Synthesis, Structure and Functionalisation of 1,2-Diazetidines

by

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

Department of Chemistry, University of Warwick
March 2011
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ACKNOWLEDGMENTS

My sincerest gratitude to Mike Shipman for his expert guidance, ideas and interest throughout this project. My appreciation also for the valuable contributions of Graham Inglis at GlaxoSmithKline.

I would like to thank Lijiang Song and Ivan Prokes at Warwick, and Sean Hindley and Richard Upton at GlaxoSmithKline for their analytical expertise; and Rob Jenkins for his help with almost everything.

My thanks to the Shipman group members, past and present: Pete, Claire, Estelle, Emma, Matt, Thuy, Karen, Alex, Penny, Greg, Ben, Sami, Nicola, Sam and Fran. A thank you also to Amélie.

I would especially like to thank Adrian Rahman, Peter Bradshaw, Guy Clarkson and Mark Davies for guiding me since the early days and passing on their seemingly limitless knowledge.

Also I thank everyone else who has contributed in many different ways over the last four years, especially Luis Hayward, Jen Burham, Dan Hughes and Gill Johnstone; also a special word for Dan Roythorne and David Morris who encouraged my undertaking of this project.

I thank as well the Engineering and Physical Sciences Research Council and GlaxoSmithKline for funding this research.
DECLARATION

Except where clearly indicated, the work reported in this thesis is an account of my own independent research at the University of Warwick and at GlaxoSmithKline, Stevenage carried out between October 2006 and October 2010.

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 publication, part of this work has appeared in the scientific literature:


ABSTRACT

The four-membered cyclic hydrazine, 1,2-diazetidine, has received little attention from the scientific community. This system has useful potential applications in medicine and synthetic chemistry, but very few compounds of this class are known. This thesis describes the synthesis, structure and functionalisation chemistry of new simple 1,2-diazetidine derivatives. Synthetic studies show a Hard–Soft Acids and Bases controlled ring closure is necessary to effect acceptable to good yields in cyclisations to saturated N–carboxyalkyl and N–sulphonyl diazetidines. Functionalisation of these systems via C–H activation was unsuccessful due to protecting group participation. Synthetic studies toward the parent 1,2-diazetidine molecule (C₂N₂H₆) using chloramine mediated N–N ring closure or deprotection strategies were also unsuccessful. Further studies show a wide range of simple 3-alkylidene-1,2-diazetidines and functionalised derivatives are accessible from commercial materials in two steps using an efficient Cu(I)-catalysed cyclisation. The scope of this cyclisation method is assessed. Pd(0)-catalysed Heck chemistry of 3-methylene-1,2-diazetidines allows a stereoselective route to arylated derivatives in moderate yields. Furthermore, diastereoselective reduction of these systems provides an efficient route to 1,2-diamines. Structural studies of a range of synthesised 1,2-diazetidines by X-ray crystallography and dynamic nuclear magnetic resonance spectroscopy are presented. Together these studies present the potential these molecules hold in synthetic chemistry.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>atm</td>
<td>Atmosphere</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxy carbonyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bus</td>
<td>tert-Butyl sulphonyl</td>
</tr>
<tr>
<td>Calcd</td>
<td>calculated</td>
</tr>
<tr>
<td>CAN</td>
<td>Cerium (IV) ammonium nitrate</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>Chz</td>
<td>Carbobenzyloxy</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation Spectroscopy</td>
</tr>
<tr>
<td>d</td>
<td>day</td>
</tr>
<tr>
<td>DBB</td>
<td>4,4'-di-tert-Butylbiphenyl</td>
</tr>
<tr>
<td>DBU</td>
<td>1,3-Diazabicyclo[5.4.0]undecane</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-Dichloroethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyanobenzoquinone</td>
</tr>
<tr>
<td>DEAD</td>
<td>Diethyl azodicarboxylate</td>
</tr>
<tr>
<td>decomp.</td>
<td>decomposed</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Di-iso-butyraluminium hydride</td>
</tr>
<tr>
<td>DMEDA</td>
<td>N,N'-Dimethylethlenediamine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N'-Dimethylformamide</td>
</tr>
<tr>
<td>DMPU</td>
<td>N,N'-Dimethylpropylene urea</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulphoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>Electron Impact</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
</tr>
<tr>
<td>ES</td>
<td>Electrospray</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier Transform</td>
</tr>
<tr>
<td>GCMS</td>
<td>Gas Chromatography Mass Spectroscopy</td>
</tr>
</tbody>
</table>
h  
hour

HMBC  
Heteronuclear Multiple Bond Coherence

HMDS  
Hexamethyldisilazane

HMPA  
Hexamethylenephamoramide

HMQC  
Heteronuclear Multiple Quantum Coherence

HOMO  
Highest Occupied Molecular Orbital

HPLC  
High Performance Liquid Chromatography

HRMS  
High Resolution Mass Spectroscopy

HSAB  
Hard-Soft Acids and Bases

INDO  
Intermediate Neglect of Diatomic Differential Overlap

IR  
Infrared

\( J \)  
Coupling constant

LCMS  
Liquid chromatography-Mass Spectroscopy

LDA  
Lithium Di-iso-propylamide

lit.  
literature

LUMO  
Lowest Unoccupied Molecular Orbital

min  
minute

MNDO-PM3  
Modified Neglect of Diatomic Differential Overlap-Parametric Method 3

MO  
Molecular Orbital

mol.  
molar

M.p.  
Melting point

Ms  
Methanesulphonyl

NAP  
2-Methylnaphthyl

NBS  
\( N \)-Bromosuccinimide

NMR  
Nuclear Magnetic Resonance

nOe  
nuclear Overhauser effect

\( p \)  
\textit{para}

PMB  
\textit{para}-Methoxybenzyl

ppm  
parts per million

\( R_f \)  
Retention factor

viii
rt room temperature
SCF Self-Consistent Field
S_N2 Nucleophilic Substitution Bimolecular

t time

\[ t_{1/2} \] half-life

\[ t_r \] retention time

T temperature

TBD 1,5,7-Triazabicyclo[4.4.0]dec-1-ene
TFA Trifluoroacetic acid
THF Tetrahydrofuran
TIC Total Ion Count

\[ \text{tlc} \] thin layer chromatography

TMEDA \( N,N,N',N'-\text{Tetramethylethylenediamine} \)
TMG \( N,N,N',N'-\text{Tetramethylguanidine} \)
TMS Trimethylsilyl

Ts \( \text{para-Toluenesulphonyl} \)

UV Ultraviolet

v/v volume per unit volume
wt weight
w/w weight per unit weight
Chapter I

Introduction
I Introduction

I.I 1,2-Diazetidines

Four-membered rings containing two nitrogen atoms are known as diazetidines. This thesis describes the synthesis, structural studies and functionalisation of a range of novel 1,2-diazetidines (Figure 1.1), and studies toward the parent molecule, 1,2-diazetidine.

![Figure 1.1]

Of the lower order cyclic amines and hydrazines, all but diazetidine and the three-membered analogue diaziridine have been isolated.

![Figure 1.2]

Diaziridine can be reliably generated and reacted successfully in situ; several routes exist to mono- and di-substituted species, and simple and general methods to trisubstituted species are available. Diazetidine has received far less attention. No routes
exist to the parent molecule, and there are only a handful of reports on simple
derivatives. Whilst these attracted industrial attention after the Second World War as
low-freezing rocket fuels, they have received relatively little attention from the academic
community, for only limited structural and mechanistic studies.

Opportunities to exploit the reactivity of small molecules arise only after general
methods for their synthesis have been devised. Almost all of the structures in Figure 1.2
form common motifs in organic chemistry and one could expect an undergraduate
student to offer routes to them. In contrast, the synthesis of diazetidines has proven a
challenge for experienced scientists, with only a few offering routes to this class of
molecule. As a result the chemistry of these systems remains largely unexplored.

I.II  Thermodynamics of Four-Membered Ring Formation

The synthesis of four-membered rings in general poses a challenge. One must
consider why these molecules are so poorly accessible.

Cyclisations to small rings have a large enthalpy of activation \( \Delta H^\ddagger \), i.e. energy is
required to ‘bend’ the molecule into the reacting conformation. Such \( S_N^2 \) ring forming
reactions have late transition states which, by the Hammond postulate, tend to resemble
the products. It is useful to think of an enthalpy cost as a ‘ring strain’ of the transition
state. We should remember here that the conventional ring strain energies of some three
and four-membered rings are almost the same (cyclopropane, 115 kJ mol\(^{-1}\); cyclobutane,
111 kJ mol\(^{-1}\)).\(^9\) In addition, recent theoretical calculations have also predicted
approximately the same standard enthalpies of formation for diaziridine (\( \Delta H_f s = 238 \pm 1\)
kJ mol\(^{-1}\)) and diazetidine (\( \Delta H_f s = 242 \pm 1\) kJ mol\(^{-1}\)).\(^10\)

Consideration of relative rates of ring closure is crucial. For a series of
bromoalkylamines, the following data was obtained:\(^11\)
Ring size formed \((n+2)\) & Relative rate \\
3 & 0.001 \\
4 & 0.00002 \\
5 & 1 \\
6 & 0.02 \\
7 & 0.00003 \\

Table 1.1

Of the series, formation of the four-membered ring is the slowest. Rate of reaction is a measure of \(\Delta G^\ddagger\) the free energy of activation, which is composed of enthalpic and entropic components:

\[
\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger
\]

Three-membered rings form readily because the unfavourable \(\Delta H^\ddagger\) change is offset by a favourable \(\Delta S^\ddagger\) term (little organisation is required to place the reacting centres in the correct conformation). In the formation of four-membered rings, greater organisation is required to reach the reacting conformation (a loss of entropy, larger negative \(\Delta S^\ddagger\)), this adds to the unfavourable \(\Delta H^\ddagger\) change, resulting in a large \(\Delta G^\ddagger\) and therefore a slow cyclisation.

Ring closures to five- and six-membered rings do not suffer from such large \(\Delta H^\ddagger\) values as the contribution from ring strain is small. This combined with a favourable \(\Delta S^\ddagger\) term (reacting conformations are readily accessible) results in a smaller \(\Delta G^\ddagger\) and faster ring closures. The relatively slow cyclisation to four-membered rings gives competing reactions, and other cyclisation modes, a better chance. Attempts to overcome these problems in the case of azetidines have been described.\(^\text{12}\)

The synthesis of four-membered rings remains thermodynamically viable but kinetically difficult. The following survey will highlight previous efforts to overcome these challenges in the context of 1,2-diazetidine synthesis. A focus on the synthetic and structural studies undertaken will provide the reader with an appreciation of the foundations upon which this project was based.
I.III  Prior Synthetic and Structural Studies

Although claims about the synthesis of diazetidines date back to the 1850’s, most of the earlier reports were later found to be erroneous.\textsuperscript{13,14} It appears the first successful attempts at the synthesis of 1,2-diazetidines were recorded in the late 1940’s.\textsuperscript{15} Only within the last five years or so have claims of efficient synthetic routes to these systems been made.\textsuperscript{16,17} The structure of these new molecules has formed the basis of several studies.

The thermal [2+2] addition of an azo compound and an alkene, although strictly forbidden by the Woodward-Hoffman rules,\textsuperscript{18,19} has been used as a route to provide the early diazetidines. In 1959, Kauer and Schneider at DuPont successfully synthesised dimethyl 3,3,4,4-tetrafluoro-1,2-diazetidine-1,2-dicarboxylate (1) (47% yield) by the thermal addition of tetrafluoroethylene to dimethyl azodicarboxylate (Scheme 1.1),\textsuperscript{20} a method patented previously by the company in 1948.\textsuperscript{15} The authors further disclosed its flash pyrolysis to methoxydifluoromethyl isocyanate.

\textbf{Scheme 1.1}

In 1964, Hoffmann and Häuser reported an efficient thermal addition of tetramethoxyethylene to diethyl azodicarboxylate to give 2 (Scheme 1.2).\textsuperscript{21} In further work, they critically considered the possible [4+2] by-product, dihydrooxadiazine 3.\textsuperscript{22} Based on IR analysis, and supported by earlier work on these six-membered rings from Gustorf,\textsuperscript{23} they discounted the dihydrooxadiazine as the major reaction product.
In 1969, Firl and Sommer reported that the reaction of dimethyl azodicarboxylate with ethyl vinyl ether in benzene gave a kinetic mixture of diazetidine 4 and dihydrooxadiazine 5 in a ratio of ca. 3:1 (Scheme 1.3). These adducts were differentiated on the basis of IR and NMR analysis. Illumination of this reaction with ultraviolet light only accelerated the reaction and no change in product ratio was observed. The authors attributed this rate increase to faster conversion of the normally trans-azodicarboxylate to the more reactive cis-azodicarboxylate conformer.

Strong evidence for the asynchronous nature of the formation of 4 came from studies of secondary α-deuterium isotope effects which revealed an unsymmetrical transition state. However, solvent trapping studies have provided a more complex picture. In one case of exclusive diazetidine formation (reaction of a 4-substituted triazolidine-dione with 2-chloroethyl vinyl ether), a 1,4-dipole intermediate was trapped with solvent; yet in other cases, such as the reaction of dimethyl azodicarboxylate with ethyl vinyl sulphide where there is competition between products, trapping of a similar 1,4-dipolar intermediate by solvent prevented completely dihydrooxadiazine formation but gave the expected amount of diazetidine product.
Determination of the mechanism of similar reactions has continued.\textsuperscript{30-32} Considering the collected evidence, it can be proposed that these ‘cycloadditions’ lie somewhere on a continuous scale between a two-step mechanism on the one hand, and a concerted transition state on the other, the position of which is highly dependent on the electronic pairing of the reacting species. Only when electron rich, or very electron poor, highly polarisable alkenes (lacking allylic hydrogens) are used does diazetidine formation compete. This greatly limits the synthetic utility of this route to simple diazetidines.

In the early 1970’s, Warrener and Nunn first synthesised the unsaturated diazetidine analogue $\tilde{\Delta}^3$-1,2-diazetine 9 (Scheme 1.4).\textsuperscript{33} Reaction of cyclobutadiene with dimethyl azodicarboxylate furnished 6 (31% yield) which underwent a thermal cycloaddition with 2,5-dimethyl-3,4-diphenylocyclopenta-2,4-dienone to give 7 (49% yield). UV irradiation promoted elimination of carbon monoxide to form 8 which underwent a spontaneous 1,2-photoaromatisation to give dimethyl $\tilde{\Delta}^3$-1,2-diazetine-1,2-dicarboxylate (9) (63% yield) and the corresponding aromatic hydrocarbon.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme1.4.png}
\caption{Scheme 1.4}
\end{figure}

Of direct relevance to our studies, catalytic hydrogenation (Pd/C) was found to yield simple 1,2-diazetidine 10 (53% yield). It has been reported that this diazetidine can be formed by the thermal addition of ethylene onto dimethyl azodicarboxylate,\textsuperscript{34} however
neither Warrener et al. nor others have been able to repeat this result. Warrener’s report represents the only well documented synthesis of a simple 1,2-diazetidine bearing carboxyalkyl groups on nitrogen. This diazetidine was found to be thermally stable, but no studies of its reactivity were reported.

In 1964, FMC Corporation patented a new route to simple 1,2-diazetidines via two successive alkylation reactions of a dialkylhydrazine (Scheme 1.5). Hall and Bigard used this method to provide a range of simple dialkyl-1,2-diazetidines to study the ring conformation of these molecules. The reactions involved the addition of a large excess of dibromoethane (3-10 equiv) over a long period (4-72 h) to a dilute solution of dialkylhydrazine in refluxing xylenes, although even under these carefully optimised conditions, yields were moderate to poor.

![Scheme 1.5](image)

These diazetidines were found to be very stable compounds. 1,2-Diethyl-1,2-diazetidine was recovered after treatment with sodium amide at room temperature for two weeks. Butyllithium had no effect on 1,2-di-iso-propyl-1,2-diazetidine, nor did concentrated hydrochloric acid or 98% sulphuric acid at room temperature. Catalytic hydrogenation (Pd/C) at 50 psi also failed to cleave the N−N bond of this molecule.

In 2006, Miao and co-workers reported the cyclisation of hydroxyethylhydrazine derivatives such as 12a to give optically pure 1,2-diazetidines in excellent yields (Scheme 1.6). These alcohols could be produced in both enantiomeric forms via the catalytic α-amination of aldehydes as reported by List. Treatment of these alcohols with methanesulphonyl chloride and strong base promoted ring closure through nitrogen
with retention of enantiomeric purity. No detailed experimental data or structural studies were reported. This route was patented by this group the following year.\textsuperscript{38}

![Scheme 1.6](image)

More recently, in 2008 Cheng and Ma provided a palladium catalysed coupling/cyclisation of aryl iodides with 2,3-allenyl hydrazines to yield \textit{trans}-1,2-diazetidines (Scheme 1.7).\textsuperscript{17} Variation at the ring carbon was limited to \textit{n}-alkyl or benzyl groups, and electron poor aryl iodides were preferred. Highly electron rich aryl iodides led to exclusive formation of the five-membered regioisomer 15.\textsuperscript{39} Yields up to 77\% were achieved with formation of the dihydropyrazole as the major by-product.

![Scheme 1.7](image)

Given the problems of competing ring closures experienced by workers in this field, it seems surprising that little effort has been made towards 1,2-diazetidines \textit{via} N–N bond formation. The most important industrial method for the synthesis of hydrazine, the Raschig process,\textsuperscript{40} involves the reaction of two molecules of ammonia in the presence of sodium hypochlorite (bleach). N–N bond formation in this way has provided robust routes to substituted diaziridines,\textsuperscript{41} and importantly has been used with success to access the parent 1,2-pyrazolidine and 1,2-piperazine systems.\textsuperscript{6} There appear to be only two reports on the synthesis of four-membered rings \textit{via} the oxidative formation of N–N
bonds. Volodarskii was able to oxidise bis-hydroxylamine 16 with sodium hypobromite to 3,3,4,4-tetramethyl-$\Delta^1$-1,2-diazetine-1,2-dioxide (17);\textsuperscript{42} and Breton and co-workers synthesised 3,4-diphenyl-$\Delta^1$-1,2-diazetine-1,2-dioxide (19) via oxidation of 2,3-diphenyl-1,2-ethylenediamine (18) with dioxirane.\textsuperscript{43}

Scheme 1.8

Access to simple 1,2-diazetidines has invited study of their structure. Rademacher was the first to study the conformation of 1,2-dimethyl-1,2-diazetidine (11a) using photoelectron spectroscopy.\textsuperscript{44} Assuming that the interaction between the electron lone pairs in the two non-bonding molecular orbitals is determined mainly by the dihedral angle between them, Rademacher was able to predict a dihedral angle of $\varphi = 145 \pm 10^\circ$ between the nitrogen lone-pairs of 11a, placing both methyl groups in a trans-equatorial position.

Figure 1.3 $\varphi$ is the dihedral angle between the lone pairs.

Several years later a detailed structural study of this molecule by Gebhardt et al. combining electron-diffraction, microwave, and normal coordinate analysis concluded that the resting conformation of this species retained $C_2$ symmetry, and that the ring was significantly distorted from planarity (ring puckering angle $\phi = 24.3^\circ$), with the methyl groups placed in a trans-equatorial position [substituent torsion ($C_{\text{methyl}}NN'C_{\text{methyl}'}$) = $105^\circ$], in agreement with Rademacher.\textsuperscript{45}
Further studies of 1,2-dimethyl-1,2-diazetidine were undertaken by Hall and Bigard using NMR spectroscopy.\textsuperscript{36} Low temperature $^1\text{H}$ NMR spectra of 11a-c (Figure 1.4) revealed an AA′BB′ pattern for the methylene hydrogens. Geminal ring hydrogens were non-equivalent as shown in conformer \textit{trans eq-11}, where (H$^1$=H$^4$ and H$^2$=H$^3$).

\begin{center}
\includegraphics[width=0.8\textwidth]{figure1.4.png}
\end{center}

\textbf{Figure 1.4}

These signals coalesced to a singlet resonance when double inversion at nitrogen became rapid. Relative rates of this process at $T = 66$ °C were determined by line-shape analysis as 1.00 : 0.78 : 0.51 : 0.74 ×10$^{-3}$ for R = Me, Et, i-Pr, t-Bu respectively, and the free energy of double nitrogen inversion for 1,2-dimethyl-1,2-diazetidine was calculated as $\Delta G_c^{\ddagger} = 68.6$ kJ mol$^{-1}$. The di-\textit{tert}-butyl compound 11d experiences a greatly restricted inversion rate as a result of steric interactions between the bulky alkyl substituents, and retains a resting conformation \textit{trans ax-11} with the alkyl groups \textit{trans}-dixial (Scheme 1.9) until coalescence of the ring methylene signals at 155 °C.
Similar dynamic NMR studies of 2 (Scheme 1.10) showed that restricted rotation about the amide bond (2 ↔ 2') was responsible for a barrier of $\Delta G^\dagger_{c} = 56.9$ kJ mol$^{-1}$ ($T_c = -27$ °C in $d_6$-acetone $d_8$-toluene solution),$^{46}$ as a result of steric interactions between the ring methoxy and N-carboxyethyl groups. However, the barrier observed in the $^{19}$F NMR spectrum for 20 ($\Delta G^\dagger_{c} = 43.9$ kJ mol$^{-1}$), was attributed to nitrogen inversion, although ring inversion (as shown in Scheme 1.10) could not be ruled out.$^{47}$ Further NMR studies of bicyclic diazetidine systems were undertaken by J.-M. Lehn$^{48}$ and other workers.$^{49,50}$

$\Delta^3$-1,2-diazetine 9 (Scheme 1.11) formally satisfies the Hückel (4n+2) rule for aromaticity, but was found to be thermally unstable [$t_{1/2} (20$ °C$) = 6.9$ h] undergoing facile electrocyclic ring opening to 1,4-diazabutadiene.$^{51}$ Computational studies (INDO
SCF) showed that the ring distorts away from planarity to minimise π-orbital overlap between the lone-pair orbitals and the double bond, and thus experiences little aromatic stabilization.

Despite the large amount of interest in the conformation processes of the 1,2-diazetidine ring, to date these molecules have eluded structural study in their solid-state by X-ray diffraction.

I.IV Purpose of Study

In addition to an inherent interest in isolating simple 1,2-diazetidines to study their physical and chemical behaviour, these molecules might be expected to find application in medicine and synthetic chemistry.

Four-membered heterocycle systems are emerging as useful tools in medicinal chemistry. The physicochemical properties of these systems offer new opportunities for drug discovery. For example, the conformationally restricted nature of functionalised azetidine rings\textsuperscript{52,53,54,55} has seen their development into a new class of nicotinic acetylcholine receptor agonists.\textsuperscript{56} Recently, oxetanes have been explored as surrogates for \textit{gem}-dimethyl groups within drug candidates, offering increased polarity within a similar molecular volume, thus allowing tuning of the solubility and lipophilicity of the molecule.\textsuperscript{57} 1,2-Diazetidines have already been explored computationally as components of β-turn mimetics,\textsuperscript{58} and may offer further potential as scaffolds for conformationally defined units within drug molecules.
The effects of constrained ring systems upon rates of nitrogen inversion have been used to probe the stereochemistry of nitrogen. Moreover, control of nitrogen inversion in aziridines has shown their application as simple molecular switches. In a similar fashion, 1,2-diazetidines hold the potential to operate as complex molecular switches, offering coupled/decoupled inversion over two centres.

Exploration of the reactivity of new highly strained heterocyclic systems such as 2-methyleneaziridines has contributed uniquely to organic synthesis. Similarly, for systems such as 1,2-diazetidine, one can expect relief of ring strain to provide a strong thermodynamic driving force for ring expansion or ring opening reactions to provide a range of functionalised nitrogen containing molecules.

We were particularly interested in the use of 1,2-diazetidines to act as scaffolds for the introduction of the 1,2-diamine moiety into larger organic molecules. Functionalisation of simple systems (those unsubstituted at the ring carbons) via C−H activation; or functionalisation of those bearing an exocyclic double bond via cross-coupling chemistry, and then subsequent cleavage of the diazetidine N−N bond could offer a conceptually new strategy to molecules containing this sub-unit.

In recent years there has been much effort toward direct sp\(^3\) C−H activation adjacent to nitrogen in heterocycles. Due to the strength of the C−H bond, organolithium bases are generally required, and the resultant organolithium must be stabilised by an electron-withdrawing, coordinating group on nitrogen. Chiral diamine ligands such as, but not exclusively, (−)-sparteine, have been used extensively to induce stereoselective deprotonation. Seminal work by Beak on the asymmetric deprotonation of N-Boc pyrrolidine (Scheme 1.12) has been elaborated by several groups to other N-Boc heterocycles including oxa-, thia- and imidazolidines and piperidines, generally with reasonable levels of enantioselectivity. Deprotonation/substitution adjacent to nitrogen in aziridines, methyleneaziridines, azetidines and pyrazoles have also been successful.
Scheme 1.12 Enantioselective deprotonation of N-Boc-pyrrolidine.

We envisaged that di-tert-butyl-1,2-diazetidine-1,2-dicarboxylate (21) may undergo deprotonation/substitution reactions in a similar fashion (Scheme 1.13). Functionalisation of the parent ring in this way followed by reductive cleavage of the N−N bond and removal of the Boc groups could yield enantioenriched 1,2-diamines. Potentially, this process could be used in an iterative manner to substitute both sp³ carbons. As such, this would represent a novel, divergent route to chiral diamines. 

Scheme 1.13
I.V Conclusions

The chemistry of 1,2-diazetidines remains largely unexplored due to the difficulties encountered in their synthesis. Of the methods employed, nucleophilic ring closure onto carbon has been the most productive, but poor control over cyclisation selectivity and low yielding reactions remain a problem.

This thesis will describe the synthesis of previously unknown simple and substituted 1,2-diazetidines and explore the structure and functionalisation of these novel systems. The synthetic studies summarised in Chapter II will begin with a critical analysis of the claims made by Miao in 2006 on the cyclisation of hydroxyethylhydrazine derivatives, and explore the synthesis of 1,2-dicarboxyalkyl-1,2-diazetidines including bis-Boc diazetidine 21. Subsequently, the synthesis of a range of simple N-substituted diazetidines will be explored. Our efforts towards the parent 1,2-diazetidine based on the formation of the N–N bond will be presented. The use of transition-metal catalysis to effect efficient ring closures to 3-alkylidene-1,2-diazetidines will also be described as a practical route to these heterocycles.

The structure and functionalisation of these systems will be explored in Chapter III. Structural studies of these new molecules combining spectroscopic and X-ray analysis will be presented. An exploration of the reactivity of these novel molecules including the C–H activation of simple 1,2-diazetidines, and functionalisation reactions of 3-alkylidene-1,2-diazetidines under palladium-catalysis will be reported.
Chapter II

Synthesis of 1,2-Diazetidines
II Synthesis of 1,2-Diazetidines

In this chapter, the development of two new approaches to 1,2-diazetidines based upon ring closure strategies is described. Initially, simple systems bearing no substitution at C-3 or C-4 were targeted in order to study their structure and lithiation chemistry (Figure 2.1). Subsequently, ring closure and deprotection strategies to the parent 1,2-diazetidine were explored. As a result of difficulties encountered from these endeavours, a second strand of work on the synthesis of 3-alkylidene-1,2-diazetidines bearing a range of N-protecting groups was undertaken through the use of copper catalysis. Structural and functionalisation studies of these systems are detailed in Chapter III.

\[
\begin{align*}
\text{X} & \quad \text{X} \\
\text{N} & \quad \text{N} \\
\text{1,2-diazetidine} & \\
\end{align*}
\]

where \(X = \text{CO}_2\text{R}, \text{Bn}, \text{SO}_2\text{R}\)

\[
\begin{align*}
\text{H} & \quad \text{NH} \\
\text{RO}_2\text{C} & \quad \text{N} \\
\text{CO}_2\text{R} & \quad \text{X} \\
\text{1,2-diazetidine} & \\
\end{align*}
\]

where \(R = \text{t-Bu}, \text{CH}_2\text{Ph}, \text{Et}\)

Figure 2.1
II.1 Synthesis of 1,2-Dicarboxyalkyl-1,2-Diazetidines

In 2006, Miao reported efficient ring closures of hydroxyethyl hydrazine derivatives to carboxybenzyl protected 3-alkyl-1,2-diazetidines (Scheme 1.6).\textsuperscript{16} We expected this would provide a simple route to bis-Boc diazetine 21.

2-Hydroxyethyl hydrazine is commercially available. Boc protection of the hydrazine nitrogens proceeded smoothly to give 22 in excellent yield (Scheme 2.2).\textsuperscript{73} However, treatment of this alcohol under Miao’s best cyclisation conditions (1.5 eq MsCl, 8 eq DBU, CH\textsubscript{2}Cl\textsubscript{2}, rt) led to a complex mixture of products.

To understand these difficulties, we elected to study the hydroxyl activation and cyclisation steps separately. Mesylation at low temperature in the presence of triethylamine proceeded efficiently (Scheme 2.3). Subsequent treatment with DBU gave a single cyclic product which displayed triplets in the \textsuperscript{1}H NMR spectrum for the methylene hydrogens (4.30 and 3.72 ppm) attached to two carbons at 65.0 and 39.2 ppm (by HMQC correlation). Comparison was made with the literature data for dimethyl 1,2-diazetidine-1,2-dicarboxylate which displayed a single resonance at 4.34 ppm for the ring hydrogens.\textsuperscript{51} Single crystal X-ray analysis of this product revealed
dihydrooxadiazine 24 as the product formed. This six-membered isomer arose from ring closure through the carbonyl oxygen of one of the Boc groups, rather than ring closure through nitrogen.

