Hz, NCHH), 3.84 (3H, s, CO₂CH₃), 3.70 (1H, dd, J = 11.2, 4.1 Hz, NHCHCH₂), 3.11 (1H, dd, J = 15.2, 4.1 Hz, NHCCHH), 2.82 (1H, dd, J = 15.2, 11.2 Hz, NHCCHH), 1.52 (9H, s, C(CH₃)₃), 1.49 (3H, s, C(CH₃)₃(CH₃)OH), 1.25 (3H, s,
C(CH₃)(CH₃)OH, piperidine NH not observed, OH not observed; δC (125 MHz, CDCl₃) 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(CH₃)₃), 77.6 (NCHC(CH₃)₂OH), 72.1 (C(CH₃)₂OH), 63.9 (NCH₂), 56.4 (NHC), 53.6 (CO₂CH₂), 52.4 (NHCHCH₂), 28.4 (C(CH₃)₃), 26.4 (C(CH₃)(CH₃)OH), 26.3 (C(CH₃)(CH₃)OH), 25.2 (NHCHCH₂); MS (ES⁺) m/z 430 (MH⁺); HRMS calcd. for C₂₃H₃₂N₃O₅ [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. Rf = 0.26 (7:3, petrol: EtOAc); [α]D³₀ +14.8 (c 0.25, CHCl₃); IR νmax (film)/cm⁻¹ 3313, 2929, 2854, 1737, 1674, 1393, 1367, 1219, 1170, 735; δH (500 MHz, CDCl₃) 8.01 (0.82H, br s, NHindole, major rotamer), 7.97 (0.18H, br s, NHindole, 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, NCHH), 4.23–4.18 (2H, m, NCHH, NCHC(CH₃)₂OH), 3.93 (1H, dd, J = 8.2, 4.6 Hz, NHCHCH₂), 3.75 (3H, s, CO₂CH₃), 3.14 (1H, dd, J = 15.2, 4.6 Hz, NHCHCHH), 2.89 (1H, dd, J = 15.2, 8.3 Hz, NHCHCHH), 1.55 (9H, s, C(CH₃)₃), 1.37 (3H, s, C(CH₃)(CH₃)OH), 1.30 (3H, s, C(CH₃)(CH₃)OH), piperidine NH not observed, OH not observed; δC (125 MHz, CDCl₃) 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(CH₃)₃), 79.6 (NCHC(CH₃)₂OH), 73.1 (NCHC(CH₃)₂OH), 64.2 (NCH₂), 55.6 (NHC), 54.2 (NHCHCH₂), 52.4 (CO₂CH₂), 28.4 (C(CH₃)₃, rotamer), 28.3 (C(CH₃)₃, rotamer), 27.4 (C(CH₃)(CH₃)OH), 26.7 (C(CH₃)(CH₃)OH), 25.1 (NHCHCH₂); MS (ES⁺) m/z 430 [MH⁺], 452 [MNa⁺]; HRMS calcd. for C₂₃H₃₁N₃NaO₅ [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 (SiO₂, 3:1, petrol: EtOAc) provided 193 (1.10 g, 92%) as a yellow oil. Rf = 0.35 (3:1, petrol: EtOAc);
\([\alpha]_D^{23} +105\) (c 0.01, CHCl\(_3\)); IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2968, 2921, 2826, 1638, 1447, 1359, 1097, 745; \(\delta_H\) (500 MHz, CDCl\(_3\)) 4.28 (1H, dt, \(J = 14.4, 2.7\) Hz, SCHH), 4.18 (1H, dt, \(J = 13.6, 2.8\) Hz, SCHH), 4.07 (1H, dd, \(J = 14.4, 2.7\) Hz, SCHH), 4.02 (1H, dd, \(J = 13.7, 2.6\) Hz, SCHH), 3.48 (1H, dd, \(J = 14.4, 2.7\) Hz, SCHH), 3.37 (3H, s, CH\(_2\)OCH\(_3\)), 3.34–3.30 (3H, m, CH\(_2\)HOC\(_3\), NC\(_{2}\)HCH\(_2\), NC\(_{2}\)H), 2.67 (1H q, \(J = 8.4\) Hz, NC\(_{2}\)H), 1.98–1.90 (3H, m, CH\(_2\), CHH), 1.90–1.82 (1H, m, CHH); \(\delta_C\) (125 MHz, CDCl\(_3\)) 144.8 (C=N), 75.1 (CH\(_2\)OCH\(_3\)), 65.9 (NCHCH\(_2\)), 59.3 (CH\(_2\)OCH\(_3\)), 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\(_9\)H\(_{16}\)N\(_2\)NaOS [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 \(\mu\)L, 0.55 mmol), followed by \(n\)butyllithium (2.43 M solution in hexanes, 226 \(\mu\)L, 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\(_2\)O (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 \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2922, 2871, 1703, 1451, 1365, 1129, 1024, 860, 770; \(\delta_H\) (400 MHz, CDCl\(_3\)) major isomer, 4.94–4.87 (1H, m, NC\(_{2}\)HCH\(_2\)), 4.41 (1H, d, \(J = 14.0\) Hz, NCHH), 4.35 (1H, dd, \(J = 14.0, 3.3\) Hz, NCHH), 3.46 (1H, dd, \(J = 9.2, 4.1\) Hz, CHHOCH\(_3\)), 3.34–3.31 (2H, m, CHHOCH\(_3\), NCHCHOCH\(_3\)), 3.30 (3H, s, CH\(_2\)OCH\(_3\)), 3.24–3.17 (1H, m, NCHHCH\(_2\)), 2.41 (1H, q, \(J = 8.3\) Hz, NCHHCH\(_2\)), 2.15–2.06 (2H, m, CH\(_2\)C≡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≡CCH\(_3\)), 1.61–1.52 (2H, m,
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(CH2CH2C≡CCH3), 1.40 (9H, s, C(CH3)3); δC (100 MHz, CDCl3) 156.3 (COO), 143.2 (C=N), 80.0 (C(CH3)3), 78.8 (C=C), 75.8 (C=C), 74.9 (CH2OCH3), 73.3 (NCHCH2), 65.9 (NCHCHOCH3), 60.1 (NCH2), 59.2 (CH2OCH3), 53.6 (NCH2CH2), 29.3 (NCHCH2), 28.2 (C(CH3)3), 26.7 (CH2), 23.0 (CH2CH2C≡CCH3), 22.7 (CH2), 18.5 (CH2C≡CCH3), 3.4 (C≡CCH3); MS (ESI+) m/z 364 (MH+), 386 (MNa+); HRMS calcd. for C20H34N3O3 [M+H]+ 364.2595, found 364.2593.

(S)-2-((Hex-4-yne)-3-oxazetidine)-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 NaHCO3 solution (10 mL), dried over MgSO4, filtered, and concentrated in vacuo to give 205 (25 mg, 90%) as a pale yellow oil, which did not require further purification. Rf = 0.57 (7:1, hexane: EtOAc); [α]D25 +93.6 (c 0.09, CHCl3); IR νmax (film)/cm−1 2923, 2860, 1820, 1701, 1433, 1364, 1127, 1060, 774; δH (400 MHz, CDCl3) 4.93−4.87 (1H, m, NCH2), 4.69 (1H, d, J = 16.7 Hz, NCHH), 4.52 (1H, dd, J = 16.7, 4.3 Hz, NCHH), 2.21−2.17 (2H, m, CH2C≡CCH3), 1.93 (2H, q, J = 7.0 Hz, NCHCH2), 1.77 (3 H, t, J = 2.4 Hz, C≡CCH3), 1.73−1.64 (2H, m, CH2CH2C≡CCH3), 1.49 (9H, s, C(CH3)3); δC (176 MHz, CDCl3) 200.7 (C=O), 156.3 (COO), 82.7 (NCHCH2), 80.9 (C(CH3)3), 78.2 (C≡C), 76.2 (C≡C), 69.0 (NCH2), 29.6 (NCHCH2), 28.3 (C(CH3)3), 24.3 (CH2CH2C≡CCH3), 18.5 (CH2C≡CCH3), 3.5 (C≡CCH3); MS (ESI+) m/z 274 (MNa+); HRMS calcd. for C14H21NNaO3 [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, H2 carrier gas, tR 46.27 min and tR 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 K₂CO₃ solution (20 mL). The layers were separated, and the aqueous layer extracted with EtOAc (20 mL), organic extracts combined, dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (SiO₂, 4:1, petrol: EtOAc) provided 269 (207 mg, 83%) as a pale yellow oil. Rᵣ = 0.44 (4:1, petrol: EtOAc); IR υₑₓₘₐₓ (film)/cm⁻¹ 3318, 2978, 1714, 1477, 1392, 1243, 1152, 755; δₜ (500 MHz, CDCl₃) 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, CO₂CH₂CH₃), 2.87−2.62 (1H, m, CHHCCOO), 2.62−2.36 (2H, m, CHHCCOO, CHHCCOO), 2.19−2.00 (2H, m, CHHCCOO, CH₂CHHCH₂), 1.98−1.83 (1H, m, CH₂CHHCH₂), 1.48 (9H, s, C(CH₃)₃), 1.41 (9H, br s, C(CH₃)₃), 1.29 (3H, t, J = 7.0 Hz, CO₂CH₂CH₃); δc (125 MHz, CDCl₃) 174.4 (COO), 156.2 (NCOO), 155.5 (NCOO), 82.1 (C(CH₃)₃), 81.1 (C(CH₃)₃), 65.9 (CH₂CCO₂), 61.3 (CO₂CH₂CH₃), 32.7 (CH₂CCO₂), 28.8 (CH₂CCO₂), 28.2 (C(CH₃)₃), 28.1 (C(CH₃)₃), 14.4 (CH₂CH₂CH₂), 14.3 (CO₂CH₂CH₃); MS (ES⁺) m/z 381 [MNa⁺]; HRMS calcd. for C₁₇H₃₀N₂NaO₆ [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 LiBH₄ (4.30 mg, 0.20 mmol), and stirred for 3 h. The reaction was quenched with saturated aqueous NH₄Cl solution (10 mL), and extracted with EtOAc (3 x 10 mL). The organic extracts were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered, and
concentrated in vacuo. Purification by column chromatography (SiO₂, 2:1, petrol: EtOAc) provided 270 (27 mg, 85%) as a white solid. M. p. 121–123 °C; Rf = 0.44 (4:1, petrol: EtOAc); IR νmax (neat)/cm⁻¹ 3328, 3208, 2955, 2935, 2874, 1702, 1455, 1394, 1359, 1258, 1161, 761; δH (500 MHz, CDCl₃) 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, CH₂OH), 3.79 (0.15H, br s, OH, minor rotamer), 3.55 (1H, t, J = 10.8 Hz, CH₂OH), 2.20–2.07 (3H, m, CH₂CH₂OH, CH₂CCH₂OH), 2.07–1.96 (1H, m, CH₂CH₂OH), 1.79–1.68 (2H, m, CH₂CH₂OH), 1.46 (9H, s, C(CH₃)₃), 1.44 (9H, s, C(CH₃)₃); δC (125 MHz, CDCl₃) 158.0 (2 x COO), 82.3 (C(CH₃)₃), 81.6 (C(CH₃)₃), 65.2 (CCH₂OH), 64.8 (CCH₂OH), 29.7 (CH₂CCH₂OH), 28.3 (C(CH₃)₃), 28.2 (C(CH₃)₃), 26.8 (CH₂CCH₂OH), 14.0 (CH₂CH₂CH₂); MS (ESI⁺) m/z 339 [M+Na⁺]; HRMS calcd. for C₁₅H₂₈N₂O₅ [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. 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 K₂CO₃ solution (50 mL) and the organic layer separated. The aqueous layer was washed with EtOAc (50 mL), the organic extracts combined, dried over MgSO₄, filtered, and concentrated in vacuo. Purification by column chromatography (SiO₂, 6:1, hexane: EtOAc) provided 272 (1.79 g, 92%) as a yellow oil. Rf = 0.31 (6:1, hexane: EtOAc); IR νmax (film)/cm⁻¹ 3322, 2977, 2932, 1705, 1391, 1366, 1239, 1154, 760; δH (500 MHz, CDCl₃) 6.26 (0.75H, br s, NH, major rotamer), 4.19–4.10 (2H, m, CO₂CH₂CH₃), 3.40–2.08 (2H, m, CH₂), 1.95–1.82 (1H, m CHH), 1.80–1.65 (3H, m, CH₂, CHH), 1.65–1.55 (3H, m, CH₂, CHH), 1.49 (9H, s, C(CH₃)₃), 1.43 (10H, s, C(CH₃)₃, CHH), 1.27–1.22 (3H, m, CO₂CH₂CH₃); δC (125 MHz, CDCl₃) 174.5 (COO), 155.8 (COO),
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155.4 (COO), 81.9 \((C(H_3)_3)\), 80.9 \((C(H_3)_3)\), 67.0 \((CCO_2H_2CH_3)\), 60.9 
\((CH_2CH_3)\), 33.7 (CH_2), 32.0 (CH_2), 28.2 \((C(H_3)_3)\), 28.1 \((C(H_3)_3)\), 25.4 (CH_2), 21.8 
\((CH_2)\), 14.3 (CH_2CH_3); MS (ESI\(^+\)) \(m/z\) 409 \([M+Na]^+\); HRMS calcd. for C_{19}H_{34}N_{2}O_{6} \([M+Na]^+\) 409.2309, found 409.2310.

**Di-tert-butyl 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\(_4\)Cl solution (30 mL) and extracted with EtOAc (3 x 30 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated \textit{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 \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3317, 3196, 2977, 2939, 1709, 1392, 1366, 1255, 1165, 763; \(\delta_H\) (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, \(CH\)OH), 3.40–3.33 (1H, m, \(CH\)OH), 2.31–2.21 (1H, m, \(CHHC\)HOH), 1.95–1.88 (1H, m, \(CHHC\)CH\(_2\)OH), 1.49–1.47 (9H, m, \(C(H_3)_3\)), 1.46–1.43 (9H, m, \(C(H_3)_3\)), 1.44–1.22 (8H, m, 4 x CH\(_2\)); \(\delta_C\) (125 MHz, CDCl\(_3\)) 158.1 (2 x COO), 82.1 \((C(H_3)_3)\), 81.4 \((C(H_3)_3)\), 66.4 \((CCH_2OH)\), 65.9 \((CCH_2OH)\), 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 \([M+Na]^+\); HRMS calcd. for C\(_{17}\)H\(_{32}\)N\(_2\)O\(_5\) \([M+Na]^+\) 367.2203, found 367.2205.

**Di-tert-butyl 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 MgSO₄, filtered, and concentrated in vacuo. Purification by column chromatography (SiO₂, 2:1, petrol: EtOAc) provided 278 (168 mg, 93%) as a colourless oil. Rf = 0.45 (2:1, petrol: EtOAc); IR υₘₚₙ (film)/cm⁻¹ 3331, 2977, 2934, 1704, 1355, 1244, 1152, 733; δₜ (500 MHz, CDCl₃) 6.33 (0.80H, br s, NH, major rotamer), 6.10 (0.20H, br s, NH, minor rotamer), 4.84–4.62 (1H, m, CH₂CH₂SCH₃), 4.38–4.19 (1H, m, CH₂CH₂SCH₃), 3.04 (3H, s, SO₂CH₃), 2.61–2.26 (2H, m, CH₂CCH₂O), 2.15–2.00 (2H, m, CH₂CCH₂O), 1.92–1.79 (1H, m, CH₂CHHCH₂), 1.76–1.68 (1H, m, CH₂CHHCH₂), 1.54–1.41 (18H, m, C(CH₃)₃); δC (125 MHz, CDCl₃) 81.1 (2 x C(CH₃)₃), 71.7 (C₂H₅OSCH₃), 62.3 (C₂H₅O), 37.4 (SO₂CH₃), 29.9 (CH₂CCH₂O), 28.2 (2 x C(CH₃)₃), 26.9 (CH₂CCH₂O), 13.9 (CH₂CH₂CH₂), COO not observed; MS (ESI⁺) m/z 417 [MNa⁺]; HRMS calcd. for C₁₆H₃₀N₂Na₂O₇S [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 CH₂Cl₂ (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 υₘₚₙ (film)/cm⁻¹ 3250, 2962, 1671, 1428, 1372, 1260, 1138, 723; δₜ (500 MHz, CDCl₃) 7.08 (3H, br s, NH, NH₂), 4.30 (2H, q, J = 7.1 Hz, CO₂CH₂CH₃), 2.57–2.49 (2H, m, CH₂CNH), 2.44–2.35 (2H, m, CH₂CNH), 2.20–2.10 (2H, m, CH₂CH₂CH₂), 1.34 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃); δC (125 MHz, CDCl₃) 172.7 (COO), 64.1 (COO₂CH₂), 62.7 (CO₂CH₂CH₃), 28.0 (2 x CH₂CNH), 14.6 (CH₂CH₂CH₂), 13.9 (CO₂CH₂CH₃); MS (ESI⁺) m/z 159 [MH⁺]; HRMS calcd. for C₁₆H₁₅N₂O₂ [M+H⁺] 159.1128, found 159.1128.
1-(1,2-Bis(tert-butoxycarbonyl)hydrazinyl)cyclobutane-1-carboxylic acid (288)

This compound was prepared according to a modified literature procedure. 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 H₂O (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 MgSO₄, filtered, and concentrated in vacuo. Purification by column chromatography (SiO₂, 95:5, CH₂Cl₂:MeOH) provided 288 (240 mg, 65%) as a white solid. M. p. 151–153 °C; R_f = 0.26 (95:5, CH₂Cl₂:MeOH); IR νₘₐₓ (neat)/cm⁻¹ 3308, 3005, 2980, 2949, 1741, 1394, 1367, 1246, 1152, 714; δ_H (500 MHz, CDCl₃) 6.84 (0.75H, br s, NH, major rotamer), 6.69 (0.25H, br s, NH, minor rotamer), 3.00–2.76 (1H, m, CH₂H₃COC₂H), 2.63–2.47 (1H, m, CHHCCO₂H), 2.29–2.15 (1H, m, CHHCCO₂H), 2.13–1.98 (2H, m, CH₂CHHCH₂, CHHCCO₂H), 1.91–1.74 (1H, m, CH₂CHHCH₂), 1.50 (9H, s, C(CH₃)₃), 1.44 (9H, s, C(CH₃)₃), COOH not observed; δ_C (125 MHz, CDCl₃) 174.2 (COO), 159.5 (COO), 153.4 (COO), 84.3 (C(CH₃)₃), 84.0 (C(CH₃)₃), 66.3 (CO₂H), 32.5 (CH₂CCO₂H), 28.8 (CH₂CCO₂H), 28.04 (C(CH₃)₃), 28.01 (C(CH₃)₃), 14.0 (CH₂CH₂CH₂); MS (ESI⁺) m/z 353 [MNa⁺]; HRMS calcd. for C₁₅H₂₆N₂NaO₆ [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. 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 H₂O (10 mL) and extracted with CH₂Cl₂ (2 x 15 mL). The organic extracts were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated in vacuo. Purification by column chromatography (SiO₂, 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 \nu_{max} (neat)/cm^{-1} 3294, 2978, 2932, 1720, 1365, 1242, 1158, 727; \delta_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, CH_2CCO_2CH_3, CHHCCO_2CH_3), 1.99–1.84 (1H, m, CH_2CHHCH_2), 1.49 (9H, s, C(CH_3)_3), 1.42 (9H, s, C(CH_3)_3); \delta_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 (CO_2CH_3), 52.4 (CO_2CH_3), 32.8 (CH_2CCO_2), 28.6 (CH_2CCO_2), 28.2 (C(CH_3)_3), 28.1 (C(CH_3)_3), 14.4 (CH_2CH_2CH_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 \nu_{max} (film)/cm^{-1} 3296, 2910, 2856, 1626, 1443, 1397, 1228, 1143, 742; \delta_H (500 MHz, CDCl_3) 6.38 (1H, br s, NH), 4.45 (2H, s, CH_2O), 2.55–2.44 (2H, m, CH_2CCH_2O), 2.03 (2H, br t, J = 8.8 Hz, CH_2CCH_2O), 1.77–1.61 (2H, m, CH_2CH_2CH_2), 1.50 (9H, s, C(CH_3)_3); \delta_C (125 MHz, CDCl_3) 155.0 (COO), 82.4 (C(CH_3)_3), 74.4 (CCH_2O), 62.3 (CCH_2O), 31.9 (2 x CH_2CCH_2O), 28.1 (C(CH_3)_3), 13.1 (CH_2CH_2CH_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 Cs₂CO₃ (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 (SiO₂, 2:1, petrol:EtOAc) provided 280 (38 mg, 86%) as a colourless oil. Rᵣ = 0.69 (2:1, petrol:EtOAc); IR νmax (film)/cm⁻¹ 2977, 2935, 1737, 1699, 1391, 1366, 1254, 1156, 715; δH (500 MHz, CDCl₃) 4.07 (2H, s, CΗ₂O), 2.77 (2H, ddd, J = 9.9, 9.9, 2.8 Hz, CΗ₂CCH₂O), 2.16–2.09 (2H, m, CΗ₂CCH₂O), 1.85–1.74 (1H, m, CH₂CHHCH₂), 1.64–1.54 (1H, m, CH₂CHHCH₂), 1.51 (9H, s, C(CH₃)₃), 1.46 (9H, s, C(CH₃)₃); δC (125 MHz, CDCl₃) 159.8 (COO), 157.4 (C=N), 81.8 (C(CH₃)₃), 81.7 (C(CH₃)₃), 67.6 (CCH₂O), 61.9 (CCH₂O), 33.5 (2 x CH₂CCH₂O), 28.3 (C(CH₃)₃), 28.1 (C(CH₃)₃), 12.9 (CH₂CH₂CH₂); MS (ESI⁺) m/z 321 [MNa⁺]; HRMS calcd. for C₁₅H₂₆N₂NaO₄ [M+Na]⁺ 321.1785, found 321.1783.