Several alternative reaction conditions were tested for this cyclisation but none of the desired diazetidine product was isolated (Table 2.1). Mitsunobu cyclisation of 22, also reported by Miao for 3-substituted substrates, again gave dihydrooxadiazine 24 as the sole product (64% yield).

In light of these results, it was decided to look more closely at Miao’s work. The majority of successful cyclisations reported involved substrates bearing Cbz groups on both nitrogens. Concerned that the nature of the N-protecting group may influence the
cyclisation outcome, we elected to prepare the corresponding substrate bearing Cbz groups.

Treatment of hydroxyethyl hydrazine with benzyl chloroformate under Schotten-Baumann conditions provided alcohol 25 in good yield (Scheme 2.4). However, reaction by Miao’s protocol again gave the corresponding dihydrooxadiazine 26. Spectroscopic data were analogous to that obtained for 24, and fully consistent with the six-membered ring product.

In light of these results, the published work was further scrutinised. A key example in this paper was the reported cyclisation of alcohol (R)-12a (Scheme 2.5). This substrate was remade by us in good yield as described by List. When subjected to Miao’s conditions, a single cyclic product 13a was formed in low yield. The material produced was spectroscopically identical to that reported in the original article. A further example, the cyclisation of alcohol (R)-12b, gave an analogous single cyclic product 13b in low yield. We were never able to reproduce the high yields in the original report for these examples.
Based on our earlier results (Schemes 2.2-2.4) we were very concerned about Miao’s structural assignments. Indeed only $^1$H NMR and chiral HPLC data had been reported for 13a. We reasoned that the products formed could well be dihydrooxadiazines rather than diazetidines (Figure 2.2).

![Figure 2.2](image)

Differentiating between these isomers was not straightforward. The ring methylene units for both the four- and six-membered rings would clearly be non-equivalent. Indeed, the $^1$H NMR spectrum of 13b displayed multiplets for the methine (4.38 ppm) and methylene (4.26 ppm) ring hydrogens.

The quaternary resonances in the carbon NMR spectra should have provided crucial evidence for the diazetidine structure. However, these signals were very weak and even with a large number of scans were not clearly observed. The significant difference in shift between the methine and methylene ring carbons (48.4 and 67.6 ppm respectively) did perhaps favour the six-membered ring product.

There have been detailed studies of the infrared spectra of some dihydrooxadiazines,$^{25,23}$ and data exist for some diazetidines.$^{26}$ Typically, dihydrooxadiazines exhibit three bands in the $\nu = 1800$-1600 cm$^{-1}$ region: one C=N vibration, and two C=O vibrations resulting from hindered rotation about the N−(C=O) bond. Two bands from inequivalent C=O stretching have been observed for diazetidines. Two bands at 1688 and 1659 cm$^{-1}$ were observed for 13b (Figure 2.3).
Fragmentation mass spectrometry (EI) of 13b and unsubstituted dihydrooxadiazine 24 (structure confirmed by X-ray analysis) both produced major ions corresponding to loss of one Cbz group. Furthermore, hydrogenation of 13b (H₂, Pd/C) gave a mixture of products, none of which we could assign to either the 1,2-diamine or the 1,2-amino alcohol.

Although taken together the evidence points to the dihydrooxadiazine isomer, this was not conclusive. Fortunately, analysis of a single crystal via X-ray diffraction confirmed our suspicions that indeed the dihydrooxadiazine was the product formed, contrary to the assignment made by Miao (Scheme 2.6). Although we have not tested all the examples reported in the original article, our results suggest that this method is likely only to produce dihydrooxadiazines. As well as discrediting the published work by Miao,¹⁶ our results also raise significant doubts surrounding the related patent based on this method for synthesising 1,2-diazetidines.³⁸
Scheme 2.6. X-ray crystal structure of dihydrooxadiazine (R)-28b.

Ring closure through oxygen in a 6-exo fashion appeared to be a much faster pathway than 4-exo ring closure through nitrogen irrespective of whether Boc or Cbz groups were used as the N-substituents. Although closure to each product occurs through different ends of the carboxamide group, these results are in keeping with the general observation that closures to six-membered rings are at least an order of magnitude faster than those to four-membered ones.\(^{75,76}\)

Undeterred by these difficulties, we explored other potential routes to the bis-Boc diazetidine. Several groups have routinely synthesised bis-Boc protected cyclic hydrazines via the reaction of bis-Boc hydrazine with the corresponding dibromoalkane under strongly basic or phase transfer conditions.\(^{77,78}\)

Scheme 2.7

An alternative approach based on this method was tested. Reaction of bis-Boc hydrazine with dibromoethane under weakly basic conditions (Na\(_2\)CO\(_3\), DMF, 100 °C, 1 h) returned only starting material (cf. Scheme 1.5).\(^{36}\) However, under more forcing phase
transfer conditions, in addition to the dihydrooxadiazine 24, we were delighted to observe two singlets in the crude $^1\text{H}$ NMR (4.12 and 1.48 ppm) resulting from 1,2-diazetidine 21 (Scheme 2.8). Column chromatography afforded this diazetidine as a stable, highly crystalline solid of which we were able to obtain an X-ray crystal structure. As far as we are aware, this is the first recorded X-ray structure of a simple 1,2-diazetidine.

![Scheme 2.8](image)

Scheme 2.8 Synthesis and X-ray crystal structure of 1,2-diazetidine 21.

Presumably, this reaction to form the diazetidine proceeds through the tethered bromide intermediate 29, which differs only from our previous cyclisation substrates in the character of the leaving group. Although no mono-alkylated intermediates were observed, we removed the potential complications of initial alkylation rate by studying the ring closure step itself. 2-Haloethyl hydrazines 30 (Cl), 31 (Br) and 32 (I) were prepared in one step from alcohol 22 using traditional methods. Tabulated cyclisation results are shown in Table 2.2.
Treatment under our best cyclisation conditions (8 eq. Cs₂CO₃, CH₃CN, rt) led to near quantitative ring closures (96-99%). For the mesylate, bromide and iodide substrates, these reactions were complete within 8 hours. In the case of chloride 30, several days were required for complete conversion.

Subjection of 21 and 24 together or individually to the reaction conditions [Cs₂CO₃ (7 eq), KI (1 eq) and NaHCO₃ (1 eq), CH₃CN, 72 h] did not lead to isomerisation or a change in product ratio as judged by ¹H NMR spectroscopy. If we assume the reaction is first order with respect to starting substrate, it is reasonable then to assume that the final ratio of products is a reflection of relative rate of ring closure. From Table 2.2, we see that preference for the diazetidine improves as the leaving halide becomes larger and more charge-diffuse. Using iodide as the leaving group has improved the rate of 4-exo closure to be at least competitive with the 6-exo closure. Fortunately, the products are easily separated by flash chromatography and ring closure of iodide 32 can be used to produce gram quantities of diazetidine 21.

To provide an explanation of these results we must consider the reacting species in detail. As no reaction occurs with solvent/base systems unable to remove the hydrazinyl hydrogen (see Appendix I), an initial deprotonation is likely occur resulting in the formation of an ambident anion, best represented as the delocalised structure 33 (Scheme 2.9).
Scheme 2.9

Ring closure of this species through oxygen (6-exo-tet) and nitrogen (4-exo-tet) are both stereoelectronically allowed. Why does this ambident anion react through oxygen when presented with a C−OSO$_2$Me bond but prefers to react through nitrogen when presented with a C−I bond?

An influence of leaving group on the regioselectivity of ambident anion alkylation was first noted in 1961 by Kornblum$^{81,82}$ and later expanded into the *Hard and Soft Acids and Bases* (HSAB) principle by Pearson.$^{83,84,85,86}$ The general principle that *Hard* nucleophiles prefer to react with *Hard* electrophiles (both highly charged species with low polarisability), and that *Soft* nucleophiles prefer to react with *Soft* electrophiles (both with low electronegativity and high polarisability) is an empirical observation that can be observed in our system.

Drago,$^{87}$ and then Klopman$^{88}$ rationalised the HSAB observations in physical terms, based on the charge-charge and molecular orbital interactions:

$$\Delta E = -q_rq_s \frac{\Gamma}{\varepsilon} + \Delta solv + \sum_{m \text{ occ}} \sum_{n \text{ unocc}} \left[ \frac{2(c_m^r)^2(c_n^s)^2\beta^2}{E_m^* - E_n^*} \right]$$  \[2\]

Klopman equation: For species r and s with frontier molecular orbitals m and n respectively, where: $\Delta E =$ energy change on interaction; $q =$ total initial charges including core electrons; $\Gamma =$ Coulomb repulsion term; $\varepsilon =$ local dielectric constant; $\Delta solv =$ solvation and desolvation change; $c =$ orbital coefficient; $E =$ energy of frontier molecular orbital and $\beta =$ perturbation energy.

Klopman described a favourable energy change, and therefore fast reaction, between two highly charged species; but also a fast reaction between two species where there is significant frontier molecular orbital interaction.
The oxygen centre of the ambident anion (low energy HOMO) reacting with the mesylate (high energy LUMO) receives little energy gain from molecular orbital interaction, and is controlled predominantly by charge interaction. At the other extreme, the nitrogen centre of the anion (high energy HOMO) and the iodide (low energy LUMO) are better matched to provide stabilisation via orbital interaction, in this case the final term contributes most to the interaction energy. These ideas may be illustrated by calculations on model carboxamide, mesylate and iodide systems.\textsuperscript{89-90,91,92,i}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.4.png}
\caption{Model of the carboxamide anion system: [CH$_3$C(O)NCH$_3$]$^-$.
\textsuperscript{i} Semi-empirical quantum mechanical calculations on model systems to illustrate these concepts. Depictions of HOMO and LUMO are shown alongside electrostatic potential mapped onto these orbitals. Molecular geometries and single point energies calculated using the MNDO-PM3 method [see references 89-92]. ArgusLab 4.0, Mark A. Thompson, Planaria Software LLC, Seattle, WA.} 
\end{figure}
In an attempt to improve the ratio of products in favour of the diazetidine even further, the influence of the base/solvent system on the cyclisation was investigated. A comprehensive range of conditions were tested (Appendix I). Selected results are highlighted in Table 2.3.
Studies on the alkylation of metal enolates have shown that the structure of the ambident ion-pair is important in controlling the site of alkylation.\textsuperscript{93,94} Reaction at carbon (\textit{Soft} terminus) is favoured by highly oxophilic counterions (\textit{e.g.} Li\textsuperscript{+}), in poorly coordinating solvents which allow this ion-pair (or aggregate) to be tightly bound. Increasing solvent polarity disrupts this arrangement and increases \textit{O}-alkylation. However, in the alkylation of metallated indoles and pyrroles (carbon \textit{Hard}, nitrogen \textit{Soft}), more azaphilic counterions (\textit{e.g.} K\textsuperscript{+}) favour alkylation at the nitrogen terminus.\textsuperscript{95} Also in this case, increasing solvent polarity favours \textit{N}-alkylation by aiding dissociation of the ion-pair.

Although one must be careful when comparing results across different solvent systems, our results tend to show that more oxophilic counter-ions promote reaction at the oxygen terminus. As the counter-ion becomes more charge diffuse, and hence more azaphilic, reaction through nitrogen is preferred.

Our best performing base, caesium carbonate, was studied under different solvent systems. This base performed equally well in the less polar, aprotic solvents acetone and

Table 2.3 \textsuperscript{a} Determined by \textsuperscript{1}H NMR analysis of the crude reaction mixture. Complete consumption of starting material unless otherwise stated; \textsuperscript{b} A ratio of 89:11 was observed for KOtBu in CH\textsubscript{3}CN. \textsuperscript{c} Reaction did not reach completion.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>solvent</th>
<th>conditions</th>
<th>6-exo (24) : 4-exo (21)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.4 eq</td>
<td>sec-BuLi</td>
<td>THF</td>
<td>−78 °C → rt, 3 h</td>
</tr>
<tr>
<td>2</td>
<td>1.2 eq</td>
<td>NaOtBu</td>
<td>THF</td>
<td>0 °C → rt, 3 h</td>
</tr>
<tr>
<td>3</td>
<td>1.7 eq</td>
<td>KOtBu</td>
<td>THF</td>
<td>0 °C → rt, 3 h</td>
</tr>
<tr>
<td>4</td>
<td>8 eq</td>
<td>TBD</td>
<td>CH\textsubscript{3}CN</td>
<td>rt, 48 h</td>
</tr>
<tr>
<td>5</td>
<td>8 eq</td>
<td>DBU</td>
<td>CH\textsubscript{3}CN</td>
<td>rt, 48 h</td>
</tr>
<tr>
<td>6</td>
<td>8 eq</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>CH\textsubscript{3}CN</td>
<td>rt, 8 h</td>
</tr>
<tr>
<td>7</td>
<td>8 eq</td>
<td>TMG</td>
<td>CH\textsubscript{3}CN</td>
<td>rt, 48 h</td>
</tr>
</tbody>
</table>
dichloromethane, although these reactions were much slower than in acetonitrile. Addition of water [solvent CH₃CN: H₂O (7:1)] prevented the reaction from occurring, presumably due to an effective lowering of the basicity of the system. Interestingly, addition of methanol [solvent CH₃CN: MeOH (7:1)] led to only a small loss of selectivity for the diazetidine, but on switching to pure methanol, no diazetidine product was observed, suggesting that disrupting the caesium ion-pair promotes reaction through oxygen.

The addition of silver salts or other Lewis acidic species to reactions of ambident anions with alkyl halides have been shown to alter alkylation regioselectivity. The silver ion has a strong affinity for halides, polarising the C–X bond and increasing the rate of the charge controlled reaction. Addition of silver nitrate to 32 alters completely the cyclisation manifold to give exclusively 34 arising from cyclisation with loss of the tert-butyl group.

![Scheme 2.10](image)

The use of iodide as a leaving group to encourage ring closures to diazetidines was extended to the synthesis of various 3-substituted-1,2-diazetidines. Alcohol 25 (Scheme 2.11) was prepared as described in Scheme 2.4 and alcohols 12a-c were prepared according to the procedure of List. Mesylation of 25 (MsCl, Et₃N, CH₂Cl₂, −78 °C to rt) gave essentially pure crude material as evidenced by ¹H NMR spectroscopy. A series of conditions were tested for the iodination step. The use of excess NaI in acetone gave poor yields. Excess lithium iodide in THF at reflux for 2.5 h gave an acceptable yield of iodide 35; which did not diminish significantly when the crude mesylate was used instead of purified material. Using wet lithium iodide or lithium iodide hydrate also gave substantially lower yields, as did prolonged heating of the reaction. Iodides 36a-c were
then produced via a one-pot mesylation and iodination sequence using these optimised conditions.

\[
\text{\[
\begin{array}{c}
\text{HO} \\
\text{R}
\end{array}
\]}
\text{\[
\begin{array}{c}
\text{N} \\
\text{NH\text{Cbz}}
\end{array}
\]}
\text{\[
\begin{array}{c}
\text{Cbz} \\
\text{R}
\end{array}
\]}
\text{\[
\begin{array}{c}
\text{Cbz} \\
\text{R}
\end{array}
\]}
\text{\[
\begin{array}{c}
\text{R} = \text{H} \\
\text{25} \rightarrow \text{35} (74%) \\
\text{Bn} \\
\text{12a} \rightarrow \text{36a} (65%) \\
\text{Pr} \\
\text{12b} \rightarrow \text{36b} (36%) \\
iPr \\
\text{12c} \rightarrow \text{36c} (10%)
\end{array}
\]}

Scheme 2.11

Ring closure of iodides 35 and 36a-c proceeded in 97-98% overall yields (Table 2.4). Although one may have expected any Thorpe-Ingold contribution to favour formation of the smaller ring size,\(^6\) increasing alkyl substitution at C-1 of the iodide increased slightly the preference for the six-membered ring. Separation of the products for the cyclisations of 36b and 36c via column chromatography proved challenging. In the case of entry 3, products were purified by preparative HPLC at GlaxoSmithKline, Stevenage.\(^i\)

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R</th>
<th>6-exo : 4-exo(^a)</th>
<th>yield(^b) 6-exo</th>
<th>yield(^b) 4-exo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>H</td>
<td>44 : 56</td>
<td>42% (37)</td>
<td>53% (38)</td>
</tr>
<tr>
<td>2</td>
<td>36b</td>
<td>Pr</td>
<td>59 : 41</td>
<td>n.d. (28b)</td>
<td>n.d. (13b)</td>
</tr>
<tr>
<td>3</td>
<td>36c</td>
<td>iPr</td>
<td>60 : 40</td>
<td>n.d. (28c)</td>
<td>n.d. (13c)</td>
</tr>
<tr>
<td>4</td>
<td>36a</td>
<td>Bn</td>
<td>65 : 35</td>
<td>64% (28a)</td>
<td>29% (13a)</td>
</tr>
</tbody>
</table>

Table 2.4 \(^a\) Determined by \(^1\)H NMR analysis of the crude reaction mixture; \(^b\) Yield after silica chromatography. n.d. = not determined.

\(^i\) Separation performed by Sean Hindley (GlaxoSmithKline).
In view of the low yields and difficulties encountered separating the products, we did not determine the optical purity of these compounds. However, we noted that the cyclised products did exhibit significant optical rotations.

We reasoned that the use of iodide as a leaving group may encourage other difficult ring closure reactions. To explore this idea further, the cyclisation of $\delta$-activated propylamines to $N$-Boc azetidine was studied. Aminopropanol 39 underwent facile Boc protection to give 40\textsuperscript{97} (Scheme 2.12). Conversion of the protected amine to mesylate 41,\textsuperscript{98} and direct iodination to 42\textsuperscript{99} using $I_2$/PPh$_3$/imidazole both proceeded well.

![Scheme 2.12](image)

A range of conditions were studied for the cyclisation of 42. The use of Cs$_2$CO$_3$ in acetonitrile returned only starting material, probably due to the decreased acidity of the carbamate in 41-42 cf. 32. Of the conditions tested, potassium tert-butoxide provided the most charge-diffuse counter-ion and cleanest conversion to products (Table 2.5).

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>X</th>
<th>6-exo (43) : 4-exo (44)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>OMs</td>
<td>100 : 0</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>I</td>
<td>90 : 9$^b$</td>
</tr>
</tbody>
</table>

Table 2.5 $^a$Determined by $^1$H NMR analysis of the crude reaction mixture. $^b$Other minor products were observed.
Dihydrooxazine 43 was unstable to silica gel chromatography and decomposition products hampered isolation of the azetidine. An authentic sample of 44 was prepared\textsuperscript{100} to ensure correct assignment of this material in the crude cyclisation \( ^1H \) NMR spectrum. Although the system appears less sensitive to a change in the leaving group, the preference for the 4-\textit{exo} product does still improve when switching to iodide. This system does not benefit from increased nucleophilicity at nitrogen \textit{via} the \( \alpha \)-effect which may have improved four-membered ring formation in the diazetidine/dihydrooxadiazine system.\textsuperscript{101,102,103} It is worthy of note, however, that the use of potassium \textit{tert}-butoxide in both systems produced very similar ratios of products (\textit{vide supra}).

Analysis of the recent literature has highlighted that competitive modes of ring closures are one of the difficulties still associated with the synthesis of 1,2-dicarboxyalkyl-1,2-diazetidines. Consideration of charge-charge and MO-MO interactions has provided a simple route to these 1,2-diazetidines. With established methods for the interconversion of leaving groups, it is hoped that consideration of these principles might be used to improve the efficiency of other difficult \( N \)-alkylation reactions.
II.II Synthesis of 1,2-Dialkyl-1,2-Diazetidines

Alongside our work on the synthesis of 1,2-dicarboxyalkyl-1,2-diazetidines, we were interested in the preparation of 1,2-diazetidines bearing benzylic groups on nitrogen including benzyl, p-methoxybenzyl and 2-naphthylmethyl (NAP) (Figure 2.7). In addition to the value of establishing a general synthetic approach to these molecules, such systems may act as precursors for the parent 1,2-diazetidine via established benzylic cleavage chemistry.

Our initial studies were directed toward the synthesis of 45. We turned to an approach based on two successive alkylation reactions of a 1,2-dialkylhydrazine with 1,2-dibromoethane, which was used by Hall and Bigard to produce a range of simple dialkyl-1,2-diazetidines in moderate to low yields (Scheme 1.5).

Condensation of two equivalents of benzaldehyde with hydrazine hydrate proceeded rapidly in acidified ethanol to produce 1,2-dibenzylidenehydrazine (48) in excellent yield (Scheme 2.13). Hydrogenation over Pd/C (1 atm) proceeded well in anhydrous ethyl acetate at room temperature to give 1,2-dibenzylhydrazine.

![Figure 2.7](image-url)
Like other dialkyl hydrazines,\textsuperscript{107} this material was found to be rather unstable and was used directly in the next reaction. On exposure to air for several hours, partial conversion to a more stable crystalline solid took place which we tentatively assign as 50 (Scheme 2.14). This activity could be reversed by hydrogenation, or prevented by storage of the hydrazine in the absence of air.

![Scheme 2.14](attachment:image.png)

**Scheme 2.14**

Reaction of 1,2-dibenzylhydrazine 49 with dibromoethane under the published conditions gave only a poor yield of 1,2-dibenzyl-1,2-diazetidine 45 (Table 2.6, entry 1).\textsuperscript{36} Optimisation of the bis-alkylation was conducted in a sealed tube and in a CEM Discover microwave to prevent loss of the electrophile at elevated temperatures, and allow careful control of reaction temperature. The reaction was found to proceed best at 100 °C in DMF with 3 equivalents of electrophile. Reaction in a sealed tube under traditional heating produced similar results to microwave heating (entry 6). The diazetidine was found to be stable to chromatography and was isolated as an oil which could be crystallized by cooling to −5 °C.
Table 2.6 $^a$ mw = microwave, st = sealed tube, traditional heating; $^b$ conversion determined by $^1$H NMR, n.d. = not determined.

Similar methodology was applied to the synthesis of 46 bearing PMB groups, which was produced in 49% overall yield from hydrazine via 51 and 52 (Scheme 2.15). This diazetidine was isolated as a highly crystalline solid, of which a single crystal X-ray structure was obtained.

Scheme 2.15 Synthesis and X-ray structure of 46.
When 2-naphthaldehyde was used in place of $p$-methoxybenzaldehyde in this sequence, 1,2-$bis$(2-naphthylmethyl)-1,2-diazetidine (47) (Figure 2.8) was obtained in approximately 34% overall yield from hydrazine. Purification of the hydrazone, hydrazine and diazetidine in this series was hampered by the insolubility of these compounds in organic solvents and these compounds could not be fully characterised. The NMR and ESMS data obtained for 47 were consistent with the expected diazetidine structure.

![Image](image1.png)

**Figure 2.8**

Through simple reaction modifications, the work of Hall and Bigard has been developed into a practical synthesis of 1,2-diazetidines bearing benzyl-type protection. Using commercially available starting materials, overall yields from hydrazine are in the range 34-57%, with only one chromatographic purification step needed. The structure of these novel 1,2-diazetidines is discussed in Chapter III.I.
II.III Synthesis of 1,2-Disulphonyl-1,2-Diazetidines

Our initial attempts at the synthesis of 1,2-diazetidines bearing carboxyalkyl groups on nitrogen were hindered by the participation of these groups in the ring closure. We wished to circumvent this problem by preparing \( N \)-sulphonyl diazetidines such as 53, 54 and 55 via similar alkylation chemistry (Figure 2.9). Again, no 1,2-diazetidines of this type are known. Sulphonamide groups have been shown to direct lithiation at the alpha-carbon of aziridines. In addition, the strongly electron withdrawing nature of these groups may enhance the reactivity of the diazetidine ring toward electrophiles, and is also expected to have a pronounced effect on the dynamics of the ring system.

![Figure 2.9](image)

The preparation of 1,2-\( \text{bis} \)(arylsulphonyl)hydrazines has been well documented. Our studies began with preparation of 1,2-\( \text{bis} \)(tosyl)hydrazine (56) via the two-step method reported by Bartmann.

![Scheme 2.16](image)

Treatment of this hydrazine with dibromoethane in DMF at 0 °C using Cs\(_2\)CO\(_3\) predominantly gave rise to elimination products. Use of the stronger base sodium hydride in DMF followed by the dropwise addition of dibromoethane gave diazetidine 53 in moderate yield (Scheme 2.17), which could be isolated by recrystallisation from
the crude reaction mixture and was identified by a sharp singlet for the methylene hydrogens at 3.66 ppm. This assignment was confirmed by X-ray crystallography.

\[
\begin{align*}
\text{Ts} & \quad \text{H} & \quad \text{H} & \quad \text{Ts} \\
\text{N} & \quad \text{N} & \quad \text{Ts} \\
\text{56} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \q
Consequently, an alternative route to these diazetidines was sought. It had been reported by Shyam that 2-hydroxyethyl hydrazine can be sulphonylated at both nitrogens and at oxygen concomitantly. This reaction was found to proceed well with several sulphonyl chlorides to give the *tris*-sulphonylated species 58-60.

![Scheme 2.17]

Treatment of tosylate 58 with NaH in DMF gave a disappointing 25% yield of diazetidine. We sought to determine if this unfavourable ring closure could be encouraged by consideration of the *Hard and Soft Acids and Bases* principle (Chapter II.I). The sulphonate esters were converted to the respective iodides with lithium iodide in THF at reflux (59→61 72%, 60→62 68%). We were pleased to observe greatly improved yields, suggesting that this concept can be expanded to ring closures to *N*-sulphonyl substituted diazetidines.

![Table 2.7](https://example.com/table2.7)

*Table 2.7* A poor mass balance was obtained. An alternative aqueous workup returned a poor mass balance. *No diazetidine was observed between 10 and 100% conversion when the reaction was performed in CD$_3$CN and monitored in situ by $^1$H NMR.*
A competing reaction which may account for the failure of the sulphonate esters to cyclise; which was originally proposed by Shyam to account for the antineoplastic activity of similar compounds\(^{110,111}\) is shown in Scheme 2.18. When the nitrogen anion and the leaving group are not suitably matched, the rate of cyclisation becomes slow and competing base induced decomposition may occur to give the highly electrophilic species \(63\), which may be captured by an ambient nucleophile. Although no such products were isolated, this pathway would account for the poor mass balance returned on the treatment of these sulphonate esters with base.

![Scheme 2.18](image)

The tert-butylsulphonyl (Bus) group\(^{112}\) has been shown to direct lithiation of aziridines.\(^{108}\) Efforts to prepare diazetidines bearing these protecting groups did not progress as we were unable to prepare 1,2-\(bis(\text{tert-butylsulphinyl})\)hydrazine (\(64\)) or the tris-sulphinylated \(65\) (Figure 2.11) under a variety of conditions. Attempts to synthesise \(64\) and \(65\) via use of iso-propylsulphonyl chloride followed by C-methylation with methyl iodide under basic conditions also failed.\(^{113}\)

![Figure 2.11](image)
Although only a few examples are discussed here, it is expected that a wider range of commercially available aryl- and alkylsulphonyl chlorides would be suitable for this chemistry. Consideration of the *Hard and Soft Acids and Bases* principle has provided highly efficient ring closures to these new *N,N*-disulphonyl-1,2-diazetidines. Solid-state structures of these molecules have also been determined and will be discussed in Chapter III.I.
II.IV Attempted Synthesis of 1,2-Diazetidine

Access to the parent 1,2-diazetidine molecule would provide valuable insight into the fundamental properties of this ring system, and would provide a useful entry point for the synthesis of other 1,2-diazetidine derivatives. Herein, we report two approaches to this molecule based upon: (i) cyclisation of 1,2-diaminoethane via N−N bond formation; and (ii) deprotection of N,N'-disubstituted diazetidines.

Through comparison with its structural analogues, 1,2-diazetidine might be expected to have a boiling point of ca. 85 °C and have good solubility in polar solvents. The molecule is expected to undergo rapid acylation/sulphonylation at nitrogen, and evidence for its formation could be readily sought by such derivitisation reactions.
II.IV.I Via N–N Bond Formation

When ammonia is treated with an equimolar amount of hypochlorite in alkaline aqueous solution, chloramine (NH₂Cl) is formed. This reagent was shown by Raschig to react with further quantities of ammonia to produce hydrazine.⁴⁰ N–N bond formation in this way forms the basis of hydrazine manufacture.¹¹⁴

\[
\text{NH}_3 + \text{NaOCl} \rightarrow \text{NH}_2\text{Cl} + \text{NaOH} \\
\text{NH}_2\text{Cl} + \text{NH}_3 \rightarrow \text{NH}_2\text{NH}_2 + \text{HCl} \tag{3}
\]

This process has been modified to yield the cyclic hydrazines 1,2-pyrazolidine and 1,2-diaziridine. The mechanism of these reactions is complex and is still debated today,¹¹⁵ although it is widely accepted that N-chloro derivatives are formed as early intermediates.

Chloramines are known to disproportionate, and poly-chlorinated organic amines, although normally stable substances, have been known to deflagrate or detonate on heating under ordinary pressure. For example, tetrachloroethylenediamine is a powerful explosive and its hazards have been well documented.¹¹⁶,¹¹⁷ Hence, our attempts to access the parent molecule via the mono-chlorinated derivative were undertaken with extreme care.