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

This known compound was prepared according to a modified literature procedure. To a solution of crotonaldehyde (4.14 mL, 50.0 mmol) in anhydrous CH₂Cl₂ (70 mL) at 0 °C was added bromine (2.56 mL, 50.0 mmol) in CH₂Cl₂ (1 mL) dropwise over 10 min. The reaction mixture was stirred at 0 °C for 1 h before the dropwise addition of Et₃N (8.36 mL, 60.0 mmol), stirred at rt over 90 min, then quenched with saturated aqueous Na₂S₂O₃ solution (30 mL). The organic layer was separated and washed with 1M HCl (20 mL), brine (20 mL), dried over MgSO₄, 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 νmax (film)/cm⁻¹ 2831, 1698, 1652, 641; δH (500 MHz, CDCl₃) 9.22 (1H, s, COH), 7.25 (1H, q, J = 6.8 Hz, CH₃CH=CBr), 2.16 (3H, d, J = 6.8 Hz, CH₃CH=CBr); δC (125 MHz, CDCl₃) 186.0 (COH), 150.8 (CH₃CH=CBr), 130.2 (C-Br), 18.0 (CH₂CH=CBr); MS (ESI⁺) m/z 171 [M⁺(Br)Na⁺], 173 [M⁺(Br)Na⁺]; HRMS calcd. for C₄H₃⁺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. To a solution of 301 (2.23 g, 15.0 mmol) in THF (10 mL) and H2O (5 mL) at 0 °C was added NaBH4 (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 MgSO4, filtered, and concentrated in vacuo to give 302 (1.95 g, 86%) as a pale yellow oil, which was used without further purification. Rf = 0.41 (4:1 petrol: EtOAc); IR νmax (film/cm−1) 3362, 2918, 2857, 1662, 1083, 809, 671; δH (500 MHz, CDCl3) 6.08 (1H, q, J = 6.5 Hz, CH3C=CH=Br), 4.25 (2H, d, J = 5.2 Hz, CH2OH), 1.92 (1H, t, J = 6.3 Hz, CH2OH), 1.78 (3H, d, J = 6.5 Hz, CH3(=CH=Br); δC (125 MHz, CDCl3) 127.8 (CBr), 125.4 (CH3C=CH=Br), 68.5 (CH2OH), 16.4 (CH2CH=CH=Br); MS (ESI+) m/z 173 [M(79Br)Na]+, 175 [M(81Br)Na]+; HRMS calcd. for C7H779BrONa [M+Na]+ 172.9572, found 172.9571. Analytical data in agreement with literature values.

(Z)-2-Bromo-3-phenylacrylaldehyde (303)

This known compound was prepared according to a literature procedure. To a solution of trans-cinnamaldehyde (1.00 g, 7.95 mmol) in anhydrous CH2Cl2 (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 CH2Cl2 (15 mL) and washed with saturated aqueous NaHSO3 solution (10%, 15 mL), H2O (15 mL) and brine (15 mL). The organic extract was dried over Na2SO4, filtered, and concentrated in vacuo to give 303 (1.65 g, 98%) as a yellow oil, which was used without further purification. Rf = 0.39 (8:1, petrol: EtOAc); IR νmax (film/cm−1) 2850, 1693, 1602, 1115, 758, 690; δH (500 MHz, CDCl3) 9.36 (1H, s, COH), 8.04–7.97 (2H, m, Ar H), 7.91 (1H, s, CH=CH=Br), 7.54–7.47 (3H, m, Ar H); δC (125 MHz, CDCl3) 187.1 (COH), 149.1 (CH=CH=Br), 132.9 (C, Ar), 131.6 (CH, Ar), 131.0 (CH, Ar), 128.8 (CH, Ar), 124.3 (CH=CH=Br);
MS (ESI+) \( m/z \) 233 [M(\text{Br})\text{Na}]^+, 235 [M(\text{Br})\text{Na}]^+; HRMS calcd. for C_9H_{17}^{79}\text{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\(_2\)O (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 \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3337, 3025, 2920, 2870, 1492, 860, 752, 694; \( \delta H \) (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=CB\(_r\)), 4.43 (2H, d, \( J = 6.2 \) Hz, CH\(_2\)OH), 2.09 (1H, t, \( J = 6.6 \) Hz, CH\(_2\)OH); \( \delta C \) (125 MHz, CDCl\(_3\)) 135.0 (C, Ar), 129.0 (CH, Ar), 128.2 (2 x CH, Ar), 127.9 (CH=CB\(_r\)), 125.3 (CH=CB\(_r\)), 69.5 (CH\(_2\)OH); MS (ESI+) \( m/z \) 212 [M(\text{Br})\text{Na}]^+, 214 [M(\text{Br})\text{Na}]^+; HRMS calcd. for C_9H_{17}^{79}\text{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\(_2\)O (20 mL), and extracted with diethyl ether (3 x 35 mL). The organic layers were combined, washed with 10% aqueous Na\(_2\)S\(_2\)O\(_3\) 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 $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3296, 2910, 2856, 1626, 1443, 1026, 896, 552; $\delta_H$ (500 MHz, CDCl$_3$) 6.40–6.38 (1H, m, $CHH=CI$), 5.88–5.85 (1H, m, $CHH=CI$), 4.18 (2H, s, CH$_2$OH), 1.97 (1H, br s, CH$_2$OH); $\delta_C$ (125 MHz, CDCl$_3$) 124.5 ($CHH=CI$), 110.5 ($CH_2=CI$), 71.1 (CH$_2$OH); GCMS (EI)$^+$ m/z 184 (M$^+$). 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 temperature 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 $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3349, 2981, 2935, 1709, 1627, 1385, 1366, 1255, 913, 752, 554; $\delta_H$ (500 MHz, CDCl$_3$) 6.41 (1H, br m, NH, major rotamer), 6.26 (1H, br m, $CHH=CI$), 6.10 (1H, br s, NH, minor rotamer), 5.88 (1H, s, $CH_2=CI$), 4.26 (2H, br s, NCH$_2$Cl), 1.50–1.45 (18H, m, (C(CH$_3$)$_3$)); $\delta_C$ (125 MHz, CDCl$_3$) 154.9 (COO), 154.6 (COO), 128.0 ($CH_2=CI$, rotamer), 127.6 ($CH_2=CI$, rotamer), 106.2 ($CH_2=CI$), 81.8 (C(CH$_3$)$_3$), 81.4 (C(CH$_3$)$_3$), 61.5 (NCH$_2$Cl, rotamer), 60.4 (NCH$_2$Cl, rotamer), 28.2 (2 x C(CH$_3$)$_3$); MS (ESI$^+$) m/z 421 [MNa$^+$]; HRMS calcd. for C$_{13}$H$_{23}$IN$_2$NaO$_4$ [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 $\nu_{\text{max}}$ (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, CHH=CBr), 5.59 (1H, s, CHH=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=CBr, rotamer), 128.78 (CH_2=CBr, rotamer), 119.5 (CH_2=CBr, rotamer), 119.1 (CH_2=CBr, rotamer), 81.9 (C(CH_3)_3), 81.6 (C(CH_3)_3), 58.3 (NCH_2CBr, rotamer), 57.1 (NCH_2CBr, rotamer), 28.19 (C(CH_3)_3), 28.15 (C(CH_3)_3); MS (ES^+) m/z 373 [M(79Br)Na^+], 375 [M(81Br)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.\textsuperscript{136} To a solution of 2-bromo-3-methylbut-2-en-1-ol\textsuperscript{199} (540 mg, 3.27 mmol) and triphenylphosphate (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 ν_{max} (film/cm\textsuperscript{-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(CH_3)(CH_3)), 1.83 (3H, s, C(CH_3)(CH_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_2CBr, rotamer), 116.1 (NCH_2CBr, rotamer), 81.3 (C(CH_3)_3, rotamer), 81.1 (C(CH_3)_3, rotamer), 53.7 (NCH_2CBr, rotamer), 53.0 (NCH_2CBr, rotamer), 28.2 (2 x C(CH_3)_3), 25.6 (C(CH_3)(CH_3)), 20.5 (C(CH_3)(CH_3)); MS (ES^+) m/z 401 [M(79Br)Na^+], 403 [M(81Br)Na^+]; HRMS calcd. for C_{15}H_{25}^{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. 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 (SiO₂, 6:1, petrol: EtOAc) provided 243 (1.40 g, 95%) as a yellow oil. R_f = 0.13 (6:1 petrol: EtOAc); IR ν_max (film/cm⁻¹) 3291, 2981, 2934, 1707, 1632, 1381, 1264, 1135, 763; δ_H (400 MHz, CDCl₃) 6.62 (1H, br m, NH, major rotamer), 6.37 (1H, br s, NH, minor rotamer), 5.82 (1H, s, CH=CHBr), 5.62 (1H, s, CH=CHBr), 4.45–4.30 (2H, m, NC₂H₂CBr), 4.26–4.16 (4H, m, 2 x CH₂CH₃), 1.28 (6H, t, J = 7.1 Hz, CH₂CH₃); δ_C (125 MHz, CDCl₃) 155.8 (COO), 150.6 (COO), 128.0 (CH₂=CHBr, rotamer), 120.4 (CH₂=CHBr, rotamer), 119.8 (CH=CH₂Br, rotamer), 64.3 (CH₂CH₃, rotamer), 63.1 (CH₂CH₃, rotamer), 62.9 (CH₂CH₃, rotamer), 62.2 (CH₂CH₃, rotamer), 58.0 (NCH₂CBr, rotamer), 57.2 (NCH₂CBr, rotamer), 14.5 (CH₂CH₃), 14.1 (CH₂CH₃); MS (ESI⁺) m/z 317 [M⁺]+, 319 [M⁺]+; HRMS calcd. for C₉H₁₅⁷⁹BrN₂O₄ [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 (SiO₂, 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 ν_max (neat)/cm⁻¹ 3318, 2931, 1712, 1393, 1368, 1255, 1158, 758; δ_H (500 MHz, CDCl₃) 6.34 (1H, br s, NH), 6.01–5.87 (1H, m, CHCH₃), 4.31 (2H, br s, NCH₂CBr), 1.77 (3H, d, J = 6.5 Hz, CHCH₃), 1.46 (18H, s, C(CH₃)₃); δ_C (125 MHz, CDCl₃) 154.9 (COO), 154.7 (COO), 126.9 (CHCH₃, rotamer), 127.6 (CHCH₃, rotamer), 123.6 (NCH₂CBr), 81.5 (C(CH₃)₃), 81.3 (C(CH₃)₃), 58.5 (NCH₂CBr,
rotamer), 57.4 (NCH₂CBr, rotamer), 28.2 (2 x C(CH₃)₃), 16.7 (CHCH₃); MS (ESI⁺) m/z 387 [M(⁷⁹Br)Na⁺], 389 [M(⁸¹Br)Na⁺]; HRMS calcd. for C₁₄H₂₅⁷⁹Br₂NaO₄ [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 (SiO₂, 6:1, petrol: EtOAc) provided 304 (1.79 g, 94%) as a yellow oil. R_f = 0.37 (6:1 petrol: EtOAc); IR ν_max (film)/cm⁻¹ 3322, 2978, 2932, 1707, 1478, 1392, 1366, 1250, 1151, 753, 694; δ_H (400 MHz, CDCl₃) 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, NC₃H₂CBr), 1.48 (18H, s, C(CH₃)₃); δ_C (125 MHz, CDCl₃) 155.7 (COO), 154.8 (COO), 135.1 (C, Ar, rotamer), 135.0 (C, Ar, rotamer), 130.8 (CH=CBr, rotamer), 130.4 (CH=CBr, rotamer), 129.0 (CH, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 121.4 (NCH₂CBr), 81.7 (C(CH₃)₃), 81.5 (C(CH₃)₃), 60.1 (NCH₂CBr, rotamer), 58.8 (NCH₂CBr, rotamer), 28.21 (C(CH₃)₃), 28.16 (C(CH₃)₃); MS (ESI⁺) m/z 449 [M(⁷⁹Br)Na⁺], 451 [M(⁸¹Br)Na⁺]; HRMS calcd. for C₁₉H₂₇⁷⁹Br₂NaO₄ [M+Na]⁺ 449.1046, found 449.1045.

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

This compound was prepared according to a modified literature procedure. 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 $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3317, 2978, 2876, 1732, 1492, 1250, 1152, 708; $\delta_{\text{H}}$ (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$_3$)$_3$); $\delta_{\text{C}}$ (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(CH$_3$)$_3$); MS (ESI$^+$) $m/z$ 285 [M$^+$Na$^+$]; HRMS calcd. for C$_{13}$H$_{14}$N$_2$NaO$_4$ [M+Na]$^+$ 285.0846, found 285.0849. Analytical data in agreement with literature values.

**tert-Butyl (2-bromoallyl)(1,3-dioxoisooindolin-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$_2$O (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$_2$SO$_4$, 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 $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2973, 2928, 1798, 1721, 1629, 1594, 1355, 1254, 1149, 918, 712; $\delta_{\text{H}}$ (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, $CHH$=CBr), 5.62 (1H, d, $J$ = 4.3 Hz, $CHH$=CBr), 4.52 (1H, s, NCH$_2$), 4.47 (1H, s, NCH$_2$), 1.52 (4H, s, C(CH$_3$)$_3$, minor rotamer), 1.34 (5H, s, C(CH$_3$)$_3$, major rotamer); $\delta_{\text{C}}$ (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 (CH$_2$=CBr, rotamer), 119.3 (CH$_2$=CBr, rotamer), 83.9 (C(CH$_3$)$_3$, rotamer), 83.1 (C(CH$_3$)$_3$, rotamer), 58.3 (NCH$_2$, rotamer), 56.8 (NCH$_2$, rotamer), 28.1 (C(CH$_3$)$_3$, rotamer), 27.8 (C(CH$_3$)$_3$, rotamer); MS (ESI$^+$) $m/z$ 403 [M($^{79}\text{Br}$)Na$^+$], 405 [M($^{81}\text{Br}$)Na$^+$]; HRMS calcd. for C$_{16}$H$_{17}^{17}\text{Br}$N$_2$NaO$_4$ [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. Rf = 0.29 (4:1, petrol: EtOAc); IR $\nu_{\text{max}}$ (film/cm$^{-1}$) 3336, 3218, 2977, 2931, 1694, 1630, 1390, 1244, 1153, 893, 731; $\delta$H (500 MHz, CDCl$_3$) 5.72 (1H, s, CH$_2$=CBr), 5.58 (1H, s, CH$_2$H=CBr), 4.22 (2H, s, NC$_2$H$_4$), 4.06 (2H, br s, NH$_2$), 1.48 (9H, s, C(C$_3$H$_3$)$_3$); $\delta$C (125 MHz, CDCl$_3$) 156.7 (COO), 129.8 (C$\text{H}_2$=CBr), 117.8 (C$\text{H}_2$=CBr), 81.3 (C(CH$_3$)$_3$), 58.5 (NC$_2$H$_4$), 28.2 (C(CH$_3$)$_3$); MS (ES$I^+$) m/z 273 [M(+79Br)Na$^+]$, 275 [M(+81Br)Na$^+]$; HRMS calcd. for C$_8$H$_{15}$79BrN$_2$NaO$_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$_2$O (40 mL) and CH$_2$Cl$_2$ (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$_2$O (40 mL) and the organic layer extracted with CH$_2$Cl$_2$ (3 x 50 mL), washed with 20% citric acid solution (60 mL), dried over Na$_2$SO$_4$, 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. Rf = 0.47 (4:1, petrol: EtOAc); IR $\nu_{\text{max}}$ (film/cm$^{-1}$) 3297, 2934, 1715, 1632, 1499, 1393, 1368, 1260, 1154, 742; $\delta$H (500 MHz, CDCl$_3$) 7.39–7.31 (5H, m, Ar H), 6.67 (1H, br d, NH), 5.79 (1H, br m, CH$_2$H=CBr), 5.58 (1H, s, CH$_2$H=CBr), 5.17 (2H, s, CH$_2$Ar), 4.45–4.16 (2H, m, NCH$_2$CBr), 1.49 (5H, br s, C(CH$_3$)$_3$, major rotamer), 1.39 (4H, br s, C(CH$_3$)$_3$, minor rotamer); $\delta$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$_2$=CBr), 120.0 (CH$_2$=CBr, rotamer), 119.5 (CH$_2$=CBr, rotamer), 82.7 (C(CH$_3$)$_3$, rotamer),...
82.1 (C(CH₃)₃, rotamer), 67.8 (CH₂Ar), 58.3 (NCH₂, rotamer), 56.9 (NCH₂, rotamer), 28.2 (C(CH₃)₃, rotamer), 28.0 (C(CH₃)₃, rotamer); MS (ESI⁺) m/z 407 [M⁺(⁷⁹Br)Na⁺], 409 [M⁺(⁸¹Br)Na⁺]; HRMS calcd. for C₁₆H₂₁⁷⁹BrN₂NaO₄ [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 CH₂Cl₂ (5 mL) and washed with 2 M HCl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (15 mL), the organic layers combined, dried over MgSO₄, filtered, and concentrated in vacuo. Purification by column chromatography (SiO₂, 4:1, petrol: EtOAc) provided 314 (50 mg, 62%) as a white solid. M. p. 120–122 °C; Rf = 0.41 (4:1, petrol: EtOAc); IR νmax (neat)/cm⁻¹ 3232, 2980, 2930, 1718, 1493, 1368, 1250, 1158, 737; δH (500 MHz, CDCl₃) 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, CHH=CBr), 5.62 (1H, s, CHH=CBr), 4.70–4.22 (1.8H, m, NCH₂, major rotamer), 3.98–3.72 (0.2H, m, NCH₂, minor rotamer), 2.41 (3H, s, ArCH₃), 1.21 (9H, m, C(CH₃)₃); δc (125 MHz, CDCl₃) 144.6 (C, Ar) 133.6 (C, Ar), 129.5 (CH, Ar), 128.7 (CH, Ar), 127.6 (CH₂=CBr), 120.2 (CH₂=CBr), 83.1 (C(CH₃)₃), 58.1 (NCH₂), 27.6 (C(CH₃)₃), 21.6 (ArCH₃), COO not observed; MS (ESΙ⁺) m/z 427 [M⁺(⁷⁹Br)Na⁺], 429 [M⁺(⁸¹Br)Na⁺]; HRMS calcd. for C₁₅H₂₁⁷⁹BrN₂NaO₄S [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), Cs₂CO₃ (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 MgSO₄, 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), Cs₂CO₃ (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 (SiO₂, 9:1, petrol: EtOAc) provided 299 (1.07 g, 77%) as a pale yellow oil. R_f = 0.34 (9:1, petrol: EtOAc); IR ν_max (film)/cm⁻¹ 2978, 2934, 1716, 1393, 1368, 1256, 1152, 841, 766; δ_H (500 MHz, CDCl₃) 4.91–4.86 (1H, m, C=C-H), 4.59 (1H, d, J = 2.3 Hz, NCHH), 4.58 (1H, d, J = 2.2 Hz, NCHH), 4.36–4.34 (1H, m, C=CHH), 1.54 (9H, s, C(CH₃)₃), 1.49 (9H, s, C(CH₃)₃); δ_C (125 MHz, CDCl₃) 159.5 (COO), 154.1 (COO), 142.7 (C=CH₂), 89.6 (C=CH₂), 83.0 (C(CH₃)₃), 82.7 (C(CH₃)₃), 57.2 (NCH₂), 28.1 (C(CH₃)₃), 28.0 (C(CH₃)₃); MS (ESI⁺) m/z 293 [MNa⁺]; HRMS calcd. for C_{13}H_{22}N₂NaO₄ [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), Cs₂CO₃ (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 (SiO₂, 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), Cs₂CO₃ (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 (SiO₂, 6:1, petrol: EtOAc) provided 315 (53 mg, 62%) as a colourless oil. Rᵢ = 0.32 (6:1, petrol: EtOAc); IR νmax (film)/cm⁻¹ 2933, 1736, 1718, 1498, 1389, 1369, 1259, 1150, 753; δH (500 MHz, CDCl₃) 7.41–7.32 (5H, m, Ar H), 5.26 (2H, s, CH₂Ar), 4.99–4.94 (1H, m, C=CHH), 4.62 (1H, d, J = 2.2 Hz, NCHH), 4.61 (1H, d, J = 2.2 Hz, NCHH), 4.43–4.40 (1H, m, C=CHH), 1.45 (9H, s, C(CH₃)₃); δC (125 MHz, CDCl₃) 159.4 (CO₂C(CH(3))₂), 155.2 (CO₂CH₂Ar), 142.3 (C=CH₂), 135.3 (C, Ar), 128.6 (CH, Ar), 128.4 (CH, Ar), 128.1 (CH, Ar), 90.6 (C=CH₂), 83.0 (C(CH₃)₃), 68.3 (CH₂Ar), 57.5 (NCH₂), 27.9 (C(CH₃)₃); MS (ESI⁺) m/z 327 [MNa⁺]; HRMS calcd. for C₁₆H₂₀N₂NaO₄ [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), Cs₂CO₃ (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 (SiO₂, 9:1 petrol: EtOAc) provided 316 (602 mg, 68%) as a white solid. M. p. 81–85 °C; Rᵢ = 0.38 (9:1, petrol: EtOAc); IR νmax (neat)/cm⁻¹ 2978, 2933, 1708, 1392, 1368, 1255, 1144, 767; δH (500 MHz, CDCl₃) 4.61 (2H, s, NCH₂), 1.81 (3H, s, C(CH₃)(CH₃)), 1.52 (9H, s, C(CH₃)₃), 1.50 (12H, s, C(CH₃)₃, C(CH₃)(CH₃)); δC (125 MHz, CDCl₃) 159.4 (COO), 156.5 (COO), 129.6 (CCH₂ or C(CH₃)₂), 112.5 (CCH₂ or C(CH₃)₂), 82.5 (C(CH₃)₃), 82.1 (C(CH₃)₃), 57.8 (CH₂), 28.13 (C(CH₃)₃), 28.09 (C(CH₃)₃), 18.9 (C(CH₃)(CH₃)), 18.6 (C(CH₃)(CH₃)); MS (ESI⁺) m/z 321 [MNa⁺]; HRMS calcd. for C₁₅H₂₄N₂NaO₄ [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), Cs₂CO₃ (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 (SiO₂, 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 ν_max (neat)/cm⁻¹ 2981, 2937, 1740, 1392, 1368, 1254, 1148, 763; δ_H (500 MHz, CDCl₃) 4.70 (1H, q, J = 7.2 Hz, CH₃), 4.58 (2H, s, NCH₂), 1.80 (3H, d, J = 7.2 Hz, CHCH₃), 1.53 (9H, s, C(CH₃)₃), 1.50 (9H, s, C(CH₃)₃); δ_C (125 MHz, CDCl₃) 159.5 (COO), 155.6 (COO), 135.6 (C=CH₂), 103.5 (CHCH₃), 82.8 (C(CH₃)₃), 82.3 (C(CH₃)₃), 58.0 (CH₂), 28.14 (C(CH₃)₃), 28.07 (C(CH₃)₃), 12.8 (CHCH₃); MS (ESI⁺) m/z 307 [MNa⁺]; HRMS calcd. for C₁₄H₂₄N₂O₄ [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), Cs₂CO₃ (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 (SiO₂, 4:1, petrol: EtOAc) provided 244 (369 mg, 36%) as a pale yellow oil. R_f = 0.38 (4:1, petrol: EtOAc); IR ν_max (film)/cm⁻¹ 2982, 2937, 1721, 1467, 1372, 1228, 1099, 748; δ_H (400 MHz, CDCl₃) 4.95 (1H, q, J = 2.8 Hz, C=CHH), 4.69 (1H, d, J = 2.2 Hz, NCHH), 4.68 (1H, d, J = 2.4 Hz, NCHH), 4.43–4.39 (1H, m, C=CHH), 4.29 (2H, q, J = 7.2 Hz, CH₂CH₃), 4.24 (2H, q, J = 7.3 Hz, CH₂CH₃), 1.32 (3H, t, J = 7.0 Hz, CH₂CH₃), 1.29 (3H, t, J = 7.0 Hz, CH₂CH₃); δ_C (125 MHz, CDCl₃) 160.6 (COO), 155.4 (COO), 142.3 (C=CH₂), 90.6 (C=CH₂), 63.2 (CH₂CH₃), 63.0 (CH₂CH₃), 57.7 (NCH₂), 14.40 (CH₂CH₃), 14.36 (CH₂CH₃); MS (ESI⁺) m/z 237 [MNa⁺]; HRMS calcd. for C₉H₁₄N₂NaO₄ [M+Na⁺] 237.0846, found 237.0848.