Prior to undertaking this work, we familiarized ourselves with this chemistry by repeating the synthesis of 1,2-pyrazolidine as reported by Lüttringhaus.⁶ 1,3-Diaminopropane was heated with sodium hypochlorite in the presence of sodium hydroxide, then the crude reaction mixture was divided and treated separately with di-tert-butyl dicarbonate and p-toluenesulphonyl chloride to give unsaturated pyrazolidines ⁶⁶ᵃ and ⁶⁶ᵇ, elimination products of the bis-protected pyrazolidines ⁶⁷ᵃ and ⁶⁷ᵇ (Scheme 2.10). These yields compare favourably with those reported by Lüttringhaus using benzenesulphonyl chloride (lit. 33%).
After demonstrating the validity of this method to access 1,2-pyrazolidines, our attention turned to 1,2-diazetidine (Scheme 2.21). When 1,2-diaminoethane was used under these conditions, treatment of the crude reaction mixture with di-tert-butyl dicarbonate gave diamine 68 but also significant quantities of 69. Treatment with p-toluenesulphonyl chloride gave similar results, as did the use of tert-butyl hypochlorite\(^{119}\) in place of commercial bleach. In each case, no diazetidine was observed.

If the two nitrogen atoms of the 1,3-diaminopropane are first linked by an aldehyde or ketone, formation of bicyclic pyrazolidine system 70 occurs in much better yield (Scheme 2.22). Indeed, diaziridines are routinely synthesised via this method.\(^{120}\) This chemistry worked well in our hands.\(^{121}\)
However, attempted formation of the analogous bicyclic diazetidine 71 using acetone in this way to encourage ring closure led only to a complex mixture of products with mass spectroscopy suggesting polymeric species (repeating unit $M_n = 14$).

Our attention turned to the double deprotection of $N,N'$-disubstituted 1,2-diazetidines to access the parent 1,2-diazetidine. Initially, we investigated the reductive cleavage of tosyl groups from 53 (Scheme 2.24). After treatment with 2 - 5 equivalents of sodium in liquid ammonia followed by evaporation of the solvent and addition of D$_2$O, NMR analysis of the crude reaction mixture gave a complex mixture of products none of which could be assigned to 1,2-diazetidine. Reducing the equivalents of sodium followed by an aqueous extraction produced equally poor results.

II.IV.II Via Deprotection of $N,N'$-Disubstituted-1,2-Diazetidines
As an alternative route, we considered deprotection of diazetidines bearing benzylic groups. \textit{bis}-Benzyl diazetidine 45 was found to be stable under standard hydrogenation conditions [H$_2$ (1 atm), Pd/C, MeOH]. No reaction occurred when Pd(OH)$_2$/C was used as an alternative catalyst. Using this latter system in the presence of one equivalent of triflic acid resulted in hydrogenolysis of the N−N bond rather than expected debenzylation. Diamine 72 was produced as the major product as suggested by $^1$H NMR and mass spectroscopy [$m/z = 241$ (MH$^+$)] (Scheme 2.25).

![Scheme 2.25](image)

We next considered methods for oxidative cleavage of protecting groups from diazetidines 46 and 47. Cerium(IV) ammonium nitrate (CAN)\textsuperscript{122} is a single electron oxidant commonly used for debenzylation of amines.\textsuperscript{123} Although cerium exhibits no NMR activity, NMR spectra of the crude reaction mixtures were too broad to provide useful information. Upon treatment with 4.2 equivalents of CAN, \textit{p}-methoxybenzaldehyde was formed rapidly as judged by tlc. Extraction with ethyl acetate returned a mixture of starting diazetidine and aldehyde in a 3:1 ratio as judged by $^1$H NMR spectroscopy (Scheme 2.26). The presence of \textit{p}-methoxybenzaldehyde was confirmed by derivatisation with 2,4-dinitrophenylhydrazine.\textsuperscript{124}

![Scheme 2.26](image)
Attempts to trap any deprotected 1,2-diazetidine by treatment of the crude reaction with benzyl chloroformate led to trace amounts of 73 as suggested by $^1$H NMR and ESMS (Figure 2.12). However, on scale up of the reaction, we were unable to isolate this species or confirm its formation.

![Figure 2.12](image)

In each experiment where an excess of CAN was used, recovery of starting diazetidine along with sub-stoichiometric quantities of free aldehyde suggested that the deprotected species were undergoing oxidative decomposition faster than further deprotection.

The strong oxidizing power of CAN [Ce$^{4+}$ → Ce$^{3+}$, $E^\circ = −1.42$ V; cf. $\frac{1}{2}$ Cl$_2$ → Cl$^-$, $E^\circ = −1.36$ V (standard hydrogen electrode)]$^{125}$ led us to investigate milder methods for this transformation. The 2-naphthylmethyl group$^{104,126}$ can be removed from tertiary amines and alcohols by the use of the milder oxidant 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)$^{127}$ On treatment of impure bis-(2-naphthylmethyl) diazetidine (47) (90% purity by $^1$H NMR) with this oxidant, significant amounts of 2-naphthaldehyde were formed, along with ring opened products as suggested by $^1$H NMR spectroscopy. Methoxybenzyl diazetidine 46 reacted more slowly with DDQ but with equally poor selectivity.

![Scheme 2.27](image)

Later studies on the functionalisation of bis-Boc diazetidine 21 revealed that the Boc group carbonyls were susceptible to nucleophilic attack (Chapter III.II.I). Treatment of
this diazetidine with lithium hydroxide in THF/water at room temperature for two weeks resulted in partial deprotection to what we tentatively assigned as 74 (Scheme 2.28), however, attempts to trap this species with pivaloyl chloride were unsuccessful.

![Scheme 2.28 Ratio observed by 1H NMR.]

Sodium methoxide was found to be a better reagent for this transformation. Addition of the diazetidine to sodium dissolved in d$_4$-methanol promoted faster deprotection (monitored by $^1$H NMR). Pieces of sodium were added until the starting diazetidine was completely consumed, then excess p-toluenesulphonyl chloride was added.

![Scheme 2.29]

$^1$H NMR spectroscopy of the crude reaction mixture indicated the presence of unsymmetrical diazetidine 75 alongside tosylamine$^{128}$ in a 2:3 ratio. These products were separated in low yield by preparative tlc and subsequent recrystallisation. Importantly, no evidence was seen for 1,2-bis(tosyl) diazetidine 53. The isolation of significant quantities of tosylamine suggests that, if formed, the parent 1,2-diazetidine is undergoing rapid decomposition to ammonia. Further studies are necessary to confirm this hypothesis.
To date, attempts to produce the parent 1,2-diazetidine have been unsuccessful and this remarkably simple heterocycle remains elusive. The isolation of ammonia derivatives in several of the attempted cyclisation and deprotection reactions may suggest that either 1,2-diazetidine is not stable under chlorinating or highly basic reaction conditions, or that alternative reaction pathways for bis-protected diazetidines exist.
II.V Synthesis of 3-Alkylidene-1,2-Diazetidines

Alongside our work on the preparation of simple 1,2-diazetidines, we wished to develop a synthetic route to 3-alkylidene-1,2-diazetidines such as 77 and 78.

![Figure 2.13](image.png)

This new class of 1,2-diazetidine bearing an exocyclic double bond may offer greater potential for functionalisation and elaboration of the diazetidine ring system via cross-coupling, cycloaddition, or simple addition reactions of the double bond to provide highly functionalised nitrogen containing heterocycles which may also serve as precursors for vicinal diamines. The recent application of palladium-catalysis to the synthesis of *trans*-substituted 1,2-diazetidines has highlighted the advantages in selectivity of a transition-metal catalysed route to such systems. Herein, we describe the development of a general synthetic route to 3-alkylidene-1,2-diazetidines utilising a highly efficient copper-catalysed ring closure.
In a series of recent reports, Li et al. highlighted the versatility of copper-catalysis for the synthesis of a range of four-membered carbocyclic and heterocyclic systems namely 79-82 starting from the appropriate vinyl halides.\textsuperscript{129,130,131,132}

![Scheme 2.30](image)

Importantly, the selectivity of this copper-catalysed system for the formation of four-membered rings was highlighted in competition experiments where a striking preference for the 4-\textit{exo} product was observed over 5-\textit{exo}, 6-\textit{exo}, 6-\textit{endo} cyclisation products.\textsuperscript{130}

![Scheme 2.31](image)

Based upon these observations, we wished to establish if a similar copper-catalysed method could be developed for cyclisations to 3-alkylidene-1,2-diazetidine 83, avoiding or minimising competitive formation of the 6-\textit{exo} product 84 (Scheme 2.32).
However, there was some evidence to suggest this route may be problematic. Li et al. showed that cyclisations to azetidines based on less acidic amines were not always fruitful. In particular, cyclisation to N-Boc substituted 2-methyleneazetidine 86 did not proceed well.\textsuperscript{133}

\begin{equation}
\begin{array}{c}
\text{Scheme 2.33 Ligand: Me}_2\text{NCH}_2\text{CO}_2\text{H.HCl.}
\end{array}
\end{equation}

However, there are reports of intermolecular copper catalysed vinylations onto bis-Boc-protected hydrazine under similar copper-catalysed conditions (for example, Scheme 2.34).\textsuperscript{134,135}

\begin{equation}
\begin{array}{c}
\text{Scheme 2.34}
\end{array}
\end{equation}

It may be in these cases that the greater acidity of the hydrazinyl protons facilitates these couplings. Based on this evidence, we began by pursuing methods for the synthesis of the hydrazine containing precursors such as 88 (Scheme 2.35). We proposed an
attractive route to these molecules involving the direct coupling of commercially available 2-bromoallyl alcohol with diethyl azodicarboxylate (DEAD).

![Scheme 2.35](image)

Reductive couplings of azodicarboxylates with aryl boronic acids\(^{136}\) and silyl enol ethers\(^{137}\) to yield mono-alkylated, diprotected hydrazines have been successful. Although protected hydrazines have been used with some success as nucleophiles in the Mitsunobu reaction,\(^{138,139}\) the direct reductive coupling of azodicarboxylates with alcohols has not been well studied. A handful of reports identify the hydrazine as a Mitsunobu reaction by-product,\(^{140}\) and the scope of this transformation has been explored but with limited success.\(^{141}\)

We proposed that in the absence of an external nucleophile, treatment of these alcohols with triphenylphosphine and an excess of azodicarboxylate would yield the hydrazine adduct. Under our first attempted conditions, the hydrazodicarboxylate derivative 88 of 2-bromoallyl alcohol was accessed in excellent yield (Scheme 2.36).

![Scheme 2.36](image)

We next focused on determining suitable ring closure conditions. Conditions that closely parallel those developed by Li for ring closures to \(\beta\)-lactams,\(^{132}\) were found to be effective in our system. Treatment of 88 with a sub-stoichiometric amount of copper(I) iodide in the presence of \(N,N'\)-dimethylethlyenediamine (DMEDA) and caesium
carbonate promoted ring closure to 3-methylene-1,2-diazetidine 89 as the only observable product in excellent yield.

Scheme 2.37

The diazetidine structure of 89 was suggested by the presence of two clearly observable quaternary resonances of the carboxyethyl groups in the $^{13}$C NMR spectrum at 160.0 and 154.7 ppm. A resonance at 57.1 ppm for the ring methylene unit (cf. 48.8 ppm in bis-Boc diazetidine 21) was also suggestive of the diazetidine ring structure.

Encouraged by this result, we sought to establish the generality of this new method. A range of suitable alcohols were prepared from commercially available starting materials. As an alternative to the expensive 2-bromoallyl alcohol, 90 was prepared in one step from propargyl alcohol using a mixture of TMSCl and NaI as reported by Ishii (Scheme 2.38).$^{142}$ Although the yield of this reaction is moderate, the reaction is easily scalable to produce gram quantities of 90. Dihalogenated alcohols such as $(E)$-91 could be used to test the relative propensity of other cyclisation manifolds. $(E)$-91 was prepared using I$_2$ activated by alumina as reported by Larson$^{143}$ in moderate yield.

Scheme 2.38

In addition, dibromides (Z)-92 and $(E)$-92 are readily accessible via selective bromination of ethyl propiolate$^{144}$ (Scheme 2.39), and have been shown by Rossi et al. to undergo efficient Negishi couplings of the terminal bromide,$^{145}$ presenting opportunity
for further functionalisation at this stage. This chemistry was tested by the synthesis of alcohol (Z)-94 through the coupling of (Z)-92 with phenylmagnesium bromide. The crude Negishi product (Z)-93 was reduced with DIBAL to aid separation from unreacted starting material, and furnish the desired alcohol (Z)-94. Selective iodo-chlorination as reported by Ogilvie also furnished (E)-95 as a single regioisomer in excellent yield which was subsequently reduced with DIBAL to give the desired alcohol in 49% yield.

Scheme 2.39

In addition, alcohols such as 90a are readily available in excellent overall yield from the corresponding α,β-unsaturated ketone via a selective halogenation with OXONE/HBr and subsequent Luche reduction. This alcohol would test the ability of the cyclisation chemistry to produce highly strained, bicyclic 1,2-diazetidine systems.

Scheme 2.40
Reductive coupling of these alcohols with a range of commercially available azodicarboxylates proceeded in good to excellent yields (Scheme 2.41). DEAD, di-tert-butyl azodicarboxylate and dibenzyl azodicarboxylate all performed well. Phenyl substituted (Z)-94 coupled with DEAD with retention of stereochemistry about the double bond as confirmed by nOe measurements, suggesting little contribution from the possible $S_N2'$ reaction pathway. This product was contaminated with 10% tetrakis-(ethoxycarbonyl)hydrazine as evidenced by NMR spectroscopy, which we were unable to remove by silica chromatography or distillation. This impurity however did not interfere with the subsequent copper-catalysed cyclisation.

Ring closures of 96-102 gave the 1,2-diazetidine as the only observable cyclic product (Scheme 2.42). When iodide 96 is used as the substrate, 89 is formed in comparable yield (99%) to the ring closure of the bromide (98%). The cyclisation
tolerates variation in the N-substituent as illustrated by the formation of Boc (77 and 107) and Cbz (78 and 106) derivatives. Secondary hydrazines cyclise to give highly strained diazabicyclo[4.2.0]octane systems 105 and 106 in near quantitative yields.

![Scheme 2.42](image)

Substitution of the alkene double bond was possible as established by the ring closure of gem-dimethyl substituted 100 to 3-isopropylidene-1,2-diazetidine 107. The structure of this product was confirmed by single crystal X-ray analysis (Figure 2.14). Moreover, phenyl substituted (Z)-99 cyclises to (Z)-108 through retention of configuration at the sp²-hybridised carbon, as evidenced by nOe measurements.
In each of the cyclisations reported above, and to the best of our knowledge in all literature examples of such copper-catalysed ring closures, the reaction proceeds to give exclusively the 4-expo cyclisation product. The relative propensity of competing cyclisation manifolds was explored using dihalogenated substrate (E)-103. This diiodide cyclised under mild conditions via a 5-endo closure to give 109 as the only discernible product by $^1$H NMR.

Scheme 2.43

HMBC and HMQC NMR correlation experiments confirmed the expected connectivity through the ring carbons at 60.2 (CH$_2$), 84.7 (C) and 132.7 ppm (CH), in full support of the dihydropyrazole structure 109. Further evidence was provided by efficient Suzuki coupling with phenyl boronic acid to give 111 resulting from isomerisation and elimination (Scheme 2.44).
Switching the halogen in the 5-position of the cyclisation substrate to chlorine improved the preference for the diazetidine product at the expense of the dihydropyrazole (Scheme 2.45). More forcing conditions were required to push this reaction to completion. Treatment under the milder conditions used to convert (E)-103 to 109 led to a similar ratio of products at 50% conversion.

Re-subjection of (E)-110 to 109 to the reaction conditions did not lead to a change in product ratio, suggesting the product distribution of the ring closure is kinetically controlled. A similar preference for I- over Cl- vinylation (ratio 5:1) has been observed under almost identical reaction conditions in the intermolecular vinylation of a β-lactam during the synthesis of chartelline alkaloids.\textsuperscript{150}
This suggests that the cyclisation outcome is determined by the affinity of copper for the carbon-halogen bond rather than a preference for the ring size formed. A suitable competition experiment involving substrate (E)-112 would add strength to this hypothesis, although practical routes to this substrate could not be conceived.

It is likely that the rate of insertion of the catalytic copper species into the carbon-halogen bond is more rapid in the case of iodine than of chlorine. Drawing further conclusions on the mechanism of this reaction based on the limited evidence gathered here may be presumptuous. Although our system is not ideal for studying the effect of the halogen in each position upon the outcome of the reaction, it is clear however that the 4-exo cyclisation mode is not fundamentally preferred in every case by the Cu(I) catalytic system as reported by Li et al in JACS.\textsuperscript{130}

In each of the examples presented above, ring closure through nitrogen was clearly preferred over closure through the carbamate oxygen. There are several examples in the literature where reaction at nitrogen is preferred over reaction at oxygen in
intermolecular vinylations by similar copper-catalysed systems.\textsuperscript{151,152,153,154} A preference for interaction with nitrogen can also be observed in the rates of exchange of free amine and hydroxide ligands with Cu(II) in aqueous solution. A plausible Cu(I) catalytic species within our system would be considered a \textit{softer} lewis acid under the \textit{Hard Soft Acids and Bases} principle, thus may display a greater preference for interaction with nitrogen if these principles apply.

There are several examples of copper-catalysed ring closures to larger ring size nitrogen heterocycles, although yields are slightly lower than for four-membered rings.\textsuperscript{155,156,157} It is likely therefore, considering the collected evidence that copper may display a \textit{fundamental} preference for reaction at nitrogen rather than a \textit{fundamental} preference for ring size formed.
II.VI Conclusions

The synthesis of a range of new simple 1,2-diazetidines and functionalised 3-alkylidene-1,2-diazetidines has been described. Our analysis of the recent literature has highlighted the difficulties associated with alkylative ring closures to 1,2-diazetidines. We have demonstrated that these problems can be overcome by matching the electronic character of the reacting centres (Scheme 2.47), and we have developed a simple route to 1,2-dicarboxylalkyl-1,2-diazetidines. This work was published in *Tetrahedron Letters* in 2010.\(^{158}\)

Moreover, these principles have been extended to the synthesis of 1,2-disulphonyl-1,2-diazetidines and have been shown to be crucial for the success of ring closures to these systems. In addition, a high yielding synthetic route to 1,2-dialkyl-1,2-diazetidines bearing \(N\)-benzyl substituents has been developed building upon the literature precedent.

Unfortunately, deprotection and chloramine mediated \(N\)–\(N\) ring closure strategies to the parent 1,2-diazetidine molecule were unsuccessful. These have failed either due to more favourable deprotection pathways of the \(bis\)-protected diazetidines studied, or due to the instability of the parent molecule under the conditions employed. This rather simple molecule remains elusive.
Finally, a general and high yielding synthetic route to 3-alkylidene-1,2-diazetidines has been developed in two steps from commercially available materials employing a highly efficient copper-catalysed ring closure.

The scope of this method for the synthesis of 1,2-diazetidines has been explored and the selectivity shown by Cu(I) to mediate such cyclisations has been rationalised as a preference for reactivity at nitrogen rather than a fundamental preference for ring size formed.

Scheme 2.48
Chapter III

Structure and Functionalisation of 1,2-Diazetidines
III Structure and Functionalisation of 1,2-Diazetidines

This chapter is focussed on the structure and functionalisation of the novel 1,2-diazetidines described in Chapter II. Spectroscopic and X-ray diffraction studies were undertaken with the aim of providing an insight into the nature of bonding in these systems and hence their reactivity. Subsequently, the general reactivity and functionalisation of bis-Boc diazetidine 21 via lithiation chemistry was explored. In addition, a detailed study of the transition-metal catalysed functionalisation of 3-alkylidene-1,2-diazetidines was undertaken. Finally, both saturated and 3-alkylidene-1,2-diazetidine systems were studied under reducing conditions to examine the potential of 1,2-diazetidines as precursors for the stereocontrolled synthesis of 1,2-diamines.
III.I Structure

The synthesised 1,2-diazetidines were found to be stable, highly crystalline solids. For example, 1,2-\textit{bis}(tosyl) diazetidine 53 was stable up to 200 °C as evidenced by thermogravimetric analysis (Appendix II). Collected physical and X-ray crystallographic data for six representative types of 1,2-diazetidine are presented in Table 3.1. In each of the symmetrical 1,2-diazetidines (21, 53, 46 and 55) the nitrogen atoms display significant pyramidal character, placing the substituents on opposite sides of the ring, in order to minimise the interaction energy between the two nitrogen lone pairs. This may also serve to minimise steric repulsion between the \textit{N}-substituents.

The N–N bonds of diazetidines 53 and (\textit{E}-131 were found to significantly longer than those in their acyclic hydrazine analogues. The N–N bond in 53 (1.475 Å) is longer than that of 1,2-\textit{bis}(tosyl)hydrazine (1.413 Å).\textsuperscript{159} Also, a significantly longer bond is observed in (\textit{E}-131 (1.4521 Å) cf. 1,2-diethylhydrazine-1,2-dicarboxylate (1.379 Å).\textsuperscript{160}

The extent of pyramidalisation at nitrogen in \textit{N}-carboxyalkyl diazetidines can be determined by quantifying the deviation of the amide unit from planarity. Amide twist angles ($\tau$) for 21, 107 and (\textit{E}-131 as defined by Winkler and Dunitz,\textsuperscript{161} and modified by Yamada,\textsuperscript{162} are shown in Table 3.1. A slight flattening of the nitrogen \textit{syn}- to the exocyclic double bond is clearly observed in (\textit{E}-131. This may be due to a stabilising effect brought about by (\textit{p}-\textit{p})\textsubscript{ex} conjugation with the exocyclic benzylidene unit, reducing the influence of this lone pair at nitrogen. Further evidence for this may be observed in a shortening of the diazetidine C–N bond adjacent to the exocyclic double bond (1.435 Å) compared to the other ring C–N bond (1.501 Å). However, in 107 no such flattening of the nitrogen \textit{syn}- to the exocyclic double bond is observed, suggesting a poorer stabilising contribution from the exocyclic isopropylidene unit.
Table 3.1 & Figure 3.1 Selected physical data and X-ray structures of 1,2-diazetidines. Ellipsoids drawn at 50% probability.
It is also useful to compare selected data from 21 against that of the acyclic analogue such as 1,2-diethylhydrazine-1,2-dicarboxylate (113) (Table 3.2). The nitrogen atoms within 21 are more highly pyramidal, displaying significant amide twist angles (τ). The infrared carbonyl stretch of the diazetidine is at higher frequency, and the N−(C=O) bond is longer than in 113, again suggesting poorer overlap of the nitrogen lone pair with the C=O group.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th></th>
<th>21</th>
<th>113</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N−N′)/Å</td>
<td>1.4505</td>
<td>1.379</td>
</tr>
<tr>
<td>(N−C_{c=0})/Å</td>
<td>1.3915</td>
<td>1.352</td>
</tr>
<tr>
<td>(C_{c=0})−N−N′−C_{c=0}′)/°</td>
<td>101.51</td>
<td>83.92</td>
</tr>
<tr>
<td>τ/°</td>
<td>33.4</td>
<td>4.3</td>
</tr>
<tr>
<td>IR (C=O)/cm⁻¹</td>
<td>1739</td>
<td>1712</td>
</tr>
<tr>
<td>NMR (C=O)/ppm</td>
<td>160.2</td>
<td>158.7</td>
</tr>
</tbody>
</table>

Table 3.2 *In CDCl₃.

The $^1$H NMR spectra of 21, 53 and 55 diazetidines bearing Boc, tosyl and methanesulphonyl groups respectively reveal that all ring hydrogens are chemically equivalent on the NMR timescale producing a single resonance. The solid-state structures show these diazetidine rings to be essentially flat with substituents in an anti-configuration. It is difficult to rationalise these observations without suggesting double inversion at nitrogen occurs rapidly on the NMR timescale (Scheme 3.1). Such a process is likely to occur (i) in a synchronous fashion; or alternatively (ii) as a consecutive process involving syn-21. It appears that the geometric constraints of the ring prevent both the nitrogens from adopting amide character in the resting conformation.
No changes were observed in the $^1$H NMR spectrum of bis-Boc diazetidine 21 over a wide range of temperatures (223-373 K), suggesting a low energy barrier ($< 30 \text{ kJ mol}^{-1}$) for this process. The electron withdrawing nature of these substituents may lower this energy barrier. The nitrogen atom must achieve planarity at the transition point to inversion, the lone pair adopting higher $p$-orbital character. Substituents that bring about $(p-p)_\pi$ conjugation (with the Boc C=O) or $(p-d)_\pi$ conjugation (with the sulphur atom) are known to stabilise the transition state and reduce the barrier to inversion.

bis-Methoxybenzyl diazetidine 46 exhibits a more interesting ring structure. The ring is significantly puckered [ring torsion (C-N-N'-C') = 20.27°]. The ambient temperature $^1$H NMR spectrum of 46 (Figure 3.2) displays two symmetrical, complex broad resonances for the geminal ring methylene hydrogens which change little on cooling to $-60 \degree \text{C}$ (in CDCl$_3$). Signals for the benzylic hydrogens coalesce on cooling to $-50 \degree \text{C}$.

Figure 3.2 $^1$H NMR (298 K) of 46 of the region 4.50-2.50 ppm.
Assuming that motion of the ring is un-coupled with the observed behaviour of the benzylic groups, an energy barrier of $\Delta G_c^\ddagger = 67.5$ kJ mol$^{-1}$ may be calculated from the coalescence of the ring hydrogen signals ($T_c = 73$ °C in $d_6$-DMSO, 600 MHz). This value is at least of the order of that calculated by Hall and Bigard for double nitrogen inversion in 1,2-dimethyl-1,2-diazetidine ($\Delta G_c^\ddagger = 68.6$ kJ mol$^{-1}$). Similar behaviour is observed in the NMR spectrum of bis-benzyl diazetidine. Coalescence of the ring methylene signals gives rise to an approximate energy barrier of $\Delta G_c^\ddagger = 65.9$ kJ mol$^{-1}$ ($T_c = 60$ °C, in $d_6$-DMSO, 400 MHz). The closeness of these values suggests a minimal contribution from inductive effects on the rate of inversion.

Taking into account the observations of Hall and Bigard, and our observations of fast nitrogen inversion in 21, 53 and 55, it seems reasonable to attribute the activation barriers observed in bis-benzyl and bis-methoxybenzyl diazetidines to double inversion at nitrogen (46 $\rightarrow$ ent-46, Scheme 3.2).

\textbf{Scheme 3.2} Illustration by Hall and Bigard,$^{36}$ where $R= \text{CH}_2(\text{C}_6\text{H}_4)\text{OMe}$.

---

$^1$ Energy barrier at the coalescence temperature ($T_c$) calculated using $\Delta G_c^\ddagger = 1.914 \times 10^{-2} T_c[10.319 + \log_{10}(T_c/k)]$ using the approximation $k = \pi \Delta v / \sqrt{2}$ where $\Delta v$ is the signal separation at slow exchange. The uncertainty presented in the measurement of $\Delta v$ gives rise to an uncertainty in $\Delta G_c^\ddagger$ of $\pm 2.3$ kJ mol$^{-1}$. 
Our observations on the structure of *bis*-methoxybenzyl diazetidine compare well with the previous studies of 1,2-dimethyl-1,2-diazetidine.⁴⁴,⁴⁵ In addition, comparable energy barriers to nitrogen inversion in the bicyclic diazetidines 114-116 (Figure 3.3) have been reported.⁵⁰ The barrier to inversion for diazetidine 114 bearing methyl groups on nitrogen (49.4 kJ mol⁻¹) was similar to the barrier for 115 bearing benzyl groups (52.3 kJ mol⁻¹) and to 116 bearing *p*-methoxybenzyl substitution (51.0 kJ mol⁻¹).

![Figure 3.3](image)

Our general observation that electron withdrawing *N*-substituents such as Boc and tosyl groups give rise to a lower barrier to nitrogen inversion than *N*-alkyl substituents has also been observed experimentally in aziridines,¹⁶⁵ azetidines,¹⁶⁶ and in *semi-empirical* calculations on diaziridines.¹⁶⁷

The significant ring distortion and long N–N bond observed in 46 suggest the difficulty the ring has in accommodating the opposing nitrogen lone pairs. As a result, these lone pairs are likely to exhibit enhanced basic character. In addition, the nature of the bonding observed in *bis*-Boc diazetidine is likely to have profound implications for the reactivity of this system.
III.II Functionalisaton of 1,2-Diazetidines

The reactivity of 1,2-diazetidines has received little attention. Initial studies on simple dialkyl 1,2-diazetidines were conducted by Hall and Bigard. These species were found to be remarkably inert. 1,2-Diethyl-1,2-diazetidine was found to be unreactive toward to sodium amide at room temperature, and neither butyllithium nor concentrated hydrochloric acid, nor 98% sulphuric acid had an observable effect on 1,2-di-iso-propyl-1,2-diazetidine.

The electron withdrawing nature of the Boc, tosyl and methanesulphonyl groups in diazetidines 21, 53 and 55 could be expected to increase the reactivity of the ring; for example, toward ring opening reactions with nucleophiles. The poor solubility of N-sulphonyl diazetidines 53 and 55 in common organic solvents led us to investigate extensively the reactivity of bis-Boc diazetidine 21 under a range of conditions, of which the significant results are highlighted here.

Interestingly, 21 was found to be inert to excess trifluoroacetic acid at room temperature in chloroform. On warming to 70 °C for 1 hour, partial conversion to another species was observed but this could not be identified, or isolated upon aqueous workup. Treatment with hydrogen chloride in ether promoted ring opening to the chloride 30, in addition to unreacted starting material.

![Scheme 3.3](image)

However, 21 showed no reactivity toward the potent electrophile ethyl triflate at room temperature in either acetonitrile or DMF, suggesting that the nitrogen lone pairs are partially deactivated by the Boc groups.
The Boc groups have been shown to be reactive toward strong oxygen based nucleophiles such as hydroxide or methoxide under mild conditions (Chapter II.IV.II). However 21 only reacted with hydrazine under very forcing conditions. No reaction was observed at 120 °C for 15 minutes using excess hydrazine under microwave irradiation in acetonitrile. When the temperature was raised to 180 °C a complex mixture of decomposition products was obtained.