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(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$_2$CO$_3$ (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 $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2979, 2934, 1713, 1495, 1369, 1254, 1144, 844, 767; $\delta_{\text{H}}$ (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, C(HAr)), 4.82 (2H, m, NC$_2$H$_2$), 1.54 (9H, s, C(C$_3$H$_3$)$_3$), 1.19 (9H, s, C(C$_3$H$_3$)$_3$); $\delta_{\text{C}}$ (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=CHAr), 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 (ES$^+$) $m/z$ 369 [MNa$^+$]; HRMS calcd. for C$_{19}$H$_{26}$N$_2$NaO$_4$ [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$_2$O (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$_2$O (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 $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2979, 2934, 1717, 1601, 1392, 1369, 1256, 1151, 847, 752; $\delta_{\text{H}}$ (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(CH₃)₃, 1.53 (9H, s, C(CH₃)₃); δC (125 MHz, CDCl₃) 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=CHAr), 83.3 (C(CH₃)₃), 82.9 (C(CH₃)₃), 58.1 (NCH₂), 28.2 (C(CH₃)₃), 28.1 (C(CH₃)₃); MS (ESI⁺) m/z 369 [MNa⁺]; HRMS calcd. for C₁₉H₂₆N₂NaO₄ [M+Na⁺] 369.1785, found 369.1788.

**Benzyl buta-2,3-dienoate (226)**

![Benzyl buta-2,3-dienoate](image)

This compound was prepared according to a literature procedure. To a solution of benzyl (triphenylphosphoranylidene)acetate (8.21 g, 20.0 mmol) in anhydrous CH₂Cl₂ (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 CH₂Cl₂ (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 (SiO₂, 15:1, petrol: EtOAc) provided 226 (2.05 g, 71%) as a yellow oil. Rf = 0.33 (15:1, petrol: EtOAc); IR νmax (film)/cm⁻¹ 3034, 2991, 2951, 1969, 1940, 1710, 1498, 1244, 1150, 735; δH (500 MHz, CDCl₃) 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, CH₂=CH₂), 5.20 (2H, s, NCH₂Ar); δC (125 MHz, CDCl₃) 216.0 (CH₂=CH₂), 165.6 (COO), 135.9 (C, Ar), 128.6 (CH, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 87.9 (C=CHCOO), 79.5 (CH₂=CH₂), 66.7 (CH₂Ar). Analytical data in agreement with literature values.

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

![Di-tert-butyl-3-(2-(benzyloxy)-2-oxoethylidene)-1,2-diazetidine-1,2-dicarboxylate](image)