The ring stability of 21 under these conditions encouraged our studies on the functionalisation of 21 via C–H activation chemistry.

III.II.I Lithiation Chemistry

Our aim was to prepare functionalised 1,2-diazetidines via lithiation chemistry of bis-Boc diazetidine 21 (Scheme 3.4). By analogy to the reactivity of N-Boc pyrrolidine and N-(triphenylacetyl)azetidine with organolithium reagents, we hoped that treatment of diazetidine 21 with sec-butyllithium would provide the stabilised organolithium 117, which would undergo substitution with carbon based electrophiles with either retention or inversion of configuration. Our studies focused on demonstrating the formation of 117 by quenching such lithiated species with highly reactive electrophiles (D+ or Me3Si+).

![Scheme 3.4](image)

Diazetidine 21 was found to be inert to treatment with LDA or LiHMDS in the presence of Me3SiCl as an in situ quench. Conditions that in our hands promoted deuteration of pyrrolidine 118 [83% yield, 92 (±2)% D] (Figure 3.4), and complete deuteration of 119 (86% yield) using sec-butyllithium were tested on diazetidine 21.
(Table 3.3, entries 1-2). Conditions reported by Seebach to promote lithiation and derivatisation of azetidine 120 using tert-butyllithium (62% yield) were also tested using d$_4$-methanol as a quench (entry 3). In each case, starting material was returned as the major product (>70% by $^1$H NMR) along with several decomposition products in small amounts.

![Figure 3.4](image)

LCMS (UV/TIC) analysis of the crude material showed a similar product distribution in each case. By correlation of these results with $^1$H NMR data, we were able to identify two products likely to contain the diazetidine ring. The first, 121 was a polar, unsymmetrical molecule (LCMS $t_r = 0.35$ min, $m/z = 159$ [M+H$^+$]). The other, 122 was of similar polarity to the starting diazetidine (LCMS $t_r = 0.88$ min, $m/z = 343$ [M+H$^+$]) with a more complex structure by $^1$H NMR.

Of a range of conditions tested, no lithiation of our diazetidine was observed, and these two decomposition products were formed in small amounts in each case. In order to determine the identity of 121 and 122, conditions were sought to push the reaction toward these products (Table 3.3).
<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>solvent, ligand&lt;sup&gt;a&lt;/sup&gt;</th>
<th>temperature (time)</th>
<th>SM : 121 : 122&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.3 eq sec-BuLi</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O, (−)-sparteine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−78 °C (2 h)</td>
<td>78 : 19 : 3</td>
</tr>
<tr>
<td>2</td>
<td>1.9 eq sec-BuLi</td>
<td>THF</td>
<td>−78 °C (6 h)</td>
<td>84 : 7 : 9</td>
</tr>
<tr>
<td>3</td>
<td>1.2 eq tert-BuLi</td>
<td>THF</td>
<td>−78 °C → −40 °C (2 h) → −15 °C (10 min)</td>
<td>84 : 10 : 6</td>
</tr>
<tr>
<td>4</td>
<td>1.0 eq sec-BuLi</td>
<td>THF</td>
<td>−78 °C (3 h)</td>
<td>84 : 16 : 0</td>
</tr>
<tr>
<td>5</td>
<td>1.5 eq sec-BuLi</td>
<td>THF</td>
<td>−78 → −40 °C (2 h)</td>
<td>62 : 34 : 4</td>
</tr>
<tr>
<td>6</td>
<td>3.1 eq sec-BuLi</td>
<td>THF</td>
<td>−78 °C (3 h)</td>
<td>30 : 67 : 3</td>
</tr>
<tr>
<td>7</td>
<td>4.0 eq sec-BuLi</td>
<td>THF</td>
<td>−78 °C (3 h)</td>
<td>14 : 81 : 5</td>
</tr>
<tr>
<td>8</td>
<td>1.2 eq sec-BuLi</td>
<td>THF, TMEDA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>−78 °C (1 h)</td>
<td>9 : 88 : 3</td>
</tr>
<tr>
<td>9</td>
<td>1.2 eq sec-BuLi</td>
<td>THF, HMPA&lt;sup&gt;d&lt;/sup&gt;</td>
<td>−78 °C (3 h)</td>
<td>83 : 10 : 6</td>
</tr>
<tr>
<td>10</td>
<td>1.2 eq sec-BuLi</td>
<td>THF, HMPA&lt;sup&gt;d&lt;/sup&gt;</td>
<td>−78 → −40 °C (3 h)</td>
<td>67 : 14 : 19</td>
</tr>
</tbody>
</table>

Table 3.3: Ligand was added to the reaction prior to addition of the butyllithium. 1.3 eq (−)-sparteine. 1.3 eq. 2.0 eq. Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture in the region 4.10-4.40 ppm.

Treatment with a stoichiometric amount of sec-butyllithium provided only minor amounts of 121 (entry 4). Increasing the reaction temperature (entry 5), or amount of butyllithium (entries 6-7) promoted formation of 121. A small amount of this material was isolated by column chromatography. The <sup>1</sup>H NMR spectrum displayed a triplet at 4.32 ppm (<i>J</i> = 8.0 Hz), and a broad singlet at 3.76 ppm for the ring hydrogens. HRMS and <sup>1</sup>H NMR data were consistent with structure 121 shown in Figure 3.5. This can conceivably result from attack of sec-butyllithium on the C=O group. In addition, <sup>1</sup>H NMR data were similar to that for 74 observed during the deprotection of 21 with sodium methoxide (Chapter II.IV.II). As might be expected for structure 121, this species decomposed quickly on isolation which prevented more complete characterisation.
Tetramethylethylenediamine (TMEDA) was found to be an effective additive for increasing the proportion of $121$ formed. Other polar additives which have a strong affinity for lithium were tested. In THF:DMPU (1:1 v/v) no observable reaction occurred. However the addition of two equivalents of HMPA combined with an increase in temperature was found to promote formation of $122$ at the expense of $121$ (Table 3.3, entry 10).

Isolating a small amount of $122$ by chromatography we were able to deduce its structure by HRMS, $^1$H, $^{13}$C and $^{15}$N NMR spectroscopy (Figure 3.6). Two slightly inequivalent resonances for the ring methylene units were observed in the $^1$H NMR [4.30 (4H, t, $J = 2.1$ Hz), 4.23 (4H, t, $J = 2.1$ Hz)] and $^{13}$C NMR spectra [50.6 (2CH$_2$) and 50.1 (2CH$_2$)]. In addition, the presence of a quaternary $^{13}$C NMR resonance at 167.1 ppm for the linking C=O group; and two magnetic environments for the nitrogen atoms at 135.4 and 133.3 ppm in the $^{15}$H HMBC spectrum (Appendix III) were entirely consistent with this structure, which may result from attack of lithiated $121$ on bis-Boc diazetidine $21$.

The formation of $121$ and $122$ can be rationalised by comparing the IR carbonyl stretch of our diazetidine to those heterocycles that have been shown to undergo successful lithiation (Figure 3.7). We see that the diazetidine Boc carbonyl absorbs at a higher frequency, more typical of a saturated ester, suggesting minimal
donation from the diazetidine lone pairs into the C=O bonds. As a consequence it is more susceptible to nucleophilic attack at the C=O than the protecting groups of these other heterocycles that successfully undergo lithiation.

\[
\text{IR (C=O)/cm}^{-1} \quad 1739 \quad 1702 \quad 1698 \quad 1633
\]

**Figure 3.7**

A plausible decomposition pathway of *bis*-Boc diazetidine under our lithiation conditions is proposed (Scheme 3.5). Evidence suggests that sec-butyllithium exists as a tetrameric structure in cyclohexane. The carbonyl of the Boc group is likely to coordinate to such a lithium species in solution, further polarising the C=O bond, and promoting nucleophilic attack of the sec-butyl anion. Substitution at the carbonyl would liberate the tert-butyl 1,2-diazetidine-1-carboxylate anion (Li-121). The presence of HMPA appears to increase the reactivity of this species, possibly through a weakening of the diazetidine–lithium bond by electron donation onto lithium from the phosphoramidate. Attack of this species on an equivalent of unreacted diazetidine would lead to the formation of 122.
The lithiation chemistry of other diazetidines was explored briefly with no success. *bis*-Benzyl diazetidine was found to be inert to *sec*-butyllithium in THF at $-78 \, ^\circ\text{C}$ (2 h). *bis*-Tosyl diazetidine 53 was found to be poorly soluble in THF at room temperature, and only sparingly soluble in diethyl ether at $-78 \, ^\circ\text{C}$. Treatment with *sec*-butyllithium returned only starting diazetidine. Performing the reaction in Et$_2$O:DMPU (10:1) to improve solubility of this diazetidine had no effect on the reaction outcome.

In addition several attempts were made at lithiation of *bis*-Boc methylenediazetidine 77 (Figure 3.8). The presence of the exocyclic double bond could be expected to increase the acidity of the ring methylene C–H bonds as is observed for 2-methyleneaziridines.$^{69,172}$

**Figure 3.8**
Sec-BuLi, sec-BuLi/TMEDA, and tert-BuLi were tested for the lithiation of 77 under the conditions described in entries 3, 5 and 8 of Table 3.3. In the crude reaction material, no deuterated diazetidine was observed. A complex mixture of 77 and multiple decomposition products were seen in each case. These results prompted us to abandon attempts at lithiation of 1,2-diazetidines in favour of exploration of cross-coupling chemistry of the double bond of diazetine 77.

After this work had been completed, Hodgson et al. published the successful lithiation of N-thiopivaloylazetidine (123, Scheme 3.6) in Angewandte Chemie.\textsuperscript{173} Under conditions of sec-butyllithium, TMEDA in THF at \(-78 \,^\circ \text{C}\) they demonstrated complete deuteration after 30 minutes and were able to obtain modest levels of enantioselectivity with (\(\sim\))-sparteine and other diamine ligands. The thiocarbonyl was shown to be inert to nucleophilic attack, although no rationale was offered for this choice of directing group.

A logical extension of this work may be to consider lithiation of thiopivaloyl diazetidine 124 (Figure 3.9). However, the geometric constraints of the ring make it unlikely that both nitrogen lone pairs will be sufficiently delocalised into the thioamide units to prevent any nucleophilic attack on the C=S group. The problems faced in the lithiation of diazetidines appear to result from the interactions of the adjacent nitrogen lone pairs. A plausible solution would be to inductively remove electron density from one nitrogen in order to encourage at least partial thioamide character at the other, as may be the case, for example, in diazetidine 125, which might be accessed via the alkylative ring closure chemistry described herein.
Figure 3.9
Although our attempts at lithiation of simple 1,2-diazetidines met with no success, we expected that the exocyclic double bond of 3-methylene-1,2-diazetidines could be used to functionalise these readily available 1,2-diazetidines into a range of nitrogen containing molecules (Scheme 3.7). For example, (i) palladium-catalysed Heck couplings with aryl or alkenyl halides;\textsuperscript{174,175} (ii) cross-metathesis with simple olefins; (iii) cycloaddition; or (iv) simple additions to the double bond could provide systems which have the potential for reduction to functionalised saturated 1,2-diazetidines such as \textbf{126}, or further reduction to vicinal diamines (\textbf{127}).

\textbf{Scheme 3.7}
III.III.I Cross-coupling chemistry

The introduction of aryl substituents onto the double bond by cross-coupling chemistry would provide a complementary route to the copper-catalysed ring closure of substrates already bearing substituents on the alkene terminus (Scheme 2.42). We began by examining the palladium-catalysed coupling of bis-Boc methylenediazetidine (77) with phenyl iodide (Table 3.4, entry 1). Jeffery reported that the combination of a tetraalkylammonium salt and a poorly soluble base can accelerate Heck reactions. However, under these conditions, no reaction occurred (entry 2). Replacing the base with dicyclohexylmethylamine and lowering the reaction temperature (entry 4) gave Heck product (E)-128 as the only observable diastereomer in the crude reaction mixture, albeit in poor yield.

![Diagram of the reaction](https://via.placeholder.com/150)

Table 3.4

<table>
<thead>
<tr>
<th>entry</th>
<th>PhX</th>
<th>base</th>
<th>catalyst</th>
<th>solvent</th>
<th>T, t</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhI</td>
<td>Cs₂CO₃</td>
<td>Pd(OAc)₂, PPh₃</td>
<td>CH₃CN</td>
<td>reflux, 16 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>PhI</td>
<td>Cs₂CO₃</td>
<td>Pd(OAc)₂, Bu₄NCl</td>
<td>DMAc</td>
<td>100 °C, 16 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>PhI</td>
<td>Cy₂NMe</td>
<td>Pd(OAc)₂, Bu₄NCl</td>
<td>DMAc</td>
<td>100 °C, 16 h</td>
<td>trace 128</td>
</tr>
<tr>
<td>4</td>
<td>PhI</td>
<td>Cy₂NMe</td>
<td>Pd(OAc)₂, Bu₄NCl</td>
<td>DMAc</td>
<td>80 °C, 48 h</td>
<td>23% 128&lt;sup&gt;g,h&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>PhBr</td>
<td>Cy₂NMe</td>
<td>Pd₂(dba)₃, [P(t-Bu)₃]BF₄&lt;sup&gt;d&lt;/sup&gt;</td>
<td>dioxane</td>
<td>80 °C, 16 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>PhBr</td>
<td>Cy₂NMe</td>
<td>Pd₂(dba)₃, [P(t-Bu)₃]BF₄&lt;sup&gt;d&lt;/sup&gt;</td>
<td>dioxane</td>
<td>80 °C, 16 h</td>
<td>trace 128</td>
</tr>
</tbody>
</table>

Table 3.4<sup>a</sup>1.5 eq PhX. <sup>b</sup>1.5 eq base. <sup>c</sup>5 mol % Pd. <sup>d</sup>15 mol % PR₃. <sup>e</sup>1 eq Bu₄NCl. <sup>f</sup>solvent 0.18-0.20 M. <sup>g</sup>Isolated yield after column chromatography; <sup>h</sup>25% starting material was recovered.

The electron rich and bulky phosphane P(t-Bu)₃ has been shown to form extremely active palladium catalyst systems. However, for the formation of 128, use of this phosphane directly or from its more stable tetrafluoroborate salt, was not fruitful (entries 6, 7).
In further studies, when silver ions were added to these reactions in the form of silver nitrate (1.5-2.0 equivalents), cleaner transformations to product were observed, but in each case the mass balance of the crude product mixture was poor.

The stereochemistry of (E)-128 was confirmed by nOe measurements. The high degree of diastereoselectivity (crude dr >95:5) observed in this transformation can be rationalized through consideration of the presumed organopalladium intermediate prior to syn-elimination of the β-hydride (Scheme 3.8). Assuming that (Z)- and (E)-128 are produced via 129 and 130 respectively, which differ only in the conformation around the C–C single bond, then one can account for the preferred formation of (E)-128 by suggesting a lower energy for the transition state from 130, where non-bonded interactions between the Ph and CO₂t-Bu groups are minimised.

Scheme 3.8

In order to improve the yield of this transformation, we investigated the coupling of the less sterically encumbered methylenediazetidine 89 bearing N-carboxyethyl substituents. When 89 was treated under our best conditions (Scheme 3.9), (E)-108 was formed in much higher yield and in half the time required to form (E)-128, and a small amount of (Z)-108 was observed in the crude reaction mixture (crude dr = 95:5). The identity of (Z)-108 was readily assigned by comparison to the same product obtained previously by ring closure (see Scheme 2.42), and the identity of (E)-108 was confirmed by single crystal X-ray diffraction. Since (Z)-108 can be accessed in excellent yield via

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copper-catalysed cyclisation chemistry; Heck coupling in this way provides a complementary route to these two stereoisomers.

Scheme 3.9 Heck coupling of 89 and X-ray structure of (E)-108.

\[ \begin{align*}
\text{EtO}_2\text{C} & \quad \text{Pd(OAc)}_2, \text{PhI} \\
\text{89} & \quad \text{Cy}_2\text{NMe}, \text{Bu}_4\text{NCl} \\
& \text{DMAc, 80°C, 24 h} \\
& 46\% \\
& (\text{crude dr} = 95:5)
\end{align*} \]

\[ \begin{align*}
\text{EtO}_2\text{C} & \quad \text{Pd(OAc)}_2, \text{ArI} \\
\text{89} & \quad \text{Cy}_2\text{NMe}, \text{Bu}_4\text{NCl} \\
& \text{DMAc, 80°C, 24 h} \\
& 40\% \\
& (\text{crude dr} = 95:5)
\end{align*} \]

Scheme 3.10

\( p \)-Methoxyphenyl iodide was also shown to couple with 89 to give the (E)-108 in 40% yield (Scheme 3.10). The use of other electrophiles in this chemistry was not investigated due to time constraints.

Although 3-alkyl-1,2-diazetidines have been shown to be stable to palladium-catalysed cross coupling conditions,\(^{17}\) it is notable that the long N–N bond of these highly strained 3-methylene-1,2-diazetidines does not undergo oxidative insertion by the Pd catalyst. Though the yields of these reactions are relatively modest, Heck couplings with the less sterically hindered \( N \)-carboxymethyl substituted diazetidine 132 (Figure 3.10) would be expected to give further improvements in yield at the expense of stereocontrol. Time constraints prevented exploration of this chemistry, however 132 should be readily accessible \textit{via} the same methodology used to provide 89 (Chapter II.V).
As an alternative approach to 1,2-diazetidines bearing substituents on the alkene terminus, several attempts were made at the cross-metathesis of bis-Boc methylenediazetidine 77 and 1-octene\textsuperscript{184} with Grubbs first and second generation catalysts.\textsuperscript{185,186} Under conditions which promoted the metathesis of \(\alpha\)-methylene-\(\beta\)-lactams\textsuperscript{187} and 3-methyleneoxetan-2-ones\textsuperscript{188} with a range of alkenes, no promising reactivity of 77 was observed. When coupling of 77 with 1-octene was attempted using Grubbs I catalyst (Scheme 3.11), instead of the expected alkylidenediazetidine product, octene homo-dimers were observed in the crude reaction material by \(^1\)H NMR spectroscopy. Although this reaction did not lead to the desired products, these observations at least suggest that 77 does not denature Grubbs I catalyst.

![Scheme 3.11](image)

Ready access to halogen substituted methylenediazetidine (\(E\))-110 invited attempts at functionalisation via Negishi and Suzuki\textsuperscript{189} type couplings (Scheme 3.12). Efficient catalytic systems for the coupling of vinyl chlorides have only recently been developed, employing as a ligand the bulky phosphane \(P(t-Bu)_3\).\textsuperscript{181,180} Attempted reaction of (\(E\))-110 under these conditions failed presumably due in part to the strength of the C–Cl bond.
However, diazetidines \((Z)-133\) and \((E)-133\) (Figure 3.11) should be readily available in moderate yield \textit{via} ring closure of the appropriate dibromide (from alcohols \((Z)-92\) and \((E)-92\), Scheme 2.39) and could be expected to be more suitable for Suzuki coupling reactions with the possibility of retention of stereochemistry about the double bond.
III.III.II  Addition Chemistry

To further explore the reactivity of the methylenediazetidine double bond, we examined simple addition chemistry under epoxidation and cyclopropanation conditions. Treatment of bis-Cbz methylenediazetidine 78 with excess mCPBA resulted in the formation of a single 1:1 adduct in moderate yield, presumably via epoxide 135, followed by ring opening at the $\alpha$- or $\beta$-carbon to give either 134$\alpha$ or 134$\beta$ respectively.

![Scheme 3.13](image)

$^1$H and $^{13}$C NMR spectra were broad as a result of nitrogen inversion in the diazetidine ring, and the product could not be conclusively assigned to structure 134$\alpha$ or 134$\beta$. A methylene resonance in the $^1$H NMR spectrum at 5.01-4.82 ppm (2H, m) correlating with a carbon at 67.3 ppm in the $^{13}$C NMR spectrum by HMQC may be more suggestive of structure 134$\beta$, resulting from ring opening at the least hindered carbon of the epoxide by $m$-chlorobenzoic acid, however, ring opening at the $\alpha$-carbon might be expected on the basis of a stepwise mechanism. The use of a less nucleophilic and less acidic epoxidising agent such as dimethyldioxirane (DMDO) may allow isolation of epoxide 135.

On attempting Simmons-Smith cyclopropanation of the double bond with 5 equivalents of Et$_2$Zn and CH$_2$I$_2$, imidazolidine 136 was isolated in moderate yield, from ring expansion of the diazetidine by insertion into the N-N bond, and concomitant
cyclopropanation of the exocyclic double bond (Scheme 3.14). When 10 eq of Et₂Zn and CH₂I₂ were used, 136 was produced in comparable yield (25%). In both cases, no products resulting from a single addition were isolated.

Scheme 3.14

To our knowledge there is just one previous report of such a ring expansion via carbenoid insertion into an N–N bond. When Taylor and Davies attempted the synthesis of aza-β-lactam 139, treatment of 137 with rhodium(II) acetate furnished the insertion product 138.¹⁹²

Scheme 3.15

Unfortunately time constraints prevented further exploration of this reactivity. By reducing the equivalents of carbenoid present, determining whether ring expansion or cyclopropanation is the faster process would give valuable insight into the potential of these diazetidines to undergo preparatively useful N–N insertion reactions.
III.IV Reduction Chemistry

To determine the scope of simple and functionalised diazetidines to act as precursors for vicinal amines, the reactivity of a range of diazetidines under reducing conditions was explored. There have been virtually no previous studies on the reduction of 1,2-diazetidines. 1,2-Di-iso-propyl-1,2-diazetidine (11c) was reported by Hall and Bigard to be unreactive towards hydrogenation (3.4 atm) over palladium on carbon.36

![Figure 3.12 Simple 1,2-diazetidines studied under reducing conditions.](image)

In our hands, bis-Boc diazetidine 21 was also found to be similarly inert to hydrogenation under 1 atm H₂ with Pd/C (100 wt %) in methanol for 16 hours. In addition, 21 also appeared inert towards an excess of BH₃·THF in THF. bis-Tosyl diazetidine 53 was insoluble in alcoholic solvents but found to be similarly inert to hydrogenation over Pd/C in ethyl acetate at 50 °C for 2 hours, or in DMF at room temperature for 4 days. In our earlier work on the attempted synthesis of 1,2-diazetidine, bis-benzyl diazetidine 45 was shown to be resilient to hydrogenation with either Pd/C, or Pd(OH)₂/C under 1 atm H₂ in methanol or ethanol, requiring the use of this latter catalyst and one equivalent of triflic acid to promote cleavage of the N=N bond as observed by ¹H NMR and ESMS (Scheme 2.25).
Our attention moved to \textit{bis}-Cbz methylenediazetidine 78. As expected, this was much more readily reduced by catalytic hydrogenation (Scheme 3.16). Exhaustive reduction occurred rapidly in methanol to the vicinal diamine 140 which was isolated by \textit{bis}-Boc protection for comparison to the literature data for this known compound.\textsuperscript{193}

![Scheme 3.16](image)

Comparing this result with our previous observations on \textit{bis}-Boc diazetidine 21 suggests that deprotection of one or both Cbz groups occurs before reduction of the N–N bond. If the diazetidine ring remains intact before reduction of the exocyclic double bond, 78 could be good potential substrate for asymmetric reduction providing a concise route to chiral 1,2-diamines.

Before such studies were undertaken, an exploration of the diastereoselective reduction of bicyclic diazetidine 105 was explored (Scheme 3.17). Hydrogenation of 105 [H\textsubscript{2} (1 atm), Pd/C (10 wt %)] in alcoholic solvents took place very rapidly. In addition to 142, small amounts of diamine product from cleavage of the N–N bond were observed by tlc after only 10 minutes. Using ethyl acetate as the solvent\textsuperscript{194} slowed this reduction, and after 30 minutes, we obtained \textit{cis}-1,2-diazetidine 142 as the only observable product by \textsuperscript{1}H and \textsuperscript{13}C NMR spectroscopy. This selectivity is likely to arise from delivery of hydrogen to the less hindered face of the diazetidine. The assignment of this stereochemical course for this reaction is detailed below. This route to saturated 1,2-diazetidines nicely complements the ring closure approaches developed in Chapter II.V.
Cleavage of the N–N bond of 105 was investigated using lithium di-tert-butylbiphenyl (LiDBB). This reagent is easily prepared by the action of lithium metal on 4,4’-di-tert-butylbiphenyl. In addition, it is intensely coloured and can be accurately titrated into the reaction. Treatment of 105 with LiDBB furnished the stable enamide 143. Moreover, treatment of saturated diazetidine 142 with LiDBB furnished cis-diamine 144 in excellent yield. To confirm the stereochemistry of 144, and hence 142, authentic samples of (1R*, 2S*)-144 (cis) and (1S, 2S)-144 (trans) were prepared from the corresponding, commercially available 1,2-diaminocyclohexanes by reaction with ethyl chloroformate.

Scheme 3.18
The cis- and trans-diamines could be differentiated on the basis of their $^{13}$C NMR spectra (Appendix IV). (1$S$, 2$S$)-144 displayed a deshielding of the ring amine carbons (55.41 ppm) relative to (1$R^*$, 2$S^*$)-144 (50.84 ppm). 144 derived from diazetidine 142 displayed a resonance at 50.86 ppm, and all other spectroscopic data was identical to that for (1$R^*$, 2$S^*$)-144, confirming the cis-stereochemistry.

A diastereocontrolled reduction in this way highlights the potential for 1,2-diazetidines to act as precursors to vicinal diamines. Future work may explore the incorporation of the alkylidenediazetidine unit into the synthesis of larger organic molecules, where a late-stage cleavage of the N–N bond is used to furnish the vicinal diamine.
III.V Conclusions

The structure and functionalisation of a range of new 1,2-diazetidines has been described. By a combination of spectroscopic and X-ray diffraction studies, the effects of the N-substituent on the diazetidine ring structure and the rate of nitrogen inversion have been determined. An insight has been provided into the nature of bonding in these systems, which we have shown can be used to rationalise their reactivity.

Attempts to functionalise bis-Boc diazetidine 21 via lithiation chemistry were unsuccessful, in part due to a lack of donation from the nitrogen lone pair into the Boc carbonyl, leaving this group susceptible to nucleophilic attack. The consideration of alternative protecting groups such as thiopivaloyl may improve the prospects for such lithiation chemistry in the future.

Functionalisation reactions of 3-alkylidene-1,2-diazetidines have been explored. 3-Methylene-1,2-diazetidines have been shown to undergo highly stereoselective palladium-catalysed Heck cross-coupling reactions. The origin of this selectivity has been rationalised in terms of steric interactions with the N-substituents. This route to arylated alkylidenediazetidines provides a complementary strategy to that using the copper-catalysed cyclisation chemistry developed in Chapter II. This work has been published in Organic Letters.196

Scheme 3.19
Moreover, ring expansion via carbene insertion into the N–N bond, and simple addition across the exocyclic double bond have been demonstrated. These encouraging observations merit further exploration.

Suitably protected 1,2-diazetidines have been shown to be stable under catalytic hydrogenation. Through the choice of Cbz protection, a single step reduction to the vicinal diamine can be achieved. Moreover, a highly diastereoselective method for the reduction of bicyclic diazetidines to saturated systems, and hence 1,2-diamines, has been demonstrated.

![Scheme 3.20](image)

It is hoped that the establishment of reliable synthetic routes to 1,2-diazetidines and the preliminary studies of their reactivity presented here will encourage further synthetic studies involving these systems. The solid-state structures reported here should encourage such studies on 1,2-diazetidines to be undertaken with confidence. Further studies may aim to develop a concise route to chiral 1,2-diamines via the asymmetric hydrogenation of Cbz protected methylenediazetidines or their derivatives made available by cross-coupling chemistry. In addition, the stability of this ring system under a range of conditions, combined with a method for facile cleavage of the N–N bond to furnish the diamine, holds promise for the use of 1,2-diazetidines as the carriers of a protected diamine unit though a synthetic sequence. Such future studies would examine the potential of this method for the construction of larger organic amines.
Chapter IV

Experimental
IV  Experimental

IV.I General

All reactions were performed under an atmosphere of dry nitrogen in flame dried glassware unless otherwise stated. Anhydrous solvents were supplied by Sigma-Aldrich in Sure/Seal™ bottles. All other solvents were used as received or purified by standard protocols. Petroleum ether refers to the fraction which boils in the range 40-60 °C. Commercially available starting materials were used without further purification.

Thin layer chromatography was performed on pre-coated aluminium-backed plates (Merck Kieselgel 60 F_{254}), visualised by UV_{254} nm then stained with potassium permanganate or ceric ammonium molybdate solution. Flash chromatography was performed using Matrex silica 60.

Melting points were recorded on a Gallenkamp MPD350 apparatus and are reported as observed.\textsuperscript{197} Single crystal X-ray diffraction data were obtained using a Siemens SMART XRD system or an Oxford Diffraction Gemini XRD system. Copies of X-ray data are available via the Cambridge Crystallographic Data Centre. Optical rotations were measured with a AA1000 polarimeter and are quoted in 10\(^{-1}\) deg cm\(^2\) g\(^{-1}\).

Nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX (300, 400, 500 or 600 MHz) spectrometers. NOe measurements were performed on a 600 MHz spectrometer. Chemical shifts are reported in parts per million relative to the standard tetramethyilsilane for \(^1\)H NMR and to the centre line of the chloroform triplet at 77.2 ppm for \(^{13}\)C NMR. The peak multiplicities were specified as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint) and octuplet (oct). Coupling constants (\(J\)) are reported in Hertz as observed, not averaged. Due to the restricted conformational nature
of substituted hydrazodicarboxylates, signals in the $^1$H and $^{13}$C NMR spectra were often broad and rotamers were observed.

Low resolution mass spectra were recorded on an Esquire 2000 platform with electrospray ionisation. High resolution mass spectra were obtained using a Bruker MicroTOF spectrometer. Conditions used for liquid chromatography mass spectrometry (LCMS) and high-performance liquid chromatography (HPLC) are detailed in section IV.XI.
IV.II Synthesis of 1,2-Dicarboxyalkyl-1,2-Diazetidines

Di-tert-butyl 1-(2-hydroxyethyl)-hydrazine-1,2-dicarboxylate \(^{73}\) (22)

To a solution of 2-hydroxyethylhydrazine (98% purity, 3.00 mL, 43.4 mmol) in CH\(_2\)Cl\(_2\) (45 mL) at 0 °C was added dropwise a solution of di-tert-butyl dicarbonate (19.9 g, 91.1 mmol) in CH\(_2\)Cl\(_2\) (75 mL). The mixture was allowed to warm to room temperature and stirred overnight. The reaction was concentrated and diethyl ether (50 mL) and water (40 mL) were added. The phases were separated and the organic phase washed with water (5 × 40 mL). The organic phases were combined, washed with brine, dried over MgSO\(_4\), filtered, and concentrated in vacuo. Trituration of the crude oil with hexane (70 mL) overnight furnished 22 (12.0 g, 94%) as a white solid. M.p. 103-104 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) 6.42 (1H, m), 3.98 (1H, m), 3.70 (2H, br s), 3.57 (2H, br s), 1.49-1.47 (18H, m); \(^13\)C NMR (125 MHz, CDCl\(_3\)) 157.2 (C), 155.1 (C), 82.2 (C), 81.6 (C), 59.5 (CH\(_2\)), 54.0 and 52.7 (CH\(_2\)), 27.8 (6CH\(_3\)); MS (ES\(^+\)) m/z = 299 ([M+Na]\(^+\), 100); HRMS (ES\(^+\)) m/z calcd for C\(_{12}\)H\(_{24}\)N\(_2\)O\(_5\)Na (M+Na)\(^+\): 299.1577; found: 299.1582.

Di-tert-butyl 1-(2-(methylsulphonyloxy)ethyl)-hydrazine-1,2-dicarboxylate (23)

To a solution of MsCl (1.35 mL, 17.4 mmol) in CH\(_2\)Cl\(_2\) (20 mL) at -78 °C was added dropwise a solution of di-tert-butyl 1-(2-hydroxyethyl)-hydrazine-1,2-dicarboxylate (22) (4.00 g, 14.5 mmol) and Et\(_3\)N (4.86 mL, 34.9 mmol) in CH\(_2\)Cl\(_2\) (30 mL). After 10 min, the reaction was allowed to warm to room temperature and stirred overnight. The reaction was brought to pH 7 by the addition of saturated aqueous ammonium chloride solution. The phases were separated and the
aqueous phase extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined organic phases were washed with brine, dried over MgSO$_4$, filtered, and concentrated in vacuo to give 23 (5.12 g, 98%) as a colourless crystalline solid. M.p. 94-94.5 °C (decomp.) (methanol); IR (neat) 3675, 3298, 2972, 1724, 1698, 1345, 1145 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 6.41 (1H, m), 4.39 (2H, br s), 3.81 (2H, br s), 3.04 (3H, s), 1.48 (18H, br s); $^{13}$C NMR (125 MHz, CDCl$_3$) 155.1 (2C), 81.8 (C), 81.5 (C), 66.6 and 66.0 (CH$_2$), 45.0 and 48.8 (CH$_2$), 37.7 (CH$_3$), 28.2 (6CH$_3$); MS (ES$^+$) $m/z$ = 377 ([M+Na]$^+$, 100); HRMS (ES$^+$) $m/z$ calcd for C$_{13}$H$_{30}$N$_3$O$_7$S (M+Na)$^+$: 372.1799; found: 372.1796.

**tert-Butyl 2-tert-butoxy-5,6-dihydro-4H-1,3,4-oxadiazine-4-carboxylate (24)**

![Diagram](https://via.placeholder.com/150)

Diethyl azodicarboxylate (111 µL, 0.71 mmol) was added dropwise to a stirred solution of di-tert-butyl 1-(2-hydroxyethyl)-hydrazine-1,2-dicarboxylate (22) (150 mg, 0.54 mmol) and triphenylphosphine (186 mg, 0.71 mmol) in THF (5 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 48 h then concentrated in vacuo. $^1$H NMR showed dihydrooxadiazine 24 as the only cyclic product which was isolated by column chromatography (petroleum ether:ethyl acetate, 8:1) (90 mg, 64%) as a colourless crystalline solid. M.p. 63-64 °C; IR (neat) 2983, 1698, 1670, 1364, 1299, 1164, 973, 852 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 4.30 (2H, t, $J = 4.8$ Hz), 3.72 (2H, t, $J = 4.8$ Hz); 1.52-1.49 (18H, m); $^{13}$C NMR$^1$ (75 MHz, CDCl$_3$) 146.6 (C), 82.4 (CH$_2$), 80.5 (CH$_2$), 65.0 (CH$_2$), 39.2 (CH$_2$), 28.4 (3CH$_3$), 28.0 (3CH$_3$); MS (ES$^+$) $m/z$ = 539 ([2M+Na]$^+$, 100); HRMS (ES$^+$) $m/z$ calcd for C$_{12}$H$_{22}$N$_2$O$_4$Na (M+Na)$^+$: 281.1472; found: 281.1472.

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$^1$ Quaternary carbon not observed.
281.1476. Crystals suitable for X-ray diffraction were grown from CH$_2$Cl$_2$/hexane by solvent diffusion.

**Dibenzyl 1-(2-hydroxyethyl)-hydrazine-1,2-dicarboxylate (25)**

Benzyl chloroformate (2.01 mL, 14.0 mmol) was added dropwise to a rapidly stirred mixture of 2-hydroxyethylhydrazine (500 μL, 6.6 mmol) and NaHCO$_3$ (2.25 g, 33.2 mmol) in diethyl ether (10 mL) and water (15 mL) at 0 °C. The heterogeneous mixture was allowed to warm to room temperature and stirred rapidly overnight. The reaction was brought to pH 7 by the addition of saturated aqueous ammonium chloride solution. The phases were separated and the aqueous phase extracted with diethyl ether (3 × 25 mL). The combined organic phases were washed with brine, dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether:ethyl acetate, 2:1) gave 25 (2.00 g, 88%) as a white solid. M.p. 67-68 °C; IR (neat) 3463, 3270, 2965, 1716, 1684, 1269, 698 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 7.53-7.02 (11H, m), 5.14 (4H, br s), 3.84-3.44 (5H, m); $^{13}$C NMR (125 MHz, CDCl$_3$) 158.3 and 157.5 (C), 156.6 and 155.9 (C), 135.7 (C), 135.3 (C), 128.7 (2CH), 128.6 (3CH), 128.3 (3CH), 128.0 (2CH), 68.5 (CH$_2$), 68.3 (CH$_2$), 59.2 (CH$_2$), 53.6, 53.3 and 52.8 (CH$_2$); MS (ES$^+$) $m/z = 367$ ([M+Na]$^+$, 100); HRMS (ES$^+$) $m/z$ calcd for C$_{18}$H$_{20}$N$_2$O$_5$Na (M+Na)$^+$: 367.1264; found: 367.1278.
Benzyl 2-(benzylxy)-5-propyl-5,6-dihydro-4H-1,3,4-oxadiazine-4-carboxylate \{(R)-28b\}

To \((R)\)-dibenzyl 1-(1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate\(^{37}\) (1.00 g, 2.59 mmol) in \(\text{CH}_2\text{Cl}_2\) (25 mL) was added DBU (3.10 mL, 20.73 mmol). This solution was cooled to 0 °C then MsCl (301 µL, 3.89 mmol) was added dropwise. After the addition, the mixture was allowed to warm to room temperature and stirred for 8 h. The solution was brought to pH 7 by the addition of saturated aqueous ammonium chloride solution. The phases were separated and the aqueous phase extracted with \(\text{CH}_2\text{Cl}_2\) (3 \(\times\) 25 mL). The combined organic phases were washed with saturated aqueous \(\text{NaHCO}_3\) (20 mL), brine (30 mL), dried over \(\text{MgSO}_4\), filtered, and concentrated in vacuo. Column chromatography [petroleum ether:ethyl acetate, 6:1 with 1\% \(\text{Et}_3\text{N}\) (v/v)] gave \((R)\)-28b (342 mg, 36\%) as a colourless crystalline solid. M.p. 81-83 °C; IR (\(\text{CCl}_4\)) 2958, 1688, 1659, 1298 cm\(^{-1}\); \(^1\)H NMR (500 MHz, \(\text{CDCl}_3\)) 7.49-7.25 (10H, m), 5.31-5.09 (4H, m), 4.36 (1H, m), 4.30-4.22 (2H, m), 1.66-1.48 (2H, m), 1.45-1.25 (2H, m), 0.92 (3H, t, \(J = 7.2\) Hz); \(^{13}\)C NMR (125 MHz, \(\text{CDCl}_3\)) 153.0 (C), 148.5 (C), 136.6 (C), 135.6 (C), 128.6 (CH), 128.5 (3CH), 128.4 (CH), 128.3 (2CH), 128.0 (CH), 127.6 (CH), 126.9 (CH), 69.8 (CH\(_2\)), 67.8 (CH\(_2\)), 67.6 (CH\(_2\)), 48.4 (CH), 31.1 (CH\(_2\)), 19.0 (CH\(_2\)), 13.7 (CH\(_3\)); MS (ES\(^+\)) \(m/z = 391\) ([M+Na]\(^+\), 100); HRMS (ES\(^+\)) \(m/z\) calcd for \(\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_4\) (M+H)\(^+\): 369.1809; found: 369.1813. Crystals suitable for X-ray diffraction were grown from ethyl acetate/petroleum ether (40-60 °C) by slow evaporation.
Di-tert-butyl 1-(2-chloroethyl)-hydrazine-1,2-dicarboxylate (30)

Triphenylphosphine (1.90 g, 7.25 mmol) was added portionwise to a stirred solution of di-tert-butyl 1-(2-hydroxyethyl)-hydrazine-1,2-dicarboxylate (22) (1 g, 3.62 mmol) and CCl$_4$ (700 µL, 7.25 mmol) in CH$_3$CN (30 mL) at 0 °C. After 20 min the reaction was allowed to warm to room temperature and stirred for 6 h. Solids were filtered over celite and the filtrate was concentrated in vacuo. Recrystallisation from MeOH/water furnished 30 (611 mg, 57%) as a colourless crystalline solid. M.p. 103.5-104 °C (methanol); IR (neat) 3663, 3311, 2987, 1704, 1367, 1055, 731 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 3.7 (1H, m), 3.83-3.62 (4H, m), 1.48 (18H, br s); $^{13}$C NMR (125 MHz, CDCl$_3$) 154.7 (C), 154.6 (C), 81.0 (broad, 2C), 51.7 and 50.8 (CH$_2$), 40.5 (CH$_2$), 27.5 (6CH$_3$); MS (ES$^+$) $m/z$ = 319 ([M$^{37}\text{Cl}$]+Na$^+$, 25), 317 ([M$^{35}\text{Cl}$]+Na$^+$, 75); HRMS (ES$^+$) $m/z$ calcd for C$_{12}$H$_{23}$ClN$_2$O$_4$Na (M+Na)$^+$: 317.1239; found: 317.1244.

Di-tert-butyl 1-(2-bromoethyl)-hydrazine-1,2-dicarboxylate (31)

Bromine (668 µL, 13.0 mmol) was added dropwise to a solution of triphenylphosphine (3.42 g, 13.0 mmol) and imidazole (888 mg, 13.0 mmol) in CH$_2$Cl$_2$ (30 mL) at 0 °C. The resultant orange suspension was allowed to warm to room temperature and di-tert-butyl 1-(2-hydroxyethyl)-hydrazine-1,2-dicarboxylate (22) (3 g, 10.9 mmol) in CH$_2$Cl$_2$ (15 mL) was added in one portion. The reaction was stirred at room temperature for 16 h then filtered over celite. The filtrate was concentrated in vacuo. Careful recrystallisation from MeOH/water gave 31 (1.57 g, 43%) as a colourless crystalline solid. M.p. 123.5-124 °C (decomp.) (methanol); IR (neat) 3674, 3312, 2987, 1705, 1394, 1056, 758 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 6.41
Di-tert-butyl 1-(2-iodoethyl)-hydrazine-1,2-dicarboxylate (32)

Iodine (3.31g, 13.0 mmol) was added portionwise to a solution of triphenylphosphine (3.42 g, 13.0 mmol) and imidazole (888 mg, 13.0 mmol) in CH$_2$Cl$_2$ (30 mL) at 0 °C. The resultant yellow suspension was allowed to warm to room temperature and di-tert-butyl 1-(2-hydroxyethyl)-hydrazine-1,2-dicarboxylate (22) (3 g, 10.9 mmol) in CH$_2$Cl$_2$ (15 mL) was added in one portion. The reaction was stirred at room temperature for 16 h then filtered over celite. The filtrate was concentrated in vacuo. Recrystallisation from MeOH/water furnished 32 (2.05 g, 49%) as a colourless crystalline solid. M.p. 129.5-130 °C (decomp.) (methanol); IR (neat) 3663, 3314, 2972, 1705, 1394, 1052 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 6.43 (1H, m), 3.80 (2H, br s), 3.29 (2H, br s), 1.48 (18H, br s); $^{13}$C NMR (125 MHz, CDCl$_3$) 153.3 (C), 152.7 (C), 79.8 (C), 79.6 (C), 51.1 and 50.3 (CH$_2$), 26.3 (6CH$_3$), 0.0 and -0.7 (CH$_2$); MS (ES$^+$) m/z = 409 ([M+Na$^+$], 100); HRMS (ES$^+$) m/z calcd for C$_{12}$H$_{23}$IN$_2$O$_4$Na (M+Na$^+$): 409.0595; found: 409.0609.
Cyclisation: General Procedure 1

To a solution of the substrate (1.0 molar equiv) in CH$_3$CN at room temperature was added in one portion Cs$_2$CO$_3$ (8.0 molar equiv). The mixture was stirred for 16 h or until tlc showed complete consumption of starting material. The reaction was filtered through celite then concentrated *in vacuo*. The concentrate was taken up in ethyl acetate and passed through a short column of silica to remove any remaining inorganic material.

Separation of diazetidine and dihydrooxadiazine products was achieved by column chromatography.

**Di-tert-butyl 1,2-diazetidine-1,2-dicarboxylate (21) and tert-Butyl 2-tert-butoxy-5,6-dihydro-4H-1,3,4-oxadiazine-4-carboxylate (24)**

Iodide 32 (131 mg, 0.34 mmol) was cyclised according to general procedure 1 with Cs$_2$CO$_3$ (885 mg, 2.72 mmol) in CH$_3$CN (10 mL) to give a mixture of diazetidine 21 and dihydrooxadiazine 24 (overall yield 86 mg, 98%) in the ratio 54:46 as judged by crude $^1$H NMR. Separation by column chromatography (petroleum ether:ethyl acetate, 8:1) gave 21 (46 mg, 53%) as a colourless crystalline solid. M.p. 93.5-94 °C; IR (neat) 2984, 1739, 1716, 1292, 1136, 774 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) 4.12 (4H, s), 1.48 (18H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) 160.2 (2C), 81.9 (2C), 48.8 (2CH$_2$), 28.1 (6CH$_3$); MS (ES$^+$) $m/z$ = 539 ([2M+Na]$^+$, 100); HRMS (ES$^+$) $m/z$ calcd for C$_{12}$H$_{22}$N$_2$O$_4$Na (M+Na)$^+$: 281.1472; found: 281.1471. Crystals suitable for X-ray diffraction were grown from
CHCl₃ by slow evaporation. Further elution gave 24 (39 mg, 44%) as a colourless crystalline solid.

Mesylate 23 (120 mg, 0.34 mmol) was cyclised according to general procedure 1 with Cs₂CO₃ (884 mg, 2.71 mmol) in CH₃CN (10 mL) to give a mixture of diazetidine 21 and dihydrooxadiazine 24 (overall yield 86 mg, 98%) in the ratio 3:97 as judged by crude ¹H NMR. Column chromatography (petroleum ether:ethyl acetate, 5:1) gave dihydrooxadiazine 24 (84 mg, 96%) as the only isolated product.

Chloride 30 (100 mg, 0.34 mmol) was cyclised according to general procedure 1 with Cs₂CO₃ (885 mg, 2.71 mmol) in CH₃CN (10 mL) to give a mixture of diazetidine 21 and dihydrooxadiazine 24 (overall yield 87 mg, 99%) in the ratio 40:60 as judged by crude ¹H NMR.

Bromide 31 (115 mg, 0.34 mmol) was cyclised according to general procedure 1 with Cs₂CO₃ (884 mg, 2.71 mmol) in CH₃CN (10 mL) to give a mixture of diazetidine 21 and dihydrooxadiazine 24 (overall yield 84 mg, 96%) in the ratio 27:73 as judged by crude ¹H NMR.

**tert-Butyl 2-oxo-1,3,4-oxadiazinanone-4-carboxylate (34)**

![Chemical structure](image)

To a solution of iodide 32 (30 mg, 0.08 mmol) in CH₃CN (5 mL) at room temperature was added Cs₂CO₃ (38 mg, 0.12 mmol) and AgNO₃ (40 mg, 0.23 mmol). The mixture was stirred for 16 h then concentrated *in vacuo*. The concentrate was taken up in ethyl acetate and washed with water (3 × 15 mL), brine, dried (MgSO₄) then concentrated *in
to give the pure product 34 (10.5 mg, 67%) as a white solid. M.p. 122-125 °C; IR (film) 3253, 2987, 1745, 1712, 1510, 1154, 745 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 6.42 (1H, m), 4.36 (2H, t, J = 7.8 Hz), 3.79 (2H, br t, J = 7.8 Hz), 1.46 (9H, s); ¹³C NMR (75 MHz, CDCl₃) 163.9 (C), 153.5 (C), 81.9 (C), 61.1 (CH₂), 45.7 (CH₂), 27.5 (3CH₃); MS (ES⁺) m/z = 225 ([M+Na]⁺, 100); HRMS (ES⁺) m/z calcd for C₈H₁₄N₂O₄ (M+Na)⁺: 225.0846; found: 225.0835.

Synthesis of Iodides: General Procedure 2

![Chemical Reaction](attachment:image.png)

To a solution of MsCl (1.2 molar equiv) in CH₂Cl₂ at -78 °C was added dropwise a solution of the alcohol (1.0 molar equiv) and triethylamine (1.2 molar equiv) in CH₂Cl₂. After 10 min, the reaction was allowed to warm to room temperature and stirred overnight. The reaction was brought to pH 7 by the addition of saturated aqueous ammonium chloride solution. The phases were separated and the aqueous phase extracted three times with CH₂Cl₂. The combined organic phases were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo.

Anhydrous lithium iodide¹ (10.0 molar equiv) and THF were added and the resultant mixture heated at reflux for 2.5 h. The reaction was allowed to cool to room temperature, concentrated in vacuo, then diethyl ether and water were added. The phases were separated and the aqueous phase extracted three times with diethyl ether. The combined

¹ Wet lithium iodide or lithium iodide hydrate gave substantially lower yields.
organic phases were washed with 10% aqueous Na$_2$S$_2$O$_3$ solution, brine, dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification of the iodide was achieved by column chromatography or recrystallisation.

**Dibenzyl 1-(2-iodoethyl)-hydrazine-1,2-dicarboxylate (35)**

Iodide 35 was prepared from alcohol 25 (380 mg, 1.10 mmol), MsCl (111 µL, 1.44 mmol), Et$_3$N (400 µL, 2.87 mmol) in CH$_2$Cl$_2$ (30 mL) then LiI (1.59 g, 11.8 mmol) in THF (20 mL) according to general procedure 2. Work-up followed by column chromatography (petroleum ether:ethyl acetate, 6:1) afforded 35 (396 mg, 74% from 25) as a white solid. An analytical sample was prepared by recrystallisation from methanol and then from hexane. M.p. 99-100 °C (hexane); IR (neat) 3273, 1738, 1682, 1235, 741, 697 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) 7.56-7.05 (10H, m), 6.83 (1H, m), 5.37-4.75 (4H, m), 3.89-3.63 (2H, m), 3.29-3.01 (2H, m); $^{13}$C NMR (125 MHz, CDCl$_3$) 156.4, 155.9 and 155.5 (2C), 135.6 (C), 135.4 (C), 128.7 (3CH), 128.6 (3CH), 128.3 (2CH), 128.1 (CH), 127.9 (CH), 68.7 and 68.3 (CH$_2$), 68.0 (CH$_2$), 53.0 and 52.7 (CH$_2$), 1.16 and 0.71 (CH$_2$); MS (ES$^+$) m/z = 472 ([M+NH$_4$]$^+$, 100); HRMS (ES$^+$) m/z calcd for C$_{18}$H$_{19}$I$_2$N$_2$O$_4$Na (M+Na)$^+$: 477.0282; found: 477.0299.

(R)-Dibenzyl 1-(1-benzyl-2-iodo-ethyl) hydrazine-1,2-dicarboxylate {(R)-36a}

Iodide (R)-36a was prepared from the corresponding alcohol 37 (366 mg, 0.84 mmol), MsCl (85 µL, 1.10 mmol), Et$_3$N (306 µL, 2.20 mmol) in CH$_2$Cl$_2$ (15 mL) then LiI (1.02 g, 7.62 mmol) in THF (10 mL) according to general procedure 2. Work-up followed by recrystallisation from MeOH/water afforded (R)-36a (298 mg, 65% from (R)-12a) as a colourless crystalline
solid. M.p. 115.5-116.5 °C (methanol); [α]_D^{21} +5.1 (c 0.45, CHCl₃); IR (neat) 3263, 3038, 1740, 1678, 1416, 1230, 695 cm⁻¹; ^1H NMR (500 MHz, CDCl₃) 7.60-7.04 (15H, m), 6.46 - 6.15 (4H, m), 4.77-4.46 (1H, m), 3.64-2.53 (4H, m); ^13C NMR (125 MHz, CDCl₃) 157.2 and 156.6 (C), 156.6 and 155.2 (C), 135.7 (C), 135.7 (C), 135.6 (C), 128.9 (2CH), 128.8 (2CH), 128.7 (2CH), 128.6 (2CH), 128.5 (CH), 128.4 (2CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 126.7 (CH), 68.6 (CH₂), 68.2 and 68.1 (CH₂), 62.1 and 61.1 (CH), 38.6 (CH₂), 6.6 and 6.4 (CH₂); MS (ES⁻) m/z = 562 ([M+NH₄]⁺, 100); HRMS (ES⁻) m/z calcd for C_{25}H_{25}IN₂O₄Na (M+Na)⁺: 567.0751; found: 567.0768.

(R)-Dibenzyl 1-(1-iodomethyl-butyl) hydrazine-1,2-dicarboxylate {(R)-36b}

Iodide (R)-36b was prepared from the corresponding alcohol^37 (869 mg, 2.25 mmol), MsCl (226 μL, 2.93 mmol), Et₃N (816 μL, 5.85 mmol) in CH₂Cl₂ (15 mL) then LiI (3.02 g, 22.5 mmol) in THF (15 mL) according to general procedure 2. Work-up followed by column chromatography (petroleum ether:ethyl acetate, 8:1) afforded (R)-36b (404 mg, 36% from (R)-12b) as a colourless crystalline solid. M.p. 83.5-84 °C (methanol); [α]_D^{21} -4.0 (c 1.10, CHCl₃); IR (neat) 3268, 2958, 1741, 1676, 1420, 1213, 698 cm⁻¹; ^1H NMR (400 MHz, CDCl₃) 7.48-7.15 (10H, m), 6.38 (1H, m), 5.32-4.90 (4H, m), 4.33 (1H, m), 3.40-3.01 (2H, m), 1.81-1.17 (4H, m), 1.03-0.55 (3H, m); ^13C NMR (125 MHz, CDCl₃) 156.5 (C), 156.0 (C), 135.2 and 135.0 (C), 134.8 (C), 128.0 (2CH), 127.9 (3CH), 127.7 (3CH), 127.5 (CH), 127.2 (CH), 68.0 (CH₂), 67.6 and 67.5 (CH₂), 59.6 and 58.5 (CH), 33.7 (CH₂), 19.2 (CH₂), 13.2 (CH₃), 6.9 (CH₂); MS (ES⁺) m/z = 514 ([M+NH₄]⁺, 100); HRMS (ES⁺) m/z calcd for C_{21}H_{25}IN₂O₄Na (M+Na)⁺: 519.0751; found: 519.0747.
(R)-Dibenzyl 1-(1-iodomethyl-2-methyl-propyl) hydrazine-1,2-dicarboxylate {(R)-36c}

Iodide (R)-36c was prepared from the corresponding alcohol 37 (1.79 g, 4.64 mmol), MsCl (467 µL, 6.03 mmol), Et₃N (1.68 mL, 12.06 mmol) in CH₂Cl₂ (30 mL) then LiI (6.21 g, 46.4 mmol) in THF (20 mL) according to general procedure 2. Work-up followed by column chromatography (petroleum ether:ethyl acetate, 9:1) afforded (R)-36c (229 mg, 10% from (R)-12c) as a colourless crystalline solid. M.p. 94.5-95.5 °C (methanol); (R)-[α]D 21 = -12.3 (c 0.4, CHCl₃) [racemate [α]D 21 = -0.2 (c 1.20, CHCl₃)]; IR (neat) 3256, 2949, 1740, 1690, 1419, 1221, 694 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.37-7.13 (10H, m), 6.49-6.22 (1H, m), 5.22-4.92 (4H, m), 3.97 (1H, m), 3.42 (1H, m), 3.13 (1H, br t, J = 11.0 Hz), 1.73 (1H, m), 1.28-0.66 (6H, m); ¹³C NMR (125 MHz, CDCl₃) 157.1, 156.6 and 156.0 (2C), 135.9 and 135.7 (C), 135.4 (C), 128.6 (4CH), 128.5 (CH), 128.3 (3CH), 128.2 (CH), 127.8 (CH), 68.6 (CH₂), 68.3 and 68.0 (CH₂), 66.3 and 65.1 (CH), 31.6 (CH), 20.8 (CH₃), 19.6 (CH₃), 6.6 (CH₂); MS (ES⁺) m/z = 514 ([M+NH₄]⁺, 100); HRMS (ES⁺) m/z calcld for C₂₁H₂₅IN₂O₄Na (M+Na): 519.0751; found: 519.0746.

Dibenzyl 1,2-diazetidine-1,2-dicarboxylate (38) and Benzyl 2-(benzyloxy)-5,6-dihydro-4H-1,3,4-oxadiazine-4-carboxylate (37)

Iodide 35 (150 mg, 0.33 mmol) was cyclised according to general procedure 1 with Cs₂CO₃ (861 mg, 2.64 mmol) in CH₃CN (15 mL) to give a mixture of diazetidine 38 and dihydrooxadiazine 37 (overall yield 104 mg, 97%) in the ratio 56:44 as judged by crude ¹H NMR. Separation by column chromatography (petroleum ether:ethyl acetate, 6:1) gave 37 (45 mg, 42%) as a colourless crystalline solid. M.p. 102-104 °C (ethyl acetate);
IR (neat) 3286, 2958, 1736, 1690, 1653, 1419, 1249, 693 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.52-7.31 (10H, m), 5.29 (2H, s), 5.21 (2H, s), 4.37 (2H, t, \(J = 4.7\) Hz), 3.85 (2H, t, \(J = 4.7\) Hz); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.24 (10H, s), 5.11 (4H, s), 4.16 (4H, s); \(^1\)C NMR (100 MHz, CDCl\(_3\)) 160.8 (2C), 135.5 (2C), 128.6 (4CH), 128.3 (2CH), 128.1 (4CH), 68.2 (2CH\(_2\)), 49.6 (2CH\(_2\)); MS (ES\(^+\)) \(m/z = 327\) (M+H\(^+\), 100); HRMS (ES\(^+\)) \(m/z\) calc'd for C\(_{18}\)H\(_{18}\)N\(_2\)O\(_4\)Na (M+Na\(^+\)): 349.1159; found: 349.1161.