This compound was prepared according to a literature procedure. 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 $\nu_{\text{max}}$/cm$^{-1}$ 2979, 2934, 1720, 1668, 1498, 1369, 839, 742; $\delta_H$ (500 MHz, CDCl$_3$) 7.39–7.31 (5H, m, Ar H), 5.72 (1H, br s, C=CH), 5.15 (2H, s, CH$_2$Ar), 4.88 (2H, d, $J = 2.2$ Hz, NCH$_2$), 1.55 (9H, s, C(CH$_3$)$_3$), 1.50 (9H, s, C(CH$_3$)$_3$); $\delta_C$ (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=CH), 84.6 (C(CH$_3$)$_3$), 66.0 (CH$_2$Ar), 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$_2$NaO$_6$ [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$_2$O (15 mL), saturated Na$_2$SO$_3$ solution (15 mL), saturated aqueous sodium bicarbonate solution (15 mL) and H$_2$O (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 $\mu$mol) and TMSCF$_3$ (123 $\mu$L, 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 \nu_{\text{max}} \ (\text{neat})/\text{cm}^{-1} 2974, 2933, 1737, 1368, 1242, 1153, 1027, 769; \delta_H \ (500 \text{ MHz, CDCl}_3) 4.34 \ (1H, d, J = 8.4 \text{ Hz, NCHH}), 4.22 \ (1H, dd, J = 8.4, 4.6 \text{ Hz, NCHH}), 2.65 \ (1H, ddd, J = 15.0, 10.1, 4.9 \text{ Hz, CH/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 \text{ Hz, CH}/HCF_2); \delta_C \ (125 \text{ MHz, CDCl}_3) 159.5 \ (\text{COO}), 156.8 \ (\text{COO}), 106.9 \ (\text{dd, } J_{CF} = 293.4, 289.9 \text{ Hz, CF}_2), 83.2 \ (C(CH_3)_3), 82.8 \ (C(CH_3)_3), 52.5 \ (\text{NCH}_2), 50.0 \ (\text{dd, } J_{CF} = 15.8, 9.8 \text{ Hz, CCH}_2), 28.1 \ (2 \times C(CH_3)_3), 16.7 \ (t, J_{CF} = 10.6 \text{ Hz, CCH}_2); \delta_F \ (376 \text{ MHz, CDCl}_3) – 136.7 \ (d, J_{FF} = 170 \text{ Hz}), –142.8 \ (d, J_{FF} = 169 \text{ Hz}); MS \ (\text{ESI}^+) \ m/z 343 \ [\text{MNa}^+]; \text{HRMS calcd. for C}_{14}H_{22}F_2N_2NaO_4 \ [\text{M+Na}^+] 343.1440, \text{found} 343.1435. \text{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) \text{ Å}, \ b = 5.73781(4) \text{ Å}, \ c = 21.00103(12) \text{ Å}, \ \beta = 102.1203(7)°, \ V = 1652.64(2) \text{ Å}^3, \ Z = 4, \ T = 150(2) K, \ \mu(\text{Cu K}\alpha) = 0.927 \text{ mm}^{-1}, \ D_{calc} = 1.287 \text{ g/cm}^3, 45210 \text{ reflections measured (8.612° ≤ 2\theta ≤ 147.208°)}, 3327 \text{ unique (R}_{int} = 0.0250, \ R_{sigma} = 0.0084) which were used in all calculations. The final R_1 was 0.0378 (I > 2\sigma(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)**

![Diagram of 3-Methylene-1,2-diazetidine](image)

3-Methylene-1,2-diazetidine 316 (90 mg, 0.30 mmol), sodium iodide (9 mg, 60 \mu\text{mol}) and TMSCF_3 (111 \mu\text{L, 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 \nu_{\text{max}} \ (\text{neat})/\text{cm}^{-1} 2980, 2935, 1727, 1394, 1367, 1254, 1153, 744; \delta_H \ (500 \text{ MHz, CDCl}_3) 4.18 \ (1H, dd, J = 8.3, 1.9 \text{ Hz, NCHH}), 3.95 \ (1H, dd, J = 8.3, 5.4 \text{ Hz, NCHH}), 1.50 \ (9H, s, C(CH_3)_3), 1.48 \ (9H, s, C(CH_3)_3), 1.38 \ (3H, s, C(CH_3)(CH_3)), 1.08 \ (3H, s, C(CH_3)(CH_3)); \delta_C \ (125 \text{ MHz, CDCl}_3) 159.3 \ (\text{COO}), 156.5 \ (\text{COO}), 111.2 \ (\text{dd, } J_{CF} = 309.6, 299.8 \text{ Hz, CF}_2), 83.0 \ (C(CH_3)_3), 82.5 \ (C(CH_3)_3), 55.6 \ (\text{dd, } J_{CF} = 13.1, 8.9 \text{ Hz, CCH}_2), 49.4 \ (d, J_{CF} = 5.9 \text{ Hz, CCH}_2), 28.1 \ (C(CH_3)_3), 27.8 \ (C(CH_3)_3), 26.2 \ (t, J_{CF} = 9.9 \text{ Hz,
C(CH$_3$)$_2$, 14.7 (d, $J = 7.6$ Hz, C(CH$_3$)(CH$_3$)), 13.2 (d, $J = 5.8$ Hz, C(CH$_3$)(CH$_3$)); $\delta_F$ (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$_2$N$_2$NaO$_4$ [M+Na]$^+$ 371.1753, found 371.1751.

$(2S, 3S)$-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 (2S, 3S)-326 (80 mg, 80%) as a colourless oil. $R_f = 0.25$ (9:1, petrol: EtOAc); IR $\nu_{max}$ (film)/cm$^{-1}$ 2980, 2936, 1714, 1393, 1368, 1255, 1146, 732; $\delta_H$ (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, N$_C$H$_H$), 1.60 – 1.51 (1H, m, C$_H$CH$_3$), 1.47 (9H, s, C(C$_H$3)$_3$), 1.32 (3H, d, $J = 6.7$ Hz, CHCH$_3$); $\delta_C$ (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, CCH$_2$), 52.6 (d, $J_{CF} = 6.0$ Hz, CCH$_2$), 28.1 (C(CH$_3$)$_3$), 27.7 (C(CH$_3$)$_3$), 24.8 (t, $J_{CF} = 9.9$ Hz, CHCH$_3$), 5.3 (d, $J_{CF} = 4.3$ Hz, CHCH$_3$); $\delta_F$ (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$_2$N$_2$NaO$_4$ [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
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 ν_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, NCHH), 4.35 (1H, dd, J = 8.5, 4.6 Hz, NCHH), 4.32–4.17 (4H, m, CH_2CH_3), 2.72 (1H, ddd, J = 15.2, 10.6, 5.2 Hz, CHHCF_2), 1.48 (1H, ddd, J = 15.5, 10.6, 5.8 Hz, CHHCF_2), 1.33–1.27 (6H, m, CH_2CH_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 (CH_2CH_3), 63.1 (CH_2CH_3), 53.0 (NCH_2), 51.0 (dd, J_CF = 15.9, 10.1 Hz, CH_2CH_2), 16.6 (t, J_CF = 11.0 Hz, CH_2CF_2), 14.33 (CH_2CH_3), 14.28 (CH_2CH_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_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 NH₄Cl solution (20 mL). The mixture was extracted with EtOAc (3 x 30 mL) and the combined extracts were dried over MgSO₄, 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 (SiO₂, 9:1, petrol: EtOAc) provided less polar 331 (64 mg, 48%) as a white solid. M. p. 122–125 °C; Rᵣ = 0.27 (9:1, petrol: EtOAc); IR νₘₐₓ (neat)/cm⁻¹ 3088, 2980, 2934, 1725, 1368, 1252, 1146, 767; δH (500 MHz, CDCl₃) 4.41 (1H, d, J = 8.9 Hz, NC₃H₃), 4.29 (1H, d, J = 8.9 Hz, NC₃H₃), 2.79 (1H, d, J = 9.5 Hz, CHCHCl₂), 1.57–1.51 (10H, m, CHHCCl₂, C(CH₃)₃), 1.49 (9H, s, C(CH₃)₃); δC (125 MHz, CDCl₃) 159.4 (COO), 156.9 (COO), 83.2 (C(CH₃)₃), 82.7 (C(CH₃)₃), 57.4 (CCL₂ or CCH₂), 56.0 (CCL₂ or CCH₂), 54.1 (NCH₂), 28.1 (2 x C(CH₃)₃), 25.6 (CH₂Cl₂); MS (ESI⁺) m/z 375 [M(35Cl)Na⁺], 377 [M(37Cl)Na⁺]; HRMS calcd. for C₁₄H₂₂³⁵Cl₂N₂NaO₄ [M+Na⁺] 375.0849, found 375.0849. A crystal for X-ray analysis was grown from CH₂Cl₂/petrol.

**Crystal Data** for C₁₄H₂₂Cl₂N₂O₄ (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) Å³, Z = 8, T = 150(2) K, μ(CuKα) = 3.384 mm⁻¹, Dcalc = 1.296 g/cm³, 37029 reflections measured (8.286° ≤ 2Θ ≤ 148.008°), 3648
unique ($R_{\text{int}} = 0.0734$, $R_{\text{sigma}} = 0.0237$) which were used in all calculations. The final $R_1$ was 0.0414 ($I > 2\sigma(I)$) 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 $\nu_{\text{max}}$/cm$^{-1}$ 3110, 2981, 2929, 1782, 1729, 1366, 1138, 769; $\delta_H$ (500 MHz, CDCl$_3$) 4.10 (1H, d, $J = 11.4$ Hz, NC$_2$H$_2$), 3.81 (1H, d, $J = 11.3$ Hz, NC$_2$H$_2$), 3.36 (1H, d, $J = 9.7$ Hz, C$_2$H$_{11}$Cl$_2$), 1.67 (1H, d, $J = 9.7$ Hz, CH/HCCl$_2$), 1.55 (9H, s, C(C$_3$H$_8$)$_3$), 1.50 (9H, s, C(CH$_3$)$_3$); $\delta_C$ (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 CCH$_2$), 46.9 (CCL$_2$ or CCH$_2$), 46.0 (NCH$_2$), 28.1 (CH$_2$CCl$_2$), 28.0 (C(CH$_3$)$_3$), 27.9 (C(CH$_3$)$_3$); MS (ESI$^+$) $m/z$ 403 [M($^{35}$Cl)Na$^+$], 405 [M($^{37}$Cl)Na$^+$]; HRMS calcd. for C$_{15}$H$_{22}$Cl$_2$N$_2$O$_5$ [M+Na$^+$] 403.0798, found 403.0800.

A crystal for X-ray analysis was grown from CH$_2$Cl$_2$/petrol.