(R)-Dibenzyl 3-benzyl-1,2-diazetidine-1,2-dicarboxylate \{(R)-13a\} and (R)-Benzyl 5-benzyl-2-(benzylxoy)-5,6-dihydro-4H-1,3,4-oxadiazine-4-carboxylate \{(R)-28a\}

Iodide (R)-36a (138 mg, 0.25 mmol) was cyclised according to general procedure 1 with Cs\(_2\)CO\(_3\) (885 mg, 2.0 mmol) in CH\(_3\)CN (10 mL) to give a mixture of diazetidine (R)-13a and dihydrooxadiazine (R)-28a (overall yield 103 mg, 98%) in the ratio 35:65 as judged by crude \(^1\)H NMR. Separation by multiple column chromatography (petroleum ether:ethyl acetate, 6:1) gave (R)-13a (30 mg, 29%) as a colourless oil. \([\alpha]_D^{2\text{1}}\) -36.1 (c 1.70, CHCl\(_3\)); IR (film) 3031, 2956, 1710, 1390, 1328, 1276, 699 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 7.31-7.07 (15H, m), 5.18 (1H, d, \(J = 12.4\) Hz), 5.09 (1H, d, \(J = 12.4\) Hz),
5.04 (1H, d, \( J = 12.4 \) Hz), 4.99 (1H, d, \( J = 12.4 \) Hz), 4.54 (1H, m), 4.17 (1H, t, \( J = 8.2 \) Hz), 3.79 (1H, dd, \( J = 8.7, 5.9 \) Hz), 3.11-2.91 (2H, m); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) 164.1 (C), 160.6 (C), 135.6 (C), 135.1 (C), 129.5 (3CH), 128.6 (4CH), 128.5 (2CH), 128.3 (CH), 128.2 (CH), 128.0 (2CH), 127.9 (CH), 127.1 (CH), 126.0 (2CH), 68.0 (2CH\(_2\)), 62.4 (CH), 53.9 (CH\(_2\)), 40.0 (CH\(_2\)); MS (ES\(^{+}\)) \( m/z \) = 417 ([M+H]\(^{+}\), 100); HRMS (ES\(^{+}\)) \( m/z \) calcd for C\(_{25}\)H\(_{24}\)N\(_2\)O\(_4\)Na (M+Na): 439.1628; found: 439.1641. Further elution gave (R)-28a (67 mg, 64%) as white solid. \([\alpha]_D^{21} +4.0 \) (c 0.21, CHCl\(_3\)); M.p. 92.5-94 °C; IR (film) 3030, 1721, 1690, 1651, 1421, 1296, 1140, 693 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.50-7.08 (15H, m), 5.31-5.06 (4H, m), 4.49 (1H, m), 4.22-4.08 (2H, m), 2.94 (1H, br dd, \( J = 13.3, 5.5 \) Hz), 2.79 (1H, dd, \( J = 13.3, 10.0 \) Hz); \(^{13}\)C NMR \(^{i}\) (75 MHz, CDCl\(_3\)) 136.7 (C), 136.3 (C), 135.5 (C), 129.5 (3CH), 128.8 (4CH), 128.2 (2CH), 127.0 (CH), 70.0 (CH\(_2\)), 67.7 (CH\(_2\)), 65.9 (CH\(_2\)), 50.3 (CH), 34.7 (CH\(_2\)); MS (ES\(^{+}\)) \( m/z \) = 349 ([M+Na]\(^{+}\), 100); HRMS (ES\(^{+}\)) \( m/z \) calcd for C\(_{25}\)H\(_{28}\)N\(_3\)O\(_4\)Na (M+NH\(_4\))\(^{+}\): 434.2074; found: 434.2071.

(R)-Dibenzyl 3-propyl-1,2-diazetidine-1,2-dicarboxylate \{(R)-13b\} and (R)-Benzyl 2-(benzyloxy)-5-propyl-5,6-dihydro-4H-1,3,4-oxadiazine-4-carboxylate \{(R)-28b\}

\[ \text{Cbz} \quad \text{N} \quad \text{N} \quad \text{Cbz} \]
\[ \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \]
\[ \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \]
\[ \text{Cbz} \quad \text{N} \quad \text{N} \quad \text{Cbz} \]

Iodide (R)-36b (321 mg, 0.65 mmol) was cyclised according to general procedure 1 with Cs\(_2\)CO\(_3\) (1.69 g, 5.2 mmol) in CH\(_3\)CN (15 mL) to give a mixture of diazetidine (R)-13b and dihydrooxadiazine (R)-28b (overall yield 233 mg, 98%) as one spot by tlc (petroleum ether:ethyl acetate, 4:1, \( R_f = 0.67 \)) in the ratio 41:59 as judged by crude \(^1\)H

\(^{i}\) Quaternary carbons not observed.
NMR. Analysis of mixture (assignments made where possible: A denotes diazetidine; B denotes dihydrooxadiazine): $^1$H NMR (300 MHz, CDCl$_3$) 7.46-7.25 (20H, m), 5.30-5.08 (8H, m), 4.41-4.29 (1H B+2H A, m), 4.25-4.16 (2H B, m), 3.85-3.76 (1H A, m), 1.84 (1H A, m), 1.71-1.25 (7H, m), 0.95-0.85 (6H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) 160.3 (C), 160.2 (C), 135.9 (C), 135.1 (C), 134.9 (C), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 126.8 (CH), 69.2 (CH$_2$ B), 67.4 (CH$_2$), 67.4 (CH$_2$), 67.2 (CH$_2$), 67.0 (CH$_2$), 61.7 (CH A), 54.4 (CH$_2$ A), 47.7 (CH B), 36.2 (CH$_2$ A), 30.4 (CH$_2$ B), 18.5 (CH$_2$ B), 17.2 (CH$_2$ A), 13.2 (CH$_3$), 13.2 (CH$_3$); MS (ES$^+$) m/z = 369 ([M+H]$^+$, 100); HRMS (ES$^+$) m/z calcd for C$_{23}$H$_{24}$N$_2$O$_4$Na (M+Na)$^+$: 391.1628; found: 391.1643.

(R)-Dibenzyl 3-isopropyl-1,2-diazetidine-1,2-dicarboxylate {($R$)-13c} and (R)-Benzy1 2-(benzyloxy)-5-isopropyl-5,6-dihydro-4H-1,3,4-oxadiazone-4-carboxylate {($R$)-28c}

Iodide ($R$)-36c (179 mg, 0.36 mmol) was cyclised according to general procedure 1 with Cs$_2$CO$_3$ (941 mg, 2.9 mmol) in CH$_3$CN (10 mL) to give a mixture of diazetidine ($R$)-13c and dihydrooxadiazine ($R$)-28c (overall yield 129 mg, 97%) as one spot by tlc (petroleum ether:ethyl acetate, 6:1, $R_f$ = 0.25) in the ratio 40:60 as judged by crude $^1$H NMR. Separation was achieved by preparative HPLC.$^1$ ($R$)-13c: $^1$H NMR (400 MHz, CDCl$_3$) 7.39-7.30 (10H, m), 5.27-5.16 (4H, m), 4.34 (1H, t, $J = 8.2$ Hz), 4.13 (1H, m), 3.90 (1H, dd, $J = 5.6, 8.2$ Hz), 1.98 (1H, oct, $J = 6.8$ Hz), 0.95 (3H, d, $J = 6.8$ Hz), 0.91 (3H, d, $J = 6.8$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) 161.1 (C), 160.6 (C), 135.8 (C), 135.7

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$^1$ HPLC separation performed by Sean Hindley (GlaxoSmithKline, Stevenage).
(C), 128.5 (2CH), 128.2 (2CH), 127.9 (6CH), 119.6 (C), 68.0 (CH₂), 67.9 (CH₂), 53.0 (CH₂), 31.8 (CH), 17.5 (CH₃), 16.7 (CH₃); LCMS (Method B, ES⁺) tᵣ = 5.17 min, m/z = 369 (M+H)⁺, 391 (M+Na)⁺; MS (ES⁺) m/z = 369 ([M+H]⁺, 100); HRMS (ES⁺) m/z calcd for C₂₁H₂₅N₂O₄ (M+H)⁺: 369.1809; found: 369.1813. (R)-28c: ¹H NMR (400 MHz, CDCl₃) 7.47-7.29 (10H, m), 5.32-5.10 (4H, m), 4.46 (1H, d, J = 10.7 Hz), 4.21 (1H, dd, J = 3.0, 10.8 Hz), 4.07 (1H, br d, J = 10.8 Hz), 1.97 (1H, m), 1.01 (3H, d, J = 6.8 Hz), 0.94 (3H, d, J = 6.8 Hz); LCMS (Method B, ES⁺) tᵣ = 5.25 min, m/z = 369 (M+H)⁺, 391 (M+Na)⁺; MS (ES⁺) m/z = 369 ([M+H]⁺, 100); HRMS (ES⁺) m/z calcd for C₂₁H₂₄N₂O₄Na (M+Na)⁺: 391.1628; found: 391.1636.

2-tert-Butoxy-5,6-dihydro-4H-1,3-oxazine (43)

\[
\begin{align*}
\text{MsO} & \quad \xrightarrow{\text{NHBoc}} \\
\text{O} & \quad \xrightarrow{\text{OfBu}} \quad \text{N}
\end{align*}
\]

N-tert-Butoxycarbonyl-3-aminopropyl methanesulfonate⁹⁸ (41) (100 mg, 0.40 mmol) in THF (3 mL) was cooled to 0 °C and 95% potassium tert-butoxide (70 mg, 0.60 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stirred for 16 h, after which time volatile components were removed in vacuo. Analysis of the crude mixture (64 mg) by ¹H NMR showed dihydrooxazine 43 as the only organic component. IR (neat) 3279, 2972, 1670, 1489, 1293, 1113, 1075, 765, 682 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 4.18 (2H, t, J = 5.4 Hz), 3.33 (2H, t, J = 5.9 Hz), 1.77 (2H, qu, J = 5.6 Hz), 1.42 (9H, s); ¹³C NMR (75 MHz, CDCl₃) 149.7 (C), 79.3 (C), 65.8 (CH₂), 41.2 (CH₂), 27.4 (3CH₃), 21.3 (CH₂); HRMS (ES⁺) m/z calcd for C₈H₁₆NO₂ (M+H)⁺: 158.1176; found: 158.1176.
**N-tert-Butoxycarbonyl azetidine**\(^{100}\) (44)

To a mixture of di-tert-butyl dicarbonate (1.17 g, 5.36 mmol) and triethylamine (746 µL, 5.36 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was added dropwise azetidine (300 µL, 4.47 mmol). The mixture was stirred for 16 h at room temperature then quenched with saturated aqueous ammonium chloride solution. The phases were separated and the aqueous phase extracted with CH\(_2\)Cl\(_2\) (3 × 25 mL). The combined organic phases were washed with water (4 × 25 mL), brine (30 mL), dried over MgSO\(_4\), filtered, and concentrated in vacuo. Column chromatography (cyclohexane:tert-butyl methyl ether 1:1) gave 44 (442 mg, 63%) as a colourless oil. IR (neat) 2975, 2889, 1698, 1390, 1365, 1247, 1133, 776 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 3.85 (4H, t, \(J = 7.6\) Hz), 2.09 (2H, qu, \(J = 7.6\) Hz), 1.35 (9H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 156.1 (C), 78.8 (C), 49.0 (br 2CH\(_2\)), 28.2 (3CH\(_3\)), 15.1 (CH\(_2\)); HRMS (ES\(^+\)) m/z calcd for C\(_8\)H\(_{15}\)NO\(_2\)Na (M+Na\(^+\)): 180.0995; found: 180.1001.

**2-tert-Butoxy-5,6-dihydro-4H-1,3-oxazine** (43) and **N-tert-Butoxycarbonyl azetidine** (44)

N-tert-butoxycarbonyl-3-aminopropyl iodide\(^{99}\) (42) (101 mg, 0.35 mmol) in THF (3 mL) was cooled to 0 °C and 95% potassium tert-butoxide (63 mg, 0.53 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stirred for 16 h, after which time the reaction was concentrated in vacuo to give a crude mixture (48 mg) of dihydrooxazine 43 and azetidine 44 in the ratio 90:9 as judged by crude \(^1\)H NMR.
IV.III Synthesis of 1,2-Dialkyl-1,2-Diazetidines

1,2-Dibenzylidenehydrazine\textsuperscript{105} (48)

\[
\text{Ph} \rightleftharpoons \text{N} \rightleftharpoons \text{N} \rightleftharpoons \text{Ph}
\]

To a solution of benzaldehyde (4.19 mL, 41.1 mmol) and acetic acid (1 mL) in ethanol (20 mL) was added dropwise hydrazine hydrate (1 mL, 20.5 mmol). The reaction was heated at reflux for 16 h then allowed to cool to room temperature. The precipitate was filtered, washed with ethanol, then recrystallised from ethanol to give 48 (4.08 g, 96%) as a yellow crystalline solid. M.p. 93-94.5 °C (ethanol); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) 8.71 (2H, s), 7.90-7.88 (4H, m), 7.51-7.47 (6H, m); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) 162.1 (2CH), 134.1 (2C), 131.3 (2CH), 128.8 (4CH), 128.6 (4CH); MS (ES\textsuperscript{+}) \textit{m/z} = 209 ([M+H]\textsuperscript{+}, 100); HRMS (ES\textsuperscript{+}) \textit{m/z} calcd for C\textsubscript{14}H\textsubscript{13}N\textsubscript{2} (M+H)\textsuperscript{+}: 209.1073; found: 209.1076.

1,2-Dibenzylhydrazine\textsuperscript{106} (49)

\[
\text{Ph} \rightleftharpoons \text{N} \rightleftharpoons \text{N} \rightleftharpoons \text{Ph}
\]

To a stirred solution of 1,2-dibenzylidenehydrazine (48) (753 mg, 3.62 mmol) in ethyl acetate (20 mL) was added 10\% palladium on carbon (75 mg, 10\% w/w) and the suspension stirred under a hydrogen atmosphere (1 atm) for 16 h. The reaction was filtered through celite (ethyl acetate) and concentrated \textit{in vacuo} to give 49 (738 mg, 96\%) as a colourless oil. This material should be used directly or stored in the absence of air. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) 7.37-7.21 (10H, m), 3.94 (4H, s), 3.38 (2H, br s); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) 138.0 (2C), 128.1 (4CH), 128.0 (4CH), 126.7 (2CH), 54.3 (2CH\textsubscript{2}); MS (ES\textsuperscript{+}) \textit{m/z} = 213 ([M+H]\textsuperscript{+}, 100); HRMS (ES\textsuperscript{+}) \textit{m/z} calcd for C\textsubscript{14}H\textsubscript{17}N\textsubscript{2} (M+H)\textsuperscript{+}: 213.1386; found: 213.1377.
Proposed structure: 1-Benzyl-2-benzylidenehydrazine (50)

\[
\text{Ph} \overset{N}{\longrightarrow} \overset{N}{\text{Ph}}
\]

On exposure of 1,2-dibenzylhydrazine to air, a more stable solid crystallised from the oil (3 h, 60% conversion). This reactivity can be minimised by storage of the hydrazine under nitrogen. We propose that aerial oxidation results in 1-benzyl-2-benzylidenehydrazine (50) with the following characteristic data:

- Colourless rhombi.
- IR (film) 3326, 3028, 1595, 1493, 1452, 1357, 1132, 748 cm\(^{-1}\);
- \(^1\)H NMR (400 MHz, CDCl\(_3\)) 7.64 (1H, s), 7.58 (2H, d, \(J = 7.3\) Hz), 7.48-7.26 (8H, m), 5.70 (1H, br s), 4.47 (2H, s);
- MS (ES\(^+\)) \(m/z = 211\) (M+H\(^+\), 100);
- HRMS (ES\(^+\)) \(m/z\) calcd for C\(_{14}\)H\(_{15}\)N\(_2\) (M+H\(^+\)): 211.1230; found: 211.1238.

1,2-Dibenzyl-1,2-diazetidine (45)

\[
\text{Bn} \overset{N}{\longrightarrow} \overset{N}{\text{Bn}}
\]

To a mixture of Na\(_2\)CO\(_3\) (150 mg, 1.42 mmol) in DMF (5 mL) was added 1,2-dibenzylhydrazine (49) (100 mg, 0.47 mmol) and 1,2-dibromoethane (122 \(\mu\)L, 1.42 mmol). The reaction vessel was sealed then subjected to microwave irradiation (100 W, 100 °C) for 1 h. After this time the reaction was allowed to cool, diluted with ethyl acetate (5 mL) and water (5 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 \(\times\) 10 mL). The combined organics were washed with water (5 \(\times\) 10 mL), dried (MgSO\(_4\)), filtered, and concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate, 6:1) furnished 45 (70 mg, 62%) as a colourless oil.

- IR (film) 2860, 1675, 1495, 1453, 1351, 733, 696 cm\(^{-1}\);
- \(^1\)H NMR (400 MHz, CDCl\(_3\)) 7.32-7.19 (10H, m), 3.74 (2H, m), 3.62 (2H, m), 3.51 (2H, m), 3.17 (2H, m);
- \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 136.8 (2C), 129.3 (4CH), 128.2 (4CH), 127.2 (2CH),
66.3 (2CH₂), 51.1 (2CH₂); MS (ES⁺) m/z = 239 ([M+H]⁺, 100); HRMS (ES⁺) m/z calcd for C₁₆H₁₉N₂(M+H)⁺: 239.1543; found: 239.1545.

1,2-bis(4-Methoxybenzylidene)hydrazine¹⁰⁵ (51)

To a solution of 4-methoxybenzaldehyde (5.01 mL, 41.1 mmol) and acetic acid (1 mL) in ethanol (20 mL) was added dropwise hydrazine hydrate (1 mL, 20.5 mmol). The reaction was heated at reflux for 16 h then allowed to cool to room temperature. The precipitate was filtered, washed with ethanol, to give 51 (5.16 g, 94%) as a yellow powder. This material can be recrystallised from toluene or ethanol. M.p. 169-171 °C (ethanol); IR (film) 2926, 1602, 1507, 1250, 1024, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 8.65 (2H, s), 7.82 (4H, d, J = 8.7 Hz), 6.99 (4H, d, J = 8.7 Hz), 3.89 (6H, s); ¹³C NMR (75 MHz, CDCl₃) 162.0 (2C), 161.1 (2CH), 130.1 (4CH), 127.0 (2C), 114.3 (4CH), 55.4 (2CH₃); MS (ES⁺) m/z = 269 ([M+H]⁺, 100); HRMS (ES⁺) m/z calcd for C₁₆H₁₆N₂O₂Na (M+Na)⁺: 269.1104; found: 269.1097.

1,2-bis(4-Methoxybenzyl)hydrazine¹⁰⁶ (52)

To a stirred solution of 1,2-bis(4-methoxybenzylidene)hydrazine (51) (1.51 g, 5.63 mmol) in ethyl acetate (20 mL) was added 10% palladium on carbon (150 mg, 10% w/w) and the suspension stirred at 40 °C under a hydrogen atmosphere (1 atm) for 16 h. The reaction was filtered through celite (ethyl acetate) and concentrated in vacuo to give 52 (1.45 g, 95%) as a colourless oil. This material should be used directly or stored in the absence of air. ¹H NMR (300 MHz,
CDCl$_3$) 7.24 (4H, d, $J = 8.6$ Hz), 6.88 (4H, d, $J = 8.6$ Hz), 3.92 (4H, s), 3.81 (6H, s), 3.14 (2H, br s); $^{13}$C NMR (75 MHz, CDCl$_3$) 158.9 (2C), 130.6 (2C), 129.8 (4CH), 113.9 (4CH), 55.3 (2CH$_3$), 54.2 (2CH$_2$); MS (ES$^+$) $m/z = 273$ ([M+H]$^+$, 100); HRMS (ES$^+$) $m/z$ calcd for C$_{16}$H$_{21}$N$_2$O$_2$ (M+H)$^+$: 273.1598; found: 273.1581.

1,2-**bis**(4-Methoxybenzyl)-1,2-diazetidine (46)

To a mixture of Na$_2$CO$_3$ (150 mg, 1.42 mmol) in DMF (5 mL) was added 1,2-*bis*(4-methoxybenzyl)hydrazine (52) (128 mg, 0.47 mmol) and 1,2-dibromoethane (122 µL, 1.42 mmol). The reaction vessel was sealed then subjected to microwave irradiation (100 W, 100 °C) for 1 h. After this time the reaction was allowed to cool, diluted with ethyl acetate (5 mL) and water (5 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organics were washed with water (5 × 10 mL), dried (MgSO$_4$), filtered, and concentrated *in vacuo*. Column chromatography (petroleum ether:ethyl acetate, 2:1) furnished 46 (73 mg, 52%) as a colourless crystalline solid. M.p. 84-86 °C (ethanol); IR (neat) 2934, 2838, 1661, 1610, 1510, 1242, 1030 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) 8.85 (4H, dt, $J = 8.7$, 2.4 Hz), 7.23 (4H, dt, $J = 8.7$, 2.4 Hz), 3.80 (6H, s), 3.68 (2H, d, $J = 11.8$ Hz), 3.57 (2H, d, $J = 11.8$ Hz), 3.48 (2H, m), 3.18 (2H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) 158.9 (2C), 130.6 (4CH), 129.0 (2C), 113.7 (4CH), 65.7 (2CH$_2$), 55.2 (2CH$_3$), 50.9 (2CH$_2$); MS (ES$^+$) $m/z = 299$ ([M+H]$^+$, 100); HRMS (ES$^+$) $m/z$ calcd for C$_{18}$H$_{25}$N$_2$O$_2$ (M+H)$^+$: 299.1754; found: 299.1760. Crystals suitable for X-ray diffraction were grown from ethanol/chloroform (95:5) by slow evaporation.
IV.IV Synthesis of 1,2-Disulphonyl-1,2-Diazetidines

1,2-\(\text{bis(Tosyl)-1,2-diazetidine (53)}\)

To a stirred slurry of sodium hydride (60% in mineral oil) (2.27 g, 56.7 mmol) in DMF (130 mL) at -10 °C was added dropwise a solution of 1,2-di(tosyl)hydrazine\(^\text{109}\) (8.77 g, 25.8 mmol) in DMF (100 mL) maintaining the temperature between -10 and 0 °C. After the addition, the reaction was stirred for 5 min at -10 °C then 1,2-dibromoethane (2.66 mL, 30.9 mmol) was added dropwise over a period of 10 min. The reaction was then allowed to warm to room temperature and stirred for 16 h, after which time the reaction was quenched with saturated aqueous ammonium chloride solution (caution). This mixture was extracted with ethyl acetate (3 × 70 mL). The combined extracts were washed with water (5 × 50 mL), brine, dried over MgSO\(_4\), filtered, and concentrated in vacuo. Recrystallisation from ethanol furnished 53 (5.29 g, 56%) as a colourless crystalline solid. M.p. 199.5-200.5 °C (DSC\(^\dagger\) (diethyl ether); UV-Vis (CHCl\(_3\)) \(\lambda_{\text{max}}\) 241 nm; IR (neat) 2941, 1597, 1401, 1313, 1211, 1147, 1079, 812, 751 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 7.91 (4H, d, \(J = 8.1 \text{ Hz}\)), 7.41 (4H, d, \(J = 8.1 \text{ Hz}\)), 3.66 (4H, s), 2.49 (6H, s); \(^13\)C NMR (100 MHz, CDCl\(_3\)) 145.7 (2C), 130.3 (4CH), 129.7 (4CH), 129.2 (2C), 47.9 (2CH\(_2\)), 21.8 (2CH\(_3\)); MS (ES\(^+\)) \(m/z = 389\) ([M+Na]\(^+\), 100); HRMS (ES\(^+\)) \(m/z\) calcd for C\(_{16}\)H\(_{18}\)N\(_2\)O\(_4\)S\(_2\)Na (M+Na\(^+\)): 389.0600; found: 389.0600. Crystals suitable for X-ray diffraction were grown from ethanol/chloroform (95:5) by slow evaporation.

\(^\dagger\) Determined by differential scanning calorimetry.
At higher addition temperatures (above 0 °C) 1,2-ditosylethane (57) could be isolated by careful recrystallisation from ethanol (15-60% yield) as a colourless crystalline solid. M.p. 200-202 °C (ethanol); \(^1\)H NMR (400 MHz, CHCl\(_3\)) 7.75 (4H, d, \(J = 8.2\) Hz), 7.39 (4H, d, \(J = 8.2\) Hz), 3.40 (4H, s), 2.48 (6H, s); \(^13\)C NMR (100 MHz, CHCl\(_3\)) 145.8 (2C), 135.1 (2C), 130.3 (4CH), 128.1 (4CH), 49.7 (2CH\(_2\)), 21.7 (2CH\(_3\)); MS (ES\(^+\)) \(m/z = 339\) ([M+H]\(^+\), 100). Crystals suitable for X-ray diffraction were grown from ethanol/chloroform (95:5) by slow cooling.

1-(2-(4-Tolylsulphonyl)oxyethyl)-1,2-bis(4-tolylsulphonyl) hydrazine (58)

To a stirred solution of 2-hydroxyethyl hydrazine (90% purity) (1.00 mL, 13.3 mmol) in pyridine (15 mL) at 0 °C was added portionwise TsCl (7.86 g, 41.2 mmol) maintaining the temperature between 0 and 10 °C. The reaction was stirred at 0 °C for 2 h then poured into a mixture of ice and concentrated HCl (2:1, v/v, 130 mL) and stirred until a clear solution was obtained. This solution was saturated with sodium chloride and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried (MgSO\(_4\)), filtered, and concentrated \textit{in vacuo} to give a yellow solid. Purification by column chromatography (petroleum ether:ethyl acetate, 3:1) furnished 58 (3.33 g, 47%) as a white crystalline solid. M.p. 201-203 °C (methanol); IR (neat) 3265, 2970, 1598, 1346, 1165, 1091, 902 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 7.78 (2H, d, \(J = 8.3\) Hz), 7.66 (2H, d, \(J = 8.4\) Hz), 7.54 (2H, d, \(J = 8.3\) Hz), 7.36 (2H, d, \(J = 8.4\) Hz), 7.25 (2H, d, \(J = 8.4\) Hz), 7.22 (2H, d, \(J = 8.3\) Hz), 6.47 (1H, s), 4.28 (2H, t, \(J = 5.8\) Hz), 3.70 (2H, t, \(J = 5.8\) Hz), 2.46 (3H, s), 2.44 (3H, s), 2.42 (3H, s); \(^13\)C NMR (100 MHz, CDCl\(_3\)) 145.3 (C), 145.1 (C), 144.8 (C), 134.4 (C), 132.7 (C), 132.3 (C), 130.0 (2CH), 129.8 (2CH), 129.6 (2CH), 128.6 (2CH), 128.5 (2CH), 128.1 (2CH), 66.6
(CH₂) 51.3 (CH₂), 21.8 (CH₃), 21.7 (2CH₃); MS (ES⁺) m/z = 561 ([M+Na]⁺, 100); HRMS (ES⁺) m/z calc for C₂₃H₃₆N₆O₈S₃ (M+NH₄)⁺: 556.1240; found: 556.1244.

1-(2-(Methylsulphonyl)oxyethyl)-1,2-bis(methylsulphonyl) hydrazine (59)

To a stirred solution of 2-hydroxyethyl hydrazine (90% purity) (1.00 mL, 13.3 mmol) in pyridine (15 mL) at 0 °C was added dropwise MsCl (3.19 mL, 41.2 mmol) maintaining the temperature between 0 and 10 °C. The reaction was stirred at 0 °C for 1 h then poured into a mixture of ice and concentrated HCl (2:1, v/v, 60 mL) and stirred until a clear solution was obtained. This solution was saturated with sodium chloride and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried (MgSO₄), filtered, and concentrated in vacuo to give a thick yellow oil. Purification by column chromatography (petroleum ether:ethyl acetate, 1:2) furnished 59 (2.33 g, 57%) as a colourless crystalline solid. M.p. 107-108 °C (ethanol); IR (neat) 3221, 2942, 1334, 1319, 1174, 955, 783 cm⁻¹; ¹H NMR (400 MHz, d₆-DMSO) 9.98 (1H, s), 4.43 (2H, t, J = 5.5 Hz), 3.72 (2H, br s), 3.21 (3H, s), 3.15 (3H, s), 3.09 (3H, s); ¹³C NMR (100 MHz, d₆-DMSO) 66.4 (CH₂), 52.1 (CH₂), 40.1 (CH₃), 36.8 (CH₃), 35.6 (CH₃); MS (ES⁺) m/z = 333 ([M+Na]⁺, 100); HRMS (ES⁺) m/z calc for C₅H₁₄N₂O₇S₃ (M+Na)⁺: 332.9855; found: 332.9853.

1-(2-(Phenylsulphonyl)oxyethyl)-1,2-bis(phenylsulphonyl) hydrazine (60)

To a stirred solution of 2-hydroxyethyl hydrazine (98% purity) (250 μL, 3.69 mmol) in pyridine (10 mL) at 0 °C was added dropwise benzenesulphonyl chloride (1.47 mL, 11.4 mmol) maintaining the
temperature between 0 and 10 °C. The reaction was stirred at 0 °C for 1 h then poured into a mixture of ice and concentrated HCl (2:1, v/v, 40 mL) and stirred until a clear solution was obtained. This solution was saturated with sodium chloride and extracted with ethyl acetate (3 × 25 mL). The combined extracts were dried (MgSO₄), filtered, and concentrated in vacuo to give a thick yellow oil. Purification by column chromatography (petroleum ether:ethyl acetate, 2:1) furnished 60 (1.11 g, 60%) as a colourless crystalline solid. M.p. 122.5-124 °C; IR (film) 3222, 2988, 1429, 1357, 1170, 741, 687 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.90-7.86 (2H, m), 7.81-7.77 (2H, m), 7.70-7.52 (7H, m), 7.50-7.38 (4H, m), 6.88 (1H, s), 4.30 (2H, t, J = 5.9 Hz), 3.70 (2H, t, J = 5.9 Hz); ¹³C NMR (100 MHz, CDCl₃) 137.5 (C), 135.6 (C), 135.3 (C), 134.2 (CH), 134.0 (2CH), 133.8 (2CH), 129.5 (CH), 129.2 (2CH), 129.0 (2CH), 128.5 (CH), 128.4 (2CH), 128.0 (2CH), 66.7 (CH₂), 51.6 (CH₂); MS (ES⁺) m/z = 497 (M+H)⁺, 100); HRMS (ES⁺) m/z calcd for C₂₀H₂₀N₂O₇S₃Na (M+Na)⁺: 519.0325; found: 519.0327.

1-(2-Iodoethyl)-1,2-bis(methylsulphonyl) hydrazine (61)

\[
\text{N} \quad \text{Ms} \\
\text{N} \quad \text{NHMs}
\]

To a solution of mesylate 59 (450 mg, 1.45 mmol) in THF (15 mL) was added LiI (1.94 g, 14.5 mmol) and the resultant mixture heated at reflux for 2.5 h. The reaction was allowed to cool to room temperature, concentrated in vacuo, and Et₂O and water were added. The phases were separated and the aqueous phase extracted three times with Et₂O. The combined organic phases were washed with 10% aqueous Na₂S₂O₃ solution, brine, dried over MgSO₄, filtered, and concentrated in vacuo. Recrystallisation from MeOH/water furnished 61 (358 mg, 72%). M.p. 153-154 °C (methanol); IR (neat) 3242, 2933, 1325, 1157, 1145, 961, 791 cm⁻¹; ¹H NMR (300 MHz, d₆-DMSO) 9.91 (1H, s), 3.69 (2H, br s), 3.37 (2H, t, J = 8.2 Hz), 3.13 (3H, s), 3.06
1-(2-Iodoethyl)-1,2-bis(phenylsulphonyl) hydrazine (62)

To a solution of 60 (753 mg, 1.52 mmol) in THF (15 mL) was added dropwise LiI (2.03 g, 15.2 mmol) in THF (6 mL) and the resultant mixture heated at reflux for 40 min. The reaction was allowed to cool to room temperature, concentrated in vacuo, and Et₂O and water were added. The phases were separated and the aqueous phase extracted three times with Et₂O. The combined organic phases were washed with 10% aqueous Na₂S₂O₃ solution, brine, dried over MgSO₄, filtered, and concentrated in vacuo. Recrystallisation from MeOH/water furnished 62 (480 mg, 68%) as white needles. M.p. 115 °C (MeOH) (decomp.); IR (film) 3250, 1449, 1351, 1339, 1173, 1159, 1086, 687 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 7.84 (2H, d, J = 8.0 Hz), 7.70-7.40 (8H, m), 6.85 (1H, m), 3.66 (2H, t, J = 8.0 Hz), 3.35 (2H, t, J = 8.0 Hz); ¹³C NMR (75 MHz, CDCl₃) 137.9 (C), 136.1 (C), 134.8 (CH), 134.6 (CH), 130.0 (2CH), 129.8 (2CH), 129.1 (4CH), 57.3 (CH₂), 0.15 (CH₂); MS (ES⁺) m/z = 489 (M+Na)⁺, 100); HRMS (ES⁺) m/z calcd for C₁₄H₁₅IN₂O₄S₂Na (M+Na)⁺: 488.9410; found: 488.9423.

1,2-bis(Methylsulfonyl)-1,2-diazetidine (55)

To iodide 61 (116 mg, 0.34 mmol) in CH₃CN (10 mL) was added Cs₂CO₃ (166 mg, 0.51 mmol) and the mixture stirred for 5 h at room temperature. The reaction was concentrated in vacuo and the residue washed with hot ethanol (4 × 5
mL). These washings were discarded and the residue washed again with hot CH$_3$CN (4 × 5 mL). These washings were collected and concentrated in vacuo. Crystallisation from DMSO/water removed any remaining inorganic material to give 55 (53 mg, 73%) as a colourless crystalline solid. M.p. 229-232 °C (DMSO); IR (neat) 2941, 1346, 1170, 1151, 1030, 949, 755 cm$^{-1}$; $^1$H NMR (300 MHz, d$_6$-DMSO) 4.29 (4H, s), 3.31 (6H, s); $^{13}$C NMR (75 MHz, d$_6$-DMSO) 47.2 (2CH$_2$), 33.1 (2CH$_3$); MS (ES$^+$) m/z = 237 ([M+Na]$^+$, 100); HRMS (ES$^+$) m/z calcd for C$_{44}$H$_{10}$N$_2$O$_4$S$_2$Na (M+Na)$^+$: 236.9974; found: 236.9979. Crystals suitable for X-ray diffraction were grown from acetonitrile by slow evaporation.

1,2-bis(Phenylsulfonyl)-1,2-diazetidine (54)

\[
\text{PhO}_2\text{S} \quad \text{N} \quad \text{N} \quad \text{SO}_2\text{Ph}
\]

To iodide 62 (163 mg, 0.35 mmol) in CH$_3$CN (10 mL) was added Cs$_2$CO$_3$ (171 mg, 0.52 mmol) and the mixture stirred for 5 h at room temperature. The mixture was filtered through celite, concentrated in vacuo, then passed through a short column of silica gel (ethyl acetate) to give 54 (115 mg, 98%) as a colourless crystalline solid. M.p. 164-166 °C (EtOH); IR (neat) 2973, 1447, 1358, 1168, 1086, 995, 722 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 7.97 (4H, d, J = 7.6 Hz), 7.68 (2H, t, J = 7.6 Hz), 7.57 (4H, t, J = 7.6 Hz), 3.63 (4H, s); $^{13}$C NMR (125 MHz, CDCl$_3$) 134.6 (2CH), 132.3 (2C), 130.3 (4CH), 129.1 (4CH), 47.8 (2CH$_2$); MS (ES$^+$) m/z = 361 ([M+Na]$^+$, 100); HRMS (ES$^+$) m/z calcd for C$_{14}$H$_{14}$N$_2$O$_4$S$_2$Na (M+Na)$^+$: 361.0287; found: 361.0294.
IV.V Attempted Synthesis of 1,2-Diazetidine

1-Tosyl-4,5-dihydro-1H-pyrazole\textsuperscript{118} (66a) and tert-Butyl 4,5-dihydro-1H-pyrazole-1-carboxylate (66b)

\[
\begin{align*}
\text{H}_2\text{N} & \text{H}_2\text{N} \quad \text{ii) \ Boc}_2\text{O or TsCl} \\
\text{H}_2\text{N} & \text{H}_2\text{N} \quad \text{i) NaOCl, NaOH} \\
\text{N} \quad \text{N} & \\
\text{R} = \text{Ts} & \quad \text{Boc} \quad 66a \\
\text{Boc} & \quad 66b
\end{align*}
\]

1,3-Diaminopropane (75 μL, 0.90 mmol) in water (10 mL) was brought to pH 7 with 2M HCl. An additional 75 μL of diamine was added. The solution, which now contained 1.80 mmol of 1,3-diaminopropane monohydrochloride, was cooled to 0 °C and commercial bleach (~5% NaOCl) (2.80 mL, approx. 1.89 mmol) was added over 15 min under vigorous stirring, ensuring the reaction temperature did not rise above 5 °C. Gelatine (45% purity, 27 mg) in water (2 mL) was then added in one portion. Cooling was stopped and NaOH (180 mg, 4.50 mmol) in water (2 mL) was added dropwise over 15 min under vigorous stirring. The reaction was heated to 60 °C for 1 h (ammonia is evolved), allowed to cool and then was divided into two equal portions A and B.

Portion A was cooled to 0 °C, and NaOH (72 mg, 1.80 mmol), and TsCl (343 mg, 1.80 mmol) in Et\textsubscript{2}O (10 mL) were added successively. After stirring for 16 h, the organic layer was separated and the aqueous layer extracted with Et\textsubscript{2}O (3 × 10 mL). The combined extracts were washed water (3 × 10 mL), brine, dried (MgSO\textsubscript{4}), filtered, and concentrated in vacuo. Purification by recrystallisation (ethanol) furnished 1-tosyl-4,5-dihydro-1H-pyrazole (66a)\textsuperscript{118} (50 mg, 26% corrected yield) as white needles. M.p. 162-163 °C (decomp.); IR (film) 2919, 1594, 1348, 1290, 1163, 1098, 641 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) 7.77 (2H, dd, \textit{J} = 8.3, 1.7 Hz), 7.32 (2H, d, \textit{J} = 8.3 Hz), 7.00 (1H, d, \textit{J} = 1.6 Hz), 3.50 (2H, dt, \textit{J} = 1.6, 9.5 Hz), 2.74 (2H, t, \textit{J} = 9.5 Hz), 2.43 (3H, s); \textsuperscript{13}C
NMR (100 MHz, CDCl$_3$) 149.9 (CH), 144.4 (C), 139.8 (C), 129.5 (2CH), 128.9 (2CH), 46.5 (CH$_2$), 34.1 (CH$_2$), 21.6 (CH$_3$); MS (ES$^+$) m/z = 225 (M+H$^+$, 100); HRMS (ES$^+$) m/z calcd for C$_{10}$H$_{12}$N$_2$O$_2$SNa (M+Na)$^+$: 247.0512; found: 247.0509.

To portion B was added NaOH (72 mg, 1.80 mmol), then di-tert-butyl dicarbonate (392 mg, 1.80 mmol) in CH$_2$Cl$_2$ (10 mL) and the mixture stirred at room temperature for 16 h. The organic layer was separated and the aqueous layer extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined extracts were washed with brine, dried (MgSO$_4$), filtered, and concentrated in vacuo. Purification by column chromatography (petroleum ether:ethyl acetate, 3:1) furnished tert-butyl 4,5-dihydro-1H-pyrazole-1-carboxylate (66b) (50 mg, 32% corrected yield) as a colourless oil. IR (film) 3326, 2925, 1692, 1515, 1367, 1251, 1156, 748 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 6.80 (1H, t, $J = 1.7$ Hz), 3.69 (2H, t, $J = 10.2$ Hz), 2.79 (2H, dd, $J = 1.7$, 10.2 Hz), 1.47 (9H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) 152.4 (C), 146.1 (CH), 81.3 (C), 43.3 (CH$_2$), 33.3 (CH$_2$), 28.4 (3CH$_3$); MS (ES$^+$) m/z = 363 ([2M+Na]$^+$, 100); HRMS (ES$^+$) m/z calcd for C$_8$H$_{14}$N$_2$O$_2$Na (M+Na)$^+$: 193.0947; found: 193.0940.

**Attempted cyclisation of 1,2-diaminoethane**

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{ii) Boc}_2\text{O} \\
\text{NH}_2 & \quad \text{BOc} \quad \text{NHBOc} + \text{BOcNH}_2 \\
\text{NaOCl, NaOH} & \quad \text{i) NaOCl, NaOH}
\end{align*}
\]

1,2-Diaminoethane (150 µL, 2.24 mmol) in water (10 mL) was reacted as described for 1,3-diaminopropane with commercial bleach (3.33 mL, approx. 2.25 mmol), NaOH (224 mg, 5.61 mmol) and gelatine (45%, 27 mg). After heating, the resultant solution was allowed to cool and reacted with di-tert-butyl dicarbonate (490 mg, 2.24 mmol) in
CH$_2$Cl$_2$ (10 mL) in the presence of NaOH (90 mg, 2.24 mmol) as described above. Column chromatography (petroleum ether:ethyl acetate, 6:1) furnished di-tert-butyl ethylenedicarbamate (68) (60 mg, 46%), M.p. 137-138 °C (lit.$^{198}$ 139-140 °C) and tert-butyl carbamate (69) (56 mg, 19%) M.p. 107-108 °C (lit.$^{199}$ 108-108.5 °C) as white crystalline solids.

**Deprotection of Di-tert-butyl 1,2-diazetidine-1,2-dicarboxylate**

\[
\begin{align*}
\text{Boc} \quad \text{N} \quad \text{N} \quad \text{Boc} & \xrightarrow{i)} 2\rightarrow12 \text{ eq Na} \\
\text{CD$_2$OD} & \\
\text{ii) TsCl, Et$_2$O} & \quad \xrightarrow{} \quad \text{Boc} \quad \text{N} \quad \text{N} \quad \text{Ts} + \text{TsNH$_2$}
\end{align*}
\]

Sodium (10 mg, 0.43 mmol) was added to $d_4$-MeOH (2 mL) under strong stirring. After the metal had dissolved, di-tert-butyl 1,2-diazetidine-1,2-dicarboxylate (55 mg, 0.21 mmol) in $d_4$-MeOH (1 mL) was added dropwise. The reaction was sampled every hour for six hours by withdrawing 100 µL of the reaction mixture via syringe and diluting with $d_4$-MeOH to the volume required for NMR, and spectra were run directly. Sodium (10 mg portions, total 60 mg, 2.50 mmol) was added to the reaction after each analysis until the diazetidine was fully consumed. The reaction was brought to pH 10 by the addition of dilute aqueous HCl (caution). Et$_2$O (1 mL) and TsCl (102 mg, 0.53 mmol) were added and the mixture stirred rapidly overnight. The reaction was concentrated in vacuo. Recrystallisation of the crude material from hot ethanol gave tosylamide$^{128}$ (76) (18 mg, 25% based on starting material nitrogen content) as a colourless solid. M.p. 132-133 °C; $^1$H NMR (400 MHz, CDCl$_3$) 7.73 (2H, d, $J = 8.3$ Hz), 7.36 (2H, d, $J = 8.3$ Hz), 7.28 (2H, s), 2.38 (3H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) 141.9 (C), 141.5 (C), 129.3 (CH), 125.7 (CH), 20.9 (CH$_3$); MS (ES$^+$) $m/z$ = 194 (M+Na)$^+$, 100; HRMS (ES$^+$) $m/z$ calcd for C$_7$H$_{10}$NO$_2$S (M+H)$^+$: 172.0427; found: 172.0424. Preparative tlc of the mother liquor ($R_f$
= 0.22, petroleum ether:ethyl acetate, 4:1) furnished tert-butyl 2-(para-toluenesulphonyl)-1,2-diazetidine-1-carboxylate (75) (7 mg, 11%) as an impure white solid. $^1$H NMR (400 MHz, CDCl$_3$) 7.88 (2H, t, $J$ = 8.3 Hz), 7.39 (2H, t, $J$ = 8.3 Hz), 4.06 (2H, t, $J$ = 7.9 Hz), 3.91 (2H, t, $J$ = 8.3 Hz), 2.48 (3H, s), 1.45 (9H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) 159.1 (C), 145.1 (C), 131.9 (2CH), 129.6 (2CH), 119.6 (C), 82.9 (C), 48.9 (CH$_2$), 47.5 (CH$_2$), 27.9 (3CH$_3$), 21.7 (CH$_3$); MS (ES$^+$) $m/z$ = 355 ([M+Na]$^+$, 100); HRMS (ES$^+$) $m/z$ calcd for C$_{14}$H$_{20}$N$_2$O$_4$SNa (M+Na)$^+$: 335.1036; found: 335.1040.
IV.VI Synthesis of 3-Alkylidene-1,2-Diazetidines

Synthesis of Hydrazodicarboxylates: General Procedure 3

To a mixture of alcohol (1.0 molar equiv) and triphenylphosphine (2.0 molar equiv) in THF at 0 °C was added dropwise the azodicarboxylate (2.0 molar equiv). The reaction was allowed to warm to room temperature, stirred until tlc showed complete consumption of starting material then concentrated in vacuo. Purification of the hydrazodicarboxylate was achieved by column chromatography (petroleum ether:ethyl acetate).

Diethyl 1-(2-bromoallyl)hydrazine-1,2-dicarboxylate (88)

To a solution of 2-bromoallyl alcohol (169 µL, 0.20 mmol) and triphenylphosphine (1.07 g, 0.41 mmol) in THF (10 mL) at 0 °C was added dropwise diethylazodicarboxylate (642 µL, 0.41 mmol). The reaction was allowed to warm to room temperature and stirred for 18 h after which time the reaction was concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate, 8:1) afforded 88 (556 mg, 92%) as a colourless oil. IR (film) 3291, 2983, 1703, 1381, 1219, 1059, 763 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 6.72 (1H, m), 5.79 (1H, br s), 5.57 (1H, d, J = 1.9 Hz), 4.41-4.23 (2H, m), 4.15 (4H, br q, J = 7.1 Hz), 1.23 (6H, t, J = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) 155.9 (C), 155.8 (C), 127.9 (C), 120.2 and 119.6 (CH₂), 64.3
and 64.0 (CH₂), 62.9 and 62.2 (CH₂), 58.0 and 57.2 (CH₂), 14.4 (2CH₃); MS (ES⁺) m/z = 319 ([M⁺Br]+Na⁺, 50), 317 ([M⁺Br]+Na⁺, 50); HRMS (ES⁺) m/z calcd for C₉H₁₆⁷⁹BrN₂O₄ (M+H)⁺: 295.0288; found: 295.0290.

Diethyl 1-(2-iodoallyl)hydrazine-1,2-dicarboxylate (96)

To a solution of 2-iodoallyl alcohol¹⁴² (1.45 g, 7.88 mmol) and triphenylphosphine (4.13 g, 15.8 mmol) in THF (30 mL) at 0 °C was added dropwise diethyl azodicarboxylate (2.48 mL, 15.8 mmol). The reaction was allowed to warm to room temperature and stirred for 24 h after which time the reaction was concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate, 8:1) afforded 96 (2.06 g, 76%) as a colourless oil. IR (film) 3295, 2982, 1706, 1380, 1259, 1217, 1058, 763 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 7.82 (1H, m), 6.22 (1H, s), 5.83 (1H, s), 4.30-4.08 (6H, m), 1.25 (3H, t, J = 7.2 Hz), 1.21 (3H, t, J = 7.1 Hz); ¹³C NMR (150 MHz, CDCl₃) 155.2 (C), 154.8 (C), 127.9 and 127.4 (CH₂), 104.4 (C), 63.6 (CH₂), 62.3 and 61.5 (CH₂), 60.7 and 59.9 (CH₂), 13.8 (CH₃), 13.5 (CH₃); MS (ES⁺) m/z = 343 ([M+H]+, 100); HRMS (ES⁺) m/z calcd for C₉H₁₆IN₂O₄ (M+H)⁺: 343.0149; found: 343.0142.

Di-tert-butyl 1-(2-iodoallyl)hydrazine-1,2-dicarboxylate (97)

To a solution of 2-iodoallyl alcohol¹⁴² (2.00 g, 10.9 mmol) and triphenylphosphine (5.71 g, 21.8 mmol) in THF (30 mL) at 0 °C was added portionwise di-tert-butyl azodicarboxylate (5.01 g, 21.8 mmol). The reaction was allowed to warm to room temperature and stirred for 24 h after which time the reaction was concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate,
10:1) afforded 97 (2.66 g, 62%) as a colourless oil. IR (film) 3323, 2978, 1708, 1478, 1366, 1143 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) 6.53-6.11 (2H, m), 5.86 (1H, s), 4.24 (2H, br s), 1.49-1.38 (18H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) 154.5 (C), 154.0 (C), 127.3 and 127.0 (CH$_2$), 105.5 (C), 81.2 (CH$_2$), 80.9 (CH$_2$), 61.0 and 59.8 (CH$_2$), 27.6 (6CH$_3$); MS (ES$^+$) m/z = 421 ([M+Na$^+$], 100); HRMS (ES$^+$) m/z calcd for C$_{13}$H$_{23}$IN$_2$O$_4$Na (M+Na)$^+$: 421.0595; found: 421.0604.

**Dibenzyl 1-(2-iodoallyl)hydrazine-1,2-dicarboxylate (98)**

To a solution of 2-iodoallyl alcohol$^{142}$ (1.25 g, 6.79 mmol) and triphenylphosphine (3.56 g, 13.6 mmol) in THF (35 mL) at 0 °C was added portionwise dibenzylazodicarboxylate (4.05 g, 13.6 mmol). The reaction was allowed to warm to room temperature and stirred for 36 h after which time the reaction was concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate, 8:1) afforded 98 (2.74 g, 87%) as a white crystalline solid. M.p. 90.0-91.0 °C (ethanol); IR (film) 3268, 2988, 1734, 1683, 1421, 1212, 749 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) 7.42-7.04 (10H, m), 6.77 (1H, m), 6.14(1H, m), 5.77 (1H, s), 5.25-4.89 (4H, m) 4.44-4.03 (2H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) 155.0 (C), 154.7 (C), 134.8 (2C), 128.4 (CH$_2$), 128.0 (4CH), 127.9 (CH), 127.8 (CH), 127.6 (3CH), 127.3 (CH), 104.1 (C), 68.2 and 67.8 (CH$_2$), 67.3 and 67.1 (CH$_2$), 60.8 and 60.1 (CH$_2$); MS (ES$^+$) m/z = 489 ([M+Na$^+$], 100); HRMS (ES$^+$) m/z calcd for C$_{19}$H$_{19}$IN$_2$O$_4$Na (M+Na)$^+$: 489.0282; found: 489.0287.
(Z)-Diethyl 1-(2-bromo-3-phenylallyl)hydrazine-1,2-dicarboxylate {(Z)-99}

To a solution of (Z)-2-bromo-3-phenylprop-2-en-1-ol\(^{145}\) (189 mg, 0.73 mmol) and triphenylphosphine (468 mg, 1.78 mmol) in THF (5 mL) at 0 °C was added dropwise diethylazodicarboxylate (281 µL, 1.78 mmol). The reaction was allowed to warm to room temperature and stirred for 16 h after which time the reaction was concentrated \textit{in vacuo}. Column chromatography (petroleum ether:ethyl acetate, 10:1) afforded (Z)-99\(^{1}\) (188 mg, 69%) as a colourless oil. IR (film) 3290, 2987, 1702, 1382, 1255, 1216, 1058, 735 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.61 (2H, d, \(J = 7.1\) Hz), 7.41-7.28 (3H, m), 7.00-6.47 (2H, m), 4.55 (2H, br s), 4.20 (4H, br q, \(J = 7.1\) Hz), 1.27 (6H, br t, \(J = 7.1\) Hz); \(^1\)C NMR (100 MHz, CDCl\(_3\)) 156.1 (2C), 134.8 (C), 131.5 and 131.0 (CH), 129.0 (2CH), 128.4 (CH), 128.2 (2CH), 120.5 (C), 62.9 (CH\(_2\)), 62.2 (CH\(_2\)), 59.8 and 59.1 (CH\(_2\)), 14.5 (2CH\(_3\)); MS (ES\(^+\)) m/z = 395 ([M\(^{81}\)Br]+Na\(^+\), 50), 393 ([M\(^{79}\)Br]+Na\(^+\), 50); HRMS (ES\(^+\)) m/z calcd for C\(_{15}\)H\(_{19}\)BrN\(_2\)O\(_4\)Na (M+Na\(^+\))= 393.0420, found: 393.0423.

\(^{1}\) Contaminated with ca. 10% tetrakis(ethoxycarbonyl)hydrazine: \(^1\)H NMR (300 MHz, CDCl\(_3\)) 4.31 (q, \(J = 7.1\) Hz), 1.31 (t, \(J = 7.1\) Hz); \(^1\)C NMR (100 MHz, CDCl\(_3\)) 150.6 (C), 64.3 (CH\(_2\)), 14.1 (CH\(_3\)); MS (ES\(^+\)) m/z = 343 ([M+Na\(^+\)], 100); HRMS (ES\(^+\)) m/z calcd for C\(_{12}\)H\(_{17}\)N\(_2\)O\(_6\) (M+H\(^+\))= 321.1292, found: 321.1294. This impurity did not affect the Cu-catalysed cyclisation.
Di-tert-butyl 1-(2-bromo-3-methylbut-2-enyl)hydrazine-1,2-dicarboxylate (100)

To a solution of 2-bromo-3-methylbut-2-en-1-ol\textsuperscript{200} (265 mg, 1.61 mmol) and triphenylphosphine (845 mg, 3.21 mmol) in THF (6 mL) at 0 °C was added portionwise di-tert-butylazodicarboxylate (740 mg, 3.21 mmol). The reaction was allowed to warm to room temperature and stirred for 24 h after which time the reaction was concentrated \textit{in vacuo}. Column chromatography (petroleum ether:ethyl acetate, 12:1) afforded \textbf{100} (419 mg, 69\%) as a white crystalline solid. M.p. 63.5-65.0 °C; IR (film) 3676, 2979, 1707, 1367, 1143, 1051, 736 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (323K, 400 MHz, CDCl\textsubscript{3}) 6.22(1H, m), 4.46 (2H, br s), 1.90 (3H, s), 1.83 (3H, s), 1.48 (9H, s), 1.47 (9H, s); \textsuperscript{13}C NMR\textsuperscript{i} (323K, 150 MHz, CDCl\textsubscript{3}) 155.3, 155.0 and 154.7 (2C), 136.7, 136.4 and 136.1 (C), 116.3 and 116.1 (C), 81.8, 81.2 and 81.0 (2C), 53.7, 53.0 and 52.8 (CH\textsubscript{2}), 28.2 (6CH\textsubscript{3}), 25.5 (CH\textsubscript{3}), 20.5 (CH\textsubscript{3}); MS (ES\textsuperscript{+}) \textit{m/z} = 403 ([M\textsuperscript{79}Br]+Na\textsuperscript{+}, 50), 401 ([M\textsuperscript{79}Br]+Na\textsuperscript{+}, 50); HRMS (ES\textsuperscript{+}) \textit{m/z} calcd for C\textsubscript{15}H\textsubscript{27}\textsuperscript{79}BrN\textsubscript{2}O\textsubscript{4}Na (M+Na\textsuperscript{+}): 401.1046; found: 401.1053.

Diethyl 1-(2-bromocyclohex-2-enyl)hydrazine-1,2-dicarboxylate (101)

To a solution of 2-bromocyclohex-2-enol\textsuperscript{148,149} (1.46 g, 8.27 mmol) and triphenylphosphine (4.34 g, 16.5 mmol) in THF (25 mL) at 0 °C was added dropwise diethylazodicarboxylate (2.60 mL, 16.5 mmol). The reaction was allowed to warm to room temperature and stirred for 24 h after which time the reaction was concentrated \textit{in vacuo}. Column chromatography (petroleum

\textsuperscript{i} Additional data: \textsuperscript{13}C NMR (298K, 150 MHz, CDCl\textsubscript{3}) 155.3, 155.0 and 154.7 (2C), 136.7, 136.4 and 136.1 (C), 116.3 and 116.1 (C), 81.8, 81.2 and 81.0 (2C), 53.7, 53.0 and 52.8 (CH\textsubscript{2}), 28.2 (6CH\textsubscript{3}), 25.5 (CH\textsubscript{3}), 20.5 (CH\textsubscript{3}).
ether:ethyl acetate, 7:1) afforded 101 (2.13 g, 77%) as a white solid. M.p. 71.5-73.5 °C; IR (film) 3661, 3290, 2981, 1751, 1705, 1303, 1221, 1061, 729 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 6.45-6.05 (2H, m), 4.91 (1H, m), 4.37-4.09 (4H, m), 2.23-1.85 (4H, m), 1.85-1.58 (2H, m), 1.39-1.12 (6H, m); ¹³C NMR (100 MHz, CDCl₃) 156.4, 155.8 and 155.6 (2C), 134.8 and 134.7 (CH), 121.1 (C), 62.3 and 62.0 (CH₂), 61.5 and 61.4 (CH₂), 59.1, 58.1 and 57.7 (CH), 28.1 and 27.8 (CH₂), 26.7 (CH₂), 19.5 (CH₂), 13.9 and 13.8 (CH₃), 13.7 and 13.5 (CH₃); MS (ES⁺) m/z = 359 ([M(⁸¹Br)+Na]⁺, 50), 357 ([M(⁷⁹Br)+Na]⁺, 50); HRMS (ES⁺) m/z calcd for C₁₂H₁₉⁷⁹BrN₂O₄Na (M+Na)⁺: 357.0422; found: 357.0424.

**Dibenzyl 1-(2-bromocyclohex-2-ethyl)hydrazine-1,2-dicarboxylate (102)**

To a solution of 2-bromocyclohex-2-enol₁₄₈,₁₄₉ (1.30 g, 7.35 mmol) and triphenylphosphine (3.85 g, 14.7 mmol) in THF (20 mL) at 0 °C was added portionwise dibenzylazodicarboxylate (4.38 g, 14.7 mmol). The reaction was allowed to warm to room temperature and stirred for 20 h after which time the reaction was concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate, 9:1) afforded 102 (2.75 g, 82%) as a white solid. M.p. 96.0-97.0 °C; IR (film) 3279, 2933, 1745, 1686, 1411, 1215, 736, 696 cm⁻¹; ¹H NMR (343K, 400 MHz, d₆-DMSO) 9.07 (1H, br s), 7.66-7.08 (10H, m), 6.30 (1H, m), 5.34-5.00 (4H, m), 4.83 (1H, br s), 2.15-1.88 (4H, m), 1.75-1.44 (2H, m); ¹³C NMR (343K, 100 MHz, d₆-DMSO) 156.6 (C), 155.1 (C), 136.4 (C), 136.3 (C), 135.0 (CH), 128.2 (4CH), 127.8 (CH), 127.7 (CH), 127.6 (2CH), 127.3 (2CH), 121.2 (C), 69.0 and 68.8 (CH), 67.2 (CH₂), 66.3 (CH₂), 28.3 (CH₂), 26.8 (CH₂), 18.9 (CH₂); MS (ES⁺) m/z = 483 ([M(⁸¹Br)+Na]⁺, 50), 481 ([M(⁷⁹Br)+Na]⁺, 50); HRMS (ES⁺) m/z calcd for C₂₂H₂₄⁷⁹BrN₂O₄ (M+H)⁺: 459.0914; found: 459.0917.
***(E)-Diethyl 1-(2,3-diiodoallyl)hydrazine-1,2-dicarboxylate {(*E)-103}***

To a solution of (*E)-2,3-diiodoprop-2-en-1-ol\(^{143}\) (233 mg, 0.75 mmol) and triphenylphosphine (394 mg, 1.50 mmol) in THF (6 mL) at 0 °C was added dropwise diethylazodicarboxylate (237 \(\mu\)L, 1.50 mmol). The reaction was allowed to warm to room temperature and stirred for 24 h after which time the reaction was concentrated \textit{in vacuo}. Column chromatography (petroleum ether:ethyl acetate, 8:1) afforded (*E)-103 (260 mg, 74%) as a yellow oil. IR (film) 3295, 2980, 1704, 1380, 1208, 1057, 759 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.13 (1H, s), 6.48 (1H, m), 4.56-4.37 (2H, m), 4.20 (4H, br q, \(J = 7.0\) Hz), 1.27 (6H, t, \(J = 7.0\) Hz); \(^13\)C NMR (75 MHz, CDCl\(_3\)) 155.8 (2C), 98.1 (C), 83.2 and 82.6 (CH), 63.2 and 63.1 (CH\(_2\)), 62.3 (CH\(_2\)), 61.1 and 60.1 (CH\(_2\)), 14.6 (2CH\(_3\)); MS (ES\(^+\)) \(m/z = 491\) ([M+Na]\(^+\), 100); HRMS (ES\(^+\)) \(m/z\) calcld for C\(_9\)H\(_{14}\)I\(_2\)N\(_2\)O\(_4\)Na (M+Na): 490.8935; found: 490.8941.