**Crystal Data** for C$_{15}$H$_{22}$Cl$_2$N$_2$O$_5$ ($M=381.24$ 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, $\beta = 102.1911(5)^\circ$, $V = 1809.971(15)$ Å$^3$, $Z = 4$, $T = 150(2)$ K, $\mu$(Cu K$\alpha$) = 3.472 mm$^{-1}$, $D_{\text{calc}} = 1.399$ g/cm$^3$, 34089 reflections measured (10.544$^\circ$ $\leq 2\Theta \leq 173.528^\circ$), 3613 unique ($R_{\text{int}} = 0.0266$, $R_{\text{sigma}} = 0.0108$) which were used in all calculations. The final $R_1$ was 0.0296 ($I > 2\sigma(I)$) 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 $\nu_{\text{max}}$/cm$^{-1}$ 2978, 2932, 1715, 1368, 1255, 1144, 858, 763; $\delta_H$ (400 MHz, CDCl$_3$) 4.12 (1H, q, $J = 8.4$ Hz, NCH$_2$), 1.59 (3H, s,
C(CH₃)(CH₃)), 1.50 (9H, C(CH₃)₃), 1.48 (9H, s, C(CH₃)₃), 1.16 (3H, s, C(CH₃)(CH₃)); δC (125 MHz, CDCl₃) 159.4 (COO), 155.4 (COO), 82.8 (C(CH₃)₃), 82.5 (C(CH₃)₃), 68.7 (CCl₂ or CCH₂), 62.0 (CCl₂ or CCH₂), 52.3 (CH₂), 32.4 (C(CH₂)₃), 28.1 (C(CH₃)₃), 27.9 (C(CH₃)₃), 20.9 (C(CH₃)CH₃), 19.3 (C(CH₃)(CH₃)); MS (ESI⁺) m/z 403 [M(35Cl)Na⁺], 405 [M(37Cl)Na⁺]; HRMS calcd. for C₁₆H₂₆Cl₂N₂NaO₄ [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; Rf = 0.17 (9:1, petrol: EtOAc); IR νmax (neat)/cm⁻¹ 2980, 2931, 1803, 1742, 1368, 1275, 1132, 771; δH (400 MHz, CDCl₃) 4.00 (1H, d, J = 11.1 Hz, NCH₂), 3.83 (1H, d, J = 11.2 Hz, NCHH), 1.54 (9H, C(CH₃)₃), 1.50 (9H, s, C(CH₃)₃), 1.46 (3H, s, C(CH₃)(CH₃)), 1.31 (3H, s, C(CH₃)(CH₃)); δC (125 MHz, CDCl₃) 150.6 (C=O), 150.2 (COO), 149.7 (COO), 84.4 (C(CH₃)₃), 84.0 (C(CH₃)₃), 71.7 (CCl₂ or CCH₂), 50.9 (CCl₂ or CCH₂), 46.9 (CH₂), 33.2 (C(CH₂)₂), 28.1 (C(CH₃)₃), 27.6 (C(CH₃)₃), 20.9 (C(CH₃)(CH₃)), 20.7 (C(CH₃)(CH₃)); MS (ESI⁺) m/z 431 [M(35Cl)Na⁺], 433 [M(37Cl)Na⁺]; HRMS calcd. for C₁₇H₂₆Cl₂N₂NaO₅ [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 (SiO₂, 9:1, petrol: EtOAc) provided less polar (2S, 3S)-335 (46 mg, 42%) as a colourless oil. Rf = 0.31 (9:1, petrol: EtOAc); IR νmax (film)/cm⁻¹ 2979, 2934, 1713, 1368, 1150, 840, 764; δH (500 MHz, CDCl₃) 4.32 (1H, d, J = 8.6 Hz, NCHH), 4.13 (1H, d, J = 8.6 Hz, NCHH), 1.63 (1H, q, J = 6.8 Hz, CHCH₃), 1.53 (3H, d, J = 6.7 Hz, CHCH₃), 1.49 (9H, s, C(CH₃)₃), 1.46 (9H, s, C(CH₃)₃); δC (125 MHz, CDCl₃) 159.4 (COO), 155.6 (COO), 82.9 (C(CH₃)₃), 82.5 (C(CH₃)₃), 63.2 (CCl₂ or CCH₂), 59.0 (CCl₂ or CCH₂), 55.0 (CH₂), 34.9 (CHCH₃), 28.1 (C(CH₃)₃), 27.9 (C(CH₃)₃), 10.7 (CHCH₃); MS
(ESI\(^+\)) \(m/z\) 389 [M\((^{35}\text{Cl})\text{Na}\)]\(^+\), 391 [M\((^{37}\text{Cl})\text{Na}\)]\(^+\); HRMS calcd. for C\(_{15}\)H\(_{24}\)\(^{35}\text{Cl}\)_2N\(_2\)Na\(_4\) [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 \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2982, 2933, 1801, 1747, 1369, 1256, 1147, 809, 736; \(\delta_H\) (400 MHz, CDCl\(_3\)) 4.06 (1H, d, \(J = 11.2\) Hz, NC\(_2\)H\(_2\)), 3.83 (1H, d, \(J = 11.2\) Hz, NCH\(_3\)), 1.79 (1H, q, \(J = 6.7\) Hz, CHCH\(_3\)), 1.57–1.52 (12H, m, CHCH\(_3\), C(CH\(_3\))\(_3\)), 1.51 (9H, s, C(CH\(_3\))\(_3\)); \(\delta_C\) (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 CCH\(_2\)), 49.9 (CCl\(_2\) or CCH\(_2\)), 48.7 (CH\(_2\)), 35.3 (CHCH\(_3\)), 28.1 (C(CH\(_3\))\(_3\)), 27.7 (C(CH\(_3\))\(_3\)), 10.3 (CHCH\(_3\)); MS (ESI\(^+\)) \(m/z\) 417 [M\((^{35}\text{Cl})\text{Na}\)]\(^+\), 419 [M\((^{37}\text{Cl})\text{Na}\)]\(^+\); HRMS calcd. for C\(_{16}\)H\(_{24}\)\(^{35}\text{Cl}\)_2N\(_2\)Na\(_5\) [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 \(\mu\)mol, 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 \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3087, 2985, 2924, 1724, 1467, 1375, 1270, 1132, 769; \(\delta_H\) (500 MHz, CDCl\(_3\)) 4.47 (1H, d, \(J = 9.0\) Hz, NC\(_2\)H\(_2\)), 4.38 (1H, d, \(J = 9.0\) Hz, NCH\(_3\)), 2.84 (1H, d, \(J = 9.7\) Hz, CHHCCl\(_2\)), 1.57 (1H, d, \(J = 9.8\) Hz, CHHCCl\(_2\)), 1.33–1.25 (6H, m, CH\(_2\)CH\(_3\)); \(\delta_C\) (125 MHz, CDCl\(_3\)) 160.5 (COO), 158.3 (COO), 63.2 (CH\(_2\)CH\(_3\)), 63.1 (CH\(_2\)CH\(_3\)), 57.2 (CCl\(_2\) or CCH\(_2\)), 56.5 (CCl\(_2\) or CCH\(_2\)), 54.5 (NCH\(_2\)), 25.6 (CH\(_2\)CCl\(_2\)), 14.4 (CH\(_2\)CH\(_3\)), 14.3 (CH\(_2\)CH\(_3\)); MS (ESI\(^+\)) \(m/z\) 319 [M\((^{35}\text{Cl})\text{Na}\)]\(^+\), 321 [M\((^{37}\text{Cl})\text{Na}\)]\(^+\); HRMS calcd. for C\(_{16}\)H\(_{14}\)\(^{35}\text{Cl}\)_2N\(_2\)Na\(_5\) [M+Na\(^+\)] 391.0223, found 391.0221.
Chapter 3: Experimental

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 (SiO₂, 8:1, petrol: EtOAc) provided less polar 343 (6 mg, 11%) as a colourless oil. R_f = 0.39 (8:1, petrol: EtOAc); IR ν_max (film)/cm⁻¹ 2978, 2930, 1712, 1498, 1393, 1369, 1255, 1153, 743; δ_H (500 MHz, CDCl₃) 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, NC₃H), 4.25 (1H, d, J = 9.2 Hz, NCH₂), 4.06 (1H, s, C(HAr)), 1.53 (9H, s, C(CH₃)₃), 1.52 (9H, s, C(CH₃)₃); δ_C (125 MHz, CDCl₃) 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(CH₃)₃), 82.8 (C(CH₃)₃), 62.3 (CCl₂ or CCH₂), 60.0 (CCl₂ or CCH₂), 51.7 (NCH₂), 35.3 (CHAr), 28.1 (C(CH₃)₃); MS (ESI⁺) m/z 451 [M⁺Na⁺], 453 [M⁺ClNa⁺]; HRMS calcd. for C₂₁H₂₆₃₅Cl₂N₂NaO₄ [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 ν_max (neat)/cm⁻¹ 2981, 2933, 1795, 1723, 1498, 1394, 1369, 1255, 1140, 737; δ_H (500 MHz, CDCl₃) 7.41–7.27 (5H, m, Ar H), 4.69 (1H, s, CHAr), 3.81 (1H, d, J = 11.8 Hz, NC₃H), 3.77 (1H, d, J = 11.8 Hz, NCH₂), 1.55 (9H, s, C(CH₃)₃), 1.53 (9H, s, C(CH₃)₃); δ_C (125 MHz, CDCl₃) 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(CH₃)₃), 84.2 (C(CH₃)₃), 66.0 (CCl₂ or CCH₂), 50.4 (CCl₂ or CCH₂), 44.2 (NCH₂), 38.1 (CHCCl₂), 28.0 (C(CH₃)₃), 27.9 (C(CH₃)₃); MS (ESI⁺) m/z 479 [M⁺ClNa⁺], 481 [M⁺ClNa⁺]; HRMS calcd. for C₂₁H₂₆₃₅Cl₂N₂NaO₅ [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 (SiO₂, 5:1 petrol: EtOAc) provided 338 (68 mg, 42%) as a colourless oil. R_f = 0.19 (5:1 petrol: EtOAc); IR υmax (film)/cm⁻¹ 2980, 2934, 1795, 1720, 1570, 1541, 1280, 1141, 773, 735, 698; δH (400 MHz, CDCl₃) 7.42 (2H, d, J = 6.7 Hz, Ar H), 7.37-7.30 (3H, m, Ar H), 5.27 (2H, s, CH₂Ar), 4.13 (1H, d, J = 11.4 Hz, NC₃H), 3.84 (1H, d, J = 11.4 Hz, NCH₃), 3.41 (1H, d, J = 9.8 Hz, CCH₂Cl₂), 1.67 (1H, d, J = 9.8 Hz, CHHClCl₂), 1.56 (9H, s, C(C₃H₃)₃); δC (125 MHz, CDCl₃) 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(C₃H₃)₃), 68.8 (CH₂Ar), 61.3 (Cl₂ or CH₂Cl), 47.1 (Cl₂ or CCH₂), 46.1 (NCH₂), 28.0 (C(CH₃)₃), 27.7 (CH₂Cl₂); MS (ESI⁺) m/z 437 [M(³⁵Cl)Na⁺], 439 [M(³⁷Cl)Na⁺]; HRMS calcd. for C₁₈H₂₀³⁵Cl₂N₂O₅ [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 (SiO₂, 5:1 petrol: EtOAc) provided 342 (15 mg, 12%) as a yellow oil. R_f = 0.35 (5:1 petrol: EtOAc); IR υmax (film)/cm⁻¹ 2980, 2933, 1822, 1727, 1498, 1370, 1253, 1137, 772; δH (400 MHz, CDCl₃) 7.38-7.30 (5H, m, Ar H), 5.15 (2H, s, CH₂Ar), 3.98 (1H, s, CHHCl₂), 3.74 (1H, d, J = 17.3 Hz, NCH₂), 2.92 (1H, d, J = 17.3 Hz, NCH₂), 1.55 (9H, C(CH₃)₃), 1.52 (9H, s, C(CH₃)₃); δC (125 MHz, CDCl₃) 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(CH₃)₃), 84.8 (C(CH₃)₃), 67.4 (CH₂Ar), 61.2 (CCl₂ or CH₂), 47.2 (CCl₂ or CH₂), 44.7 (CHCCl₂), 33.0 (NCH₂), 27.9 (C(CH₃)₃), 27.8 (C(CH₃)₃); MS (ESI⁺) m/z 537 [M(³⁵Cl)Na⁺], 539 [M(³⁷Cl)Na⁺]; HRMS calcd. for C₂₃H₂₈³⁵Cl₂N₂O₇ [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 NH₄Cl solution (10 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by column chromatography (SiO₂, 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; δH (400 MHz, CDCl₃) 3.87 (1H, d, J = 10.7 Hz, NC₃H), 3.69 (1H, dd, J = 10.8, 6.4 Hz, NC₃H), 3.21 (1H, dd, J = 13.4, 9.9, 5.5 Hz, CHHCF₂), 1.54 (9H, s, C(CH₃)₃), 1.52 (9H, s, C(CH₃)₃), 1.48–1.44 (1H, m CHHCF₂); δC (125 MHz, CDCl₃) 149.6 (C=O), 149.1 (COO), 148.6 (COO), 108.8 (t, JCF = 294.8 Hz, CF₂), 84.5 (C(CH₃)₃), 84.0 (C(CH₃)₃), 43.7 (d, JCF = 6.5 Hz, NCH₂), 41.9 (dd, JCF = 10.9, 9.3 Hz, CCF₂), 28.0 (C(CH₃)₃), 27.9 (C(CH₃)₃), 18.5 (t, JCF = 10.3 Hz, CH₂CF₂); δF (376 MHz, CDCl₃) −125.8 (d, JFF = 167 Hz), −147.9 (d, JFF = 167 Hz); MS (ESI⁺) m/z 371 [MNa⁺]; HRMS calcd. for C₁₅H₂₂F₂N₂NaO₅ [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 CH₂Cl₂ (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 CH₂Cl₂ (10 mL), and
washed with a saturated solution of aqueous sodium bicarbonate (10 mL) and H₂O (10 mL). The aqueous layer was washed with CH₂Cl₂ (10 mL), the organic extracts combined, dried over MgSO₄, filtered, and concentrated *in vacuo* to provide 359 (53 mg, 91%) as a yellow oil. IR \( \nu_{\text{max}} \) (film)/cm⁻¹ 3259, 3030, 2962, 2899, 1709, 1749, 1244, 1077, 699; \( \delta_h \) (400 MHz, CDCl₃) 7.38–7.29 (5H, m, Ar H), 5.60 (1H, br s, NH), 5.22 (1H, d, \( J = 12.2 \) Hz, CHHAr), 5.11 (1H, d \( J = 12.2 \) Hz, CHHAr), 4.07 (1H, br m, CCH), 3.87 (1H, br m, CCH), 2.67 (1H, br m, CHHCF₂), 1.38 (1H, ddd, \( J = 15.5, 10.1, 5.2 \) Hz, CHHCF₂); \( \delta_c \) (125 MHz, CDCl₃) 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, CF₂), 67.7 (CH₂Ar), 53.5 (dd, \( J_{CF} = 16.2, 9.8 \) Hz, CCH₂), 46.2 (CCH₂), 17.2 (t, \( J_{CF} = 9.4 \) Hz, CH₂CF₂); \( \delta_F \) (376 MHz, CDCl₃) –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 C₁₂H₁₂F₂N₂O₂ [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 N₂ was added 299 (149 mg, 0.55 mmol) and rhodium (II) acetate dimer (24 mg, 55 \( \mu \)mol) in anhydrous CH₂Cl₂ (5 mL). Ethyl diazoacetate (64 μL, 0.61 mmol) in anhydrous CH₂Cl₂ (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 (SiO₂, 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 \( \nu_{\text{max}} \) (film)/cm⁻¹ 2979, 2934, 1708, 1369, 1257, 1161, 767; \( \delta_h \) (500 MHz, CDCl₃) 6.23 (0.66H, s, \( HC=CH \) minor product), 4.30 (1H, d, \( J = 9.0 \) Hz, NCHH), 4.27–4.22 (2.32H, m, NCHH, CH₂CH₃ minor product), 4.14 (2H, q, \( J = 7.1 \) Hz, CH₂CH₃), 2.40 (1H, dd, \( J = 9.8, 6.8 \) Hz, NCCH), 2.00 (1H, dd, \( J = 9.7, 6.7 \) Hz, NCCCHH), 1.50 (9H, s, C(CH₃)₃), 1.48 (9H, s, C(CH₃)₃), 1.33–1.25 (4.98H, m, CH₂CH₃, CH₂CH₃ minor product), 1.22 (1H, t, \( J = 6.4 \) Hz, NCCCHH); \( \delta_c \) (125 MHz, CDCl₃) 171.0 (COO),
165.3 (2 x COO, minor product), 159.7 (COO), 156.8 (COO), 129.8 (H-C=CH, minor product), 82.7 (C(CH$_3$)$_3$), 82.4 (C(CH$_3$)$_3$), 61.3 (CH$_2$CH$_3$, minor product), 61.0 (CH$_2$CH$_3$), 54.9 (NCH$_2$), 52.8 (NCCH), 28.2 (C(CH$_3$)$_3$), 28.1 (C(CH$_3$)$_3$), 21.1 (NC), 14.5 (NCCH), 14.3 (CH$_2$CH$_3$), 14.0 (CH$_2$CH$_3$, minor product); MS (ESI$^+$) m/z 379 [M+Na$^+$]; HRMS calcd. for C$_{17}$H$_{28}$N$_2$O$_6$ [M+Na$^+$] 379.1840, found 379.1850.

### Diethyl 2-diazomalonate (355)

This compound was prepared 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$_2$Cl$_2$ (20 mL) and concentrated in vacuo. Purification by column chromatography (SiO$_2$, 1:1, petrol: Et$_2$O) provided 355 (186 mg, 100%) as a yellow oil. R$_f$ = 0.50 (1:1, petrol: Et$_2$O); IR $\nu_{max}$ (film)/cm$^{-1}$ 2982, 2930, 2138, 1752, 1087, 739; $\delta_{H}$ (500 MHz, CDCl$_3$) 4.30 (4H, q, $J = 7.1$ Hz, CH$_2$CH$_3$), 1.31 (6H, t, $J = 7.1$ Hz); $\delta_{C}$ (125 MHz, CDCl$_3$) 161.1 (COO), 61.6 (CH$_2$CH$_3$), 14.4 (CH$_2$CH$_3$), C=N$_2$ signal not observed; MS (ESI$^+$) m/z 209 [MNa$^+$]; HRMS calcd. for C$_7$H$_{10}$N$_2$NaO$_4$ [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$_2$Cl$_2$ (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 (SiO₂, 2:1, petrol: EtOAc) provided 362 (71 mg, 99%) as a white solid. M. p. 149–151 °C; Rf = 0.55 (2:1, petrol: EtOAc); IR νmax (neat)/cm⁻¹ 2988, 1714, 1502, 1397, 1148, 723; δH (500 MHz, acetone-d₆) 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, CHHAr), 4.91 (1H, d, J = 10.4 Hz, NCHH), 4.68 (1H, d, J = 10.4 Hz, NCHH), 4.52 (1H, d, J = 15.4 Hz, CHH(CN)₂), 4.03 (1H, d, J = 15.4 Hz, CHH(CN)₂); δC (125 MHz, acetone-d₆) 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(CH₃)₃), 69.7 (C(CN)₂), 68.2 (CH₂Ar), 50.2 (CCH₂), 40.9 (CH₂C(CN)₂), 31.7 (CH₂C(CN)₂), 27.2 (C(CH₃)₃); MS (ES⁺) m/z 455 [MNa⁺]; Anal. calcd. for C₂₂H₂₀N₆O₄: C, 61.10; H, 4.66; N, 19.43%. Found: C, 61.17; H, 4.71; N, 19.05%.

(3R, 7S)-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 CH₂Cl₂ (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 (SiO₂, 5:1, petrol: EtOAc) provided the major diastereomer (3R, 7S)-363a (54 mg, 73%) as a white solid. M. p. 65–68 °C; Rf = 0.35 (5:1, petrol: EtOAc); IR νmax (neat)/cm⁻¹ 2981, 2937, 1717, 1370, 1136, 836, 763; δH (500 MHz, acetone-d₆) 4.80 (1H, q, J = 7.0 Hz, CHCH₃), 4.43 (1H, d, J = 10.8 Hz, NCHH), 1.70 (3H, d, J = 7.1 Hz, CHCH₃), 1.55 (9H, s, C(CH₃)₃), 1.51 (9H, s, C(CH₃)₃); δC (125 MHz, acetone-d₆) 158.6 (COO), 153.8 (COO), 110.5 (CN), 109.1 (CN), 109.0 (CN), 108.6 (CN), 84.4 (C(CH₃)₃), 82.9 (C(CH₃)₃), 73.2 (C(CN)₂), 53.4 (NCH₂), 48.4 (CCH₂), 45.5 (CHCH₃), 37.3 (CH₂C(CN)₂), 27.21 (C(CH₃)₃), 27.19 (C(CH₃)₃), 11.4 (CHCH₃); MS (ES⁺) m/z 435 [MNa⁺]; Anal. calcd. for C₂₀H₂₄N₆O₄: C, 58.24; H, 5.87; N, 20.38%. Found: C, 58.21; H, 5.91; N, 20.24%.
References


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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, H₂ carrier gas)

Chiral GC traces of 2-allylated azetidin-3-one 159.
Appendix II – Chiral HPLC analysis of (S)-170

(Chiralcel OJ column (0.46 cm 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