***(E)-Diethyl 1-(3-chloro-2-iodoallyl)hydrazine-1,2-dicarboxylate {(*E)-104}***

To a solution of (*E)-3-chloro-2-iodoprop-2-en-1-ol\(^{147}\) (881 mg, 4.04 mmol) and triphenylphosphine (2.12 g, 8.08 mmol) in THF (12 mL) at 0 °C was added dropwise diethylazodicarboxylate (1.27 mL, 8.08 mmol). The reaction was allowed to warm to room temperature and stirred for 16 h after which time the reaction was concentrated \textit{in vacuo}. Column chromatography (petroleum ether:ethyl acetate, 7:1) afforded (*E)-104 (1.21 g, 79%) as a colourless oil. IR (film) 3290, 2982, 1704, 1380, 1256, 1212, 1058, 777 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) 6.77-6.28 (2H, m), 4.68-4.41 (2H, m), 4.21 (4H, br q, \(J = 7.1\) Hz), 1.27 (6H, t, \(J = 7.1\) Hz); \(^13\)C NMR (75 MHz, CDCl\(_3\)) 155.2 (2C), 122.8 and 122.3 (CH), 96.1 (C), 62.4 (CH\(_2\)), 61.7 (CH\(_2\)),
53.5 and 52.6 (CH₂), 13.9 (2CH₃); MS (ES⁺) m/z = 399 ([M(³⁵Cl)+Na]⁺, 75), 401 ([M(³⁷Cl)+Na]⁺, 25); HRMS (ES⁺) m/z calcd for C₉H₁₄³⁵ClIN₂O₄Na (M+Na): 398.9579; found: 398.9585.

**Ring Closure: General Procedure 4**

To a mixture of hydrazodicarboxylate (1.0 molar equiv), CuI (0.2 molar equiv) and Cs₂CO₃ (2.0 molar equiv) in the specified solvent was added dropwise N,N'-dimethylethylenediamine (DMEDA) (0.4 molar equiv) and the mixture heated at reflux until tlc showed complete consumption of starting material. The reaction was allowed to cool to room temperature and filtered with ethyl acetate through layers of celite, silica and MgSO₄, then concentrated *in vacuo*. The crude product was essentially pure. It could be further purified by column chromatography (petroleum ether:ethyl acetate).

**Diethyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (89)**

EtO₂C

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Hydrazodicarboxylate 88 (400 mg, 1.36 mmol) was cyclised according to the general procedure with CuI (52 mg, 0.27 mmol), Cs₂CO₃ (887 mg, 2.72 mmol) and DMEDA (59 µL, 0.54 mmol) in THF (8 mL). After 12h, workup afforded 89 (286 mg, 98%) as a colourless oil. IR (film) 2984, 1720, 1371, 1317, 1227, 1096, 734 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 4.94 (1H, dt, J = 3.3, 2.7 Hz), 4.65 (2H, t, J = 2.3 Hz), 4.40 (1H, dt, J = 3.3, 2.1 Hz), 4.28 (2H, q, J = 7.1 Hz), 4.22
(2H, q, \( J = 7.1 \) Hz), 1.31 (3H, t, \( J = 7.1 \) Hz), 1.28 (3H, t, \( J = 7.1 \) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) 160.0 (C), 154.7 (C), 141.7 (C), 90.0 (CH\(_2\)), 62.5 (CH\(_2\)), 62.3 (CH\(_2\)), 57.1 (CH\(_2\)), 13.8 (CH\(_3\)), 13.7 (CH\(_3\)); MS (ES\(^{+}\)) \( m/\ell = 237 \) ([M+Na]\(^{+}\), 100); HRMS (ES\(^{+}\)) \( m/\ell \) calcd for C\(_9\)H\(_{15}\)N\(_2\)O\(_4\) (M+H): 215.1026; found: 215.1027.

**Diethyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (89) from 96** (2.01 g, 5.87 mmol) was cyclised according to the general procedure with CuI (224 mg, 1.17 mmol), Cs\(_2\)CO\(_3\) (3.82 g, 11.7 mmol) and DMEDA (253 \( \mu \)L, 2.35 mmol) in THF (35 mL). After 24h, workup afforded 89 (1.24 g, 99\%) as a colourless oil.

**Di-tert-butyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (77)**

\[
\text{Boc} \quad \text{N} \quad \text{N} \quad \text{Boc}
\]

Hydrazodicarboxylate 97 (2.67 g, 6.70 mmol) was cyclised according to the general procedure with CuI (255 mg, 1.34 mmol), Cs\(_2\)CO\(_3\) (4.37 g, 13.4 mmol) and DMEDA (288 \( \mu \)L, 2.68 mmol) in THF (35 mL). After 6h, workup afforded 77 (1.79 g, 99\%) as a colourless oil. IR (film) 2979, 1715, 1367, 1151, 1117, 842 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 4.89 (1H, m), 4.59 (2H, t, \( J = 2.3 \) Hz), 4.36 (1H, m), 1.54 (9H, s), 1.50 (9H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) 163.8 (2C), 142.1 (C), 89.0 (CH\(_2\)), 82.4 (C), 82.1 (C), 56.6 (CH\(_2\)), 27.5 (3CH\(_3\)), 27.4 (3CH\(_3\)); MS (ES\(^{+}\)) \( m/\ell = 293 \) ([M+Na]\(^{+}\), 100); HRMS (ES\(^{+}\)) \( m/\ell \) calcd for C\(_{13}\)H\(_{22}\)N\(_2\)O\(_4\)Na (M+Na): 293.1472; found: 293.1475.
Dibenzyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (78)

Hydrazodicarboxylate 98 (2.21 g, 4.73 mmol) was cyclised according to the general procedure with CuI (180 mg, 0.95 mmol), Cs$_2$CO$_3$ (3.08 g, 9.47 mmol) and DMEDA (204 µL, 1.89 mmol) in THF (35 mL). After 12h, workup afforded 78 (1.54 g, 96%) as a colourless oil. IR (film) 2964, 1721, 1385, 1310, 1264, 1219, 1095, 736 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 7.39-7.25 (10H, m), 5.25 (2H, s), 5.20 (2H, s), 4.97 (1H, m), 4.69 (2H, t, $J = 2.2$ Hz), 4.43 (1H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) 160.4 (C), 155.2 (C), 142.1 (C), 135.2 (2C), 128.6 (4CH), 128.5 (CH), 128.4 (CH), 128.2 (2CH), 128.1 (2CH), 91.1 (CH$_2$), 68.6 (CH$_2$), 68.5 (CH$_2$), 57.9 (CH$_2$); MS (ES$^+$) $m/z = 361$ ([M+Na]$^+$, 100); HRMS (ES$^+$) $m/z$ calcd for C$_{19}$H$_{18}$N$_2$O$_4$Na (M+Na)$^+$: 361.1159; found: 361.1155.

Diethyl 7,8-diazabicyclo[4.2.0]oct-1-ene-7,8-dicarboxylate (105)

Hydrazodicarboxylate 101 (100 mg, 0.30 mmol) was cyclised according to the general procedure with CuI (11 mg, 0.06 mmol), Cs$_2$CO$_3$ (195 mg, 0.60 mmol) and DMEDA (13 µL, 0.12 mmol) in THF (2 mL). After 16h, workup afforded 105 (72 mg, 95%) as a colourless solid. M.p. 66.5-67.0 °C; IR (film) 2972, 2909, 1766, 1729, 1372, 1243, 1064, 1095, 776 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 5.22 (1H, m), 4.46 (1H, m), 4.28-4.09 (4H, m), 2.24-1.97 (3H, m), 1.80 (1H, m), 1.52 (1H, m), 1.35 (1H, m), 1.24 (3H, t, $J = 7.2$ Hz), 1.22 (3H, t, $J = 7.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) 160.8 (C), 156.6 (C), 139.5 (C), 98.5 (CH), 67.1 (CH), 62.9 (2CH$_2$), 27.7 (CH$_2$), 22.6 (CH$_2$), 18.3 (CH$_2$), 14.4 (2CH$_3$); MS (ES$^+$) $m/z = 531$ ([2M+Na]$^+$, 100); HRMS (ES$^+$) $m/z$ calcd for C$_{12}$H$_{18}$N$_2$O$_4$Na (M+Na)$^+$: 277.1159, found: 277.1160.
Dibenzyl 7,8-diazabicyclo[4.2.0]oct-1-ene-7,8-dicarboxylate (106)

Hydrazodicarboxylate 102 (1 g, 2.18 mmol) was cyclised according to the general procedure with CuI (83 mg, 0.44 mmol), Cs_2CO_3 (1.42 g, 4.36 mmol) and DMEDA (94 μL, 0.87 mmol) in THF (20 mL). After 20 h, usual workup and column chromatography (petroleum ether:ethyl acetate, 7:1) afforded 106 (794 mg, 96%) as a colourless oil. IR (film) 2951, 1734, 1384, 1305, 1265, 1062, 732, 695 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.37-7.28 (10H, m), 5.31 (1H, m), 5.30-5.17 (4H, m), 4.58 (1H, m), 2.29-2.02 (3H, m), 1.86 (1H, m), 1.62(1H, m), 1.39 (1H, m); ¹³C NMR (100 MHz, CDCl₃) 160.7 (C), 156.5 (C), 139.3 (C), 135.5 (C), 135.3 (C), 128.6 (4CH), 128.4 (2CH), 128.0 (4CH), 99.2 (CH), 68.4 (2CH₂), 67.3 (CH₂), 27.6 (CH₂), 22.7 (CH₂), 18.3 (CH₂); MS (ES⁺) m/z = 401 ([M+Na]⁺, 100); HRMS (ES⁺) m/z calcd for C₂₂H₂₂N₂O₄Na (M+Na)⁺: 401.1472, found: 401.1472.

Di-tert-butyl 3-(propan-2-ylidene)-1,2-diazetidine-1,2-dicarboxylate (107)

Hydrazodicarboxylate 100 (293 mg, 0.77 mmol) was cyclised according to the general procedure with CuI (29 mg, 0.16 mmol), Cs₂CO₃ (504 mg, 1.55 mmol) and DMEDA (33 μL, 0.31 mmol) in THF (7 mL). After 24 h, usual workup and column chromatography (petroleum ether:ethyl acetate, 14:1) afforded 107 (215 mg, 93%) as a colourless crystalline solid. M.p. 79.0-80.0 °C (ethanol); IR (neat) 2973, 1738, 1674, 1302, 1256, 1135, 753 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 4.62 (2H, br s), 1.81 (3H, s), 1.52 (9H, s), 1.50 (12H, s); ¹³C NMR (100 MHz, CDCl₃) 159.4 (C), 156.5 (C), 129.5 (C), 112.4 (C), 82.5 (C), 82.1 (C), 57.8 (CH₂), 28.1 (3CH₃), 27.9 (3CH₃), 18.9 (CH₃), 18.6 (CH₃); MS (ES⁺) m/z = 321 ([M+Na]⁺, 100); HRMS (ES⁺) m/z...
calcd for C$_{15}$H$_{28}$N$_2$O$_4$Na (M+Na)$^+$: 321.1785, found: 321.1781. Crystals suitable for X-ray diffraction were grown from ethanol by slow evaporation.

(Z)-Diethyl 3-benzylidene-1,2-diazetidine-1,2-dicarboxylate {(Z)-108}

(Hydrazodicarboxylate) (Z)-99 (74 mg, 0.20 mmol) was cyclised according to the general procedure with CuI (8 mg, 0.04 mmol), Cs$_2$CO$_3$ (130 mg, 0.40 mmol) and DMEDA (9 µL, 0.08 mmol) in THF (2 mL). After 16h, usual workup and column chromatography (petroleum ether:ethyl acetate, 6:1) afforded (Z)-108 (48 mg, 83%) as a colourless solid. M.p. 79.5-80.5 °C; IR (film) 2983, 1739, 1717, 1370, 1259, 1060, 694 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) 7.31 (2H, d, $J = 7.4$ Hz), 7.27 (2H, t, $J = 7.4$ Hz), 7.19 (1H, t, $J = 7.3$ Hz), 5.74 (1H, t, $J = 2.1$ Hz), 4.90 (2H, d, $J = 2.1$ Hz), 4.32 (2H, q, $J = 7.2$ Hz), 4.08 (2H, q, $J = 7.2$ Hz), 1.36 (3H, t, $J = 7.2$ Hz), 0.94 (3H, t, $J = 7.2$ Hz); $^{13}$C NMR (150 MHz, CDCl$_3$) 160.4 (C), 156.4 (C), 135.6 (C), 134.4 (C), 128.8 (2CH), 127.6 (2CH), 126.8 (CH), 108.9 (CH), 63.1 (2CH$_2$), 59.3 (CH$_2$), 14.4 (CH$_3$), 13.6 (CH$_3$); MS (ES$^+$) $m/z = 313 ([\text{M+Na}]^+, 100)$; HRMS (ES$^+$) $m/z$ calcd for C$_{15}$H$_{18}$N$_2$O$_4$Na (M+Na)$^+$: 313.1159; found: 313.1155.

![Diagram of (Z)-108]
Diethyl 4-iodo-1\textit{H}-pyrazole-1,2(3\textit{H})-dicarboxylate (109)

\[
\text{EtO}_2\text{C} \quad \text{N} \quad \text{N} \quad \text{EtO}_2\text{C}
\]

To a mixture of (\textit{E})-103 (412 mg, 0.88 mmol), CuI (51 mg, 0.26 mmol) and Cs\textsubscript{2}CO\textsubscript{3} (574 mg, 1.76 mmol) in THF (8 mL) was added dropwise DMEDA (57 \textmu L, 0.53 mmol) and the mixture heated at reflux for 12 h. After workup, column chromatography (petroleum ether:ethyl acetate, 8:1) afforded 109 (281 mg, 94\%) as a white solid. M.p. 97.0-98.5 °C (ethanol); IR (film) 3105, 2981, 1712, 1371, 1320, 1304, 1156, 1048, 752 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) 6.88 (1H, t, \textit{J} = 2.1 Hz), 4.48 (2H, br s), 4.25 (4H, q, \textit{J} = 7.2 Hz), 1.30 (3H, t, \textit{J} = 7.2 Hz), 1.29 (3H, t, \textit{J} = 7.2 Hz); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) 157.1 (C), 152.2 (C), 132.7 (CH), 84.7 (C), 62.6 (CH\textsubscript{2}), 62.5 (CH\textsubscript{2}), 60.2 (CH\textsubscript{2}), 13.8 (2CH\textsubscript{3}); MS (ES\textsuperscript{+}) \textit{m/z} = 363 ([M+Na]\textsuperscript{+}, 100); HRMS (ES\textsuperscript{+}) \textit{m/z} calcd for C\textsubscript{9}H\textsubscript{13}IN\textsubscript{2}O\textsubscript{4}Na (M+Na)\textsuperscript{+}: 362.9812; found: 362.9802.

Ethyl 4-phenyl-4,5-dihydro-1\textit{H}-pyrazole-1-carboxylate (111)

\[
\text{EtO}_2\text{C} \quad \text{N} \quad \text{N} \quad \text{EtO}_2\text{C}
\]

\[
\begin{array}{c}
\text{Suzuki} \\
\text{PhB(OH)\textsubscript{2}, Pd(PPh\textsubscript{3})\textsubscript{4}}
\end{array}
\]

To a stirred solution of diethyl 4-iodo-1\textit{H}-pyrazole-1,2(3\textit{H})-dicarboxylate (109) (75 mg, 0.22 mmol), Pd(PPh\textsubscript{3})\textsubscript{4} (13 mg, 0.01 mmol) and Cs\textsubscript{2}CO\textsubscript{3} (144 mg, 0.44 mmol) in toluene (1 mL) and ethanol (1 mL) was added PhB(OH)\textsubscript{2} (54 mg, 0.44 mmol) in one portion and the resultant mixture heated to 100 °C for 1 h. The reaction was allowed to cool, diluted with ethyl acetate (5 mL) and water (5 mL), the phases separated and the aqueous layer extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine, dried (MgSO\textsubscript{4}), filtered, and concentrated \textit{in vacuo}. Column chromatography
(petroleum ether:ethyl acetate, 5:1) furnished 111 (37 mg, 77%) as a colourless oil. IR (film) 2982, 1725, 1694, 1429, 1380, 1134, 700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 7.40-7.27 (3H, m), 7.16 (2H, d, J = 7.0 Hz), 6.91 (1H, s), 4.37-4.30 (3H, m), 4.26 (1H, q, J = 10.7 Hz), 3.80 (2H, dd, J = 10.7, 7.1 Hz), 1.37 (3H, t, J = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) 153.1 (C), 148.5 (CH), 138.7 (C), 129.2 (2CH), 127.9 (CH), 127.5 (2CH), 62.4 (CH₂), 52.6 (CH₂), 51.9 (CH), 14.7 (CH₃); MS (ES⁺) m/z = 459 (2M+Na)⁺, 100; HRMS (ES⁺) m/z calcd for C₁₂H₁₄N₂O₂Na (M+Na)⁺: 241.0947; found: 241.0947.

(E)-Diethyl 3-(chloromethylene)-1,2-diazetidine-1,2-dicarboxylate {(E)-110}

To a mixture of hydrazodicarboxylate (E)-104 (300 mg, 0.80 mmol), CuI (46 mg, 0.24 mmol) and Cs₂CO₃ (520 mg, 1.60 mmol) in toluene (15 mL) was added dropwise DMEDA (52 μL, 0.48 mmol) and the mixture heated at reflux for 26 h. After usual workup, column chromatography (petroleum ether:ethyl acetate, 11:1) afforded methylenediazetidine (E)-110 (140 mg, 71%) as a colourless oil. IR (film) 2984, 1758, 1724, 1372, 1313, 1267, 1240, 1051, 769 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 6.06 (1H, t, J = 2.6 Hz), 4.69 (2H, d, J = 2.6 Hz), 4.29 (2H, q, J = 7.1 Hz), 4.24 (2H, q, J = 7.1 Hz), 1.32 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) 160.2 (C), 155.0 (C), 137.7 (C), 98.8 (CH), 63.5 (CH₂), 63.4 (CH₂), 56.5 (CH₂), 14.3 (CH₃), 14.3 (CH₃); MS (ES⁺) m/z = 271 ([M(³⁵Cl)+Na]⁺, 75), 273 ([M(³⁷Cl)+Na]⁺, 25); HRMS (ES⁺) m/z calcd for C₉H₁₃³⁵ClN₂O₄Na (M+Na)⁺: 271.0456; found: 271.0455. Further elution gave 110 (41 mg, 15%) as a white solid.
IV.VII Functionalisation of 1,2-Diazetidines

Di-tert-butyl 1-(2-chloroethyl)-hydrazine-1,2-dicarboxylate (30) from 21

To a stirred solution of di-tert-butyl 1,2-diazetidine-1,2-dicarboxylate (35 mg, 0.14 mmol) in Et₂O (1 mL) was added dropwise hydrogen chloride in ether Et₂O (2.0M, 71 µL, 0.14 mmol). After 16 h, the reaction was concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate, 5:1) furnished 30 (28 mg, 70%) as a white solid.
**IV.VIII Lithiation Chemistry**

*tert*-Butyl 1,2-diazetidine-1-carboxylate (121)

To a stirred solution of di-*tert*-butyl 1,2-diazetidine-1,2-dicarboxylate (70 mg, 0.27 mmol) in THF (2 mL) at -78 °C was added dropwise *sec*-butyllithium (1.3M in cyclohexane) (209 μL, 0.27 mmol). After 30 min, the reaction was sampled for LCMS as follows. A 75 μL aliquot was withdrawn via syringe and injected into a 0.1 M NH₄Cl solution (1 mL). The sample was run directly. The presence of starting diazetidine was noted and a further equivalent of *sec*-butyllithium (209 μL, 0.27 mmol) was added. This sequence was repeated every 30 mins until a total of 835 μL, 1.09 mmol of *sec*-butyllithium was used. The reaction was stirred for a further 30 min (total 3 h) then quenched by the addition of *d₄*-MeOH (50 μL) and allowed to warm to room temperature. Water (5 mL) and Et₂O (5 mL) were added and the organic phase separated. The aqueous phase was extracted with Et₂O (3 × 5 mL) and the combined organic phases were washed with water (5 × 5 mL), brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. Column chromatography (petroleum ether:ethyl acetate, 2:1→1:4) (Rᶠ = 0.07 in petroleum ether:ethyl acetate, 1:1) furnished **121** (2.0 mg, 5%) as a colourless oil. This material decomposed completely over a 24 h period. ¹H NMR (400 MHz, CDCl₃) 5.43 (1H, br s), 4.32 (2H, t, J = 8.0 Hz), 3.76 (2H, br s), 1.49 (9H, s); LCMS (Method A, ES⁺) tᵣ = 0.35 min, m/z = 159 (M+H)⁺; HRMS (ES⁺) m/z calcd for C₇H₁₄N₂O₂Na (M+Na)⁺: 181.0947; found: 181.0955.
**tert-Butyl 2,2'-carbonyl-bis(1,2-diazetidine-1-carboxylate) (122)**

To a stirred solution of di-tert-butyl 1,2-diazetidine-1,2-dicarboxylate (70 mg, 0.27 mmol) and hexamethylphosphoramide (94 µL, 0.54 mmol) in THF (2 mL) at -78 °C was added dropwise sec-butyllithium (1.4M in cyclohexane) (233 µL, 0.33 mmol). The mixture was allowed to warm to -40 °C over 30 mins and held at this temperature for 2.5 h. The reaction was quenched by the addition of d₄-MeOH (50 µL) and then allowed to warm to room temperature. Water (5 mL) and Et₂O (5 mL) were added and the organic phase separated. The aqueous phase was extracted with Et₂O (3 × 5 mL) and the combined organic phases were washed with water (5 × 5 mL), brine, dried (MgSO₄), filtered, and concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate, 8:1; then petroleum ether:ethyl acetate, 4:1) furnished 122 (1.1 mg, 1%) as a white solid. ¹H NMR (600 MHz, CDCl₃) 4.30 (4H, t, J = 2.1 Hz), 4.23 (4H, t, J = 2.1 Hz), 1.50 (18H, s); ¹⁵N NMR (extracted from ¹⁵N HMBC, Appendix III) (60 MHz, CDCl₃) 135.4 (2N), 133.3 (2N); ¹³C NMR (125 MHz, CDCl₃) 167.1 (C), 159.6 (2C), 82.2 (2C), 50.6 (2CH₂), 50.1 (2CH₂), 27.9 (6CH₃); LCMS (Method A, ES⁺) tᵣ = 0.88 min, m/z = 343 (M+H)+; HRMS (ES⁺) m/z calcd for C₁₅H₂₇N₄O₅ (M+H)+: 343.1981; found: 343.1985.
IV.IX Functionalisation of 3-Alkylidene-1,2-Diazetidines

\((E)\)-Di-\textit{tert}-butyl 3-benzylidene-1,2-diazetidine-1,2-dicarboxylate \(((E)-128)\)

\[
\begin{align*}
\text{Boc} & \quad \text{Heck} \quad \text{Pd(OAc)\textsubscript{2}, Phl} \\
& \quad \text{(crude dr > 95:5)} \\
\text{Boc} & \quad \text{N} \quad \text{N} \quad \text{Boc} \\
\end{align*}
\]

To a stirred mixture of di-\textit{tert}-butyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (77) (109 mg, 0.40 mmol), phenyl iodide (68 \(\mu\)L, 0.61 mmol), \(\text{Bu}_4\text{NCl}\) (112 mg, 0.40 mmol) and palladium(II) acetate (5 mg, 0.02 mmol) in dimethylacetamide (2 mL) was added \(\text{Cy}_2\text{NMe}\) (128 \(\mu\)L, 0.61 mmol). The reaction was heated at 80 °C for 48 h, allowed to cool to room temperature, then diluted with Et\(_2\)O (4 mL) and water (5 mL). The phases were separated and the aqueous layer extracted with Et\(_2\)O (3 \(\times\) 10 mL). The combined extracts were washed with water (5 \(\times\) 10 mL), dried (MgSO\(_4\)), filtered, and concentrated \textit{in vacuo}. Column chromatography (petroleum ether:ethyl acetate, 14:1) furnished \((E)-128\) (31 mg, 23%) as a colourless oil. IR (film) 2980, 1715, 1335, 1254, 1144, 845, 735 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.30 (2H, t, \(J = 7.4\) Hz), 7.17 (1H, t, \(J = 7.4\) Hz), 7.02 (2H, d, \(J = 7.3\) Hz), 6.40 (1H, t, \(J = 2.5\) Hz), 4.92 (2H, d, \(J = 2.5\) Hz), 1.58 (9H, s), 1.53 (9H, s); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) 159.3 (C), 154.1 (C), 137.7 (C), 135.1 (C), 128.8 (2CH), 126.6 (2CH), 126.3 (CH), 107.2 (CH), 83.3 (C), 82.9 (C), 58.1 (CH\(_2\)), 28.1 (3CH\(_3\)), 28.0 (3CH\(_3\)); MS (ES\(^+\)) \textit{m/z} = 369 ([M+Na]\(^+\), 100); HRMS (ES\(^+\)) \textit{m/z} calcd for C\(_{19}\)H\(_{26}\)N\(_2\)O\(_4\)Na (M+Na\(^+\)): 369.1785; found: 369.1789.
(E)-Diethyl 3-benzylidene-1,2-diazetidine-1,2-dicarboxylate \{(E)-108\}

![Chemical structure diagram]

To a stirred mixture of diethyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (89) (50 mg, 0.23 mmol), phenyl iodide (39 µL, 0.35 mmol), Bu₄NCl (65 mg, 0.23 mmol) and palladium(II) acetate (3 mg, 0.01 mmol) in dimethylacetamide (1 mL) was added Cy₂NMe (74 µL, 0.35 mmol). The reaction was heated at 80 °C for 24 h, allowed to cool to room temperature, then diluted with Et₂O (4 mL) and water (5 mL). The phases were separated and the aqueous layer extracted with Et₂O (3 × 10 mL). The combined extracts were washed with water (5 × 10 mL), dried (MgSO₄), filtered, and concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate, 8:1) furnished (E)-108 (31 mg, 46%) as a colourless crystalline solid. M.p. 88.0-89.5 °C \((\text{tert-butyl methyl ether})\); IR (film) 2983, 1719, 1372, 1316, 1272, 1050, 752 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) 7.31 (2H, t, J = 7.7 Hz), 7.18 (1H, t, J = 7.5 Hz), 7.03 (2H, d, J = 7.5 Hz), 6.49 (1H, s), 5.00 (2H, d, J = 2.5 Hz), 4.35 (2H, q, J = 7.1 Hz), 4.29 (2H, q, J = 7.2 Hz), 1.38 (3H, t, J = 7.2 Hz), 1.33 (3H, t, J = 7.1 Hz); ¹³C NMR (150 MHz, CDCl₃) 160.4 (C), 155.4 (C), 137.1 (C), 134.7 (C), 128.8 (2CH), 126.6 (2CH), 126.5 (CH), 108.0 (CH), 63.3 (CH₂), 63.2 (CH₂), 58.5 (CH₂), 14.4 (CH₃), 14.4 (CH₃); MS (ES⁺) m/z = 313 ([M+Na]⁺, 100); HRMS (ES⁺) m/z calcd for C₁₅H₁₈N₂O₄Na (M+Na)⁺: 313.1159; found: 313.1160. Crystals were grown from tert-butyl methyl ether/petroleum ether by slow evaporation.
(E)-Diethyl 3-(4-methoxybenzylidene)-1,2-diazetidine-1,2-dicarboxylate {(E)-131}

EtO2C-\( \stackrel{\text{E}}{\text{N}} \) CO2Et Prepared from diethyl 3-methylene-1,2-diazetidine-1,2-
dicarboxylate (89) (50 mg, 0.23 mmol), 1-iodo-4-methoxybenzene
\( \text{C}_6\text{H}_4\text{OMe} \) (82 mg, 0.35 mmol), Bu4NCl (65 mg, 0.23 mmol),
palladium(II)acetate (3 mg, 0.01 mmol) and Cy2NMe (74 µL, 0.35 mmol) in
dimethylacetamide (1 mL) using the procedure as described for (E)-131. Column
chromatography (petroleum ether:ethyl acetate, 8:1) furnished (E)-131 (30 mg, 40%) as
a colourless oil. IR (film) 2985, 1718, 1514, 1373, 1265, 1247, 1177, 1031, 702 cm\(^{-1}\); \(^1\)H
NMR (300 MHz, CDCl\(_3\)) 6.94 (2H, dt, \( J = 8.9, 2.3 \) Hz), 6.83 (2H, dt, \( J = 8.9, 2.3 \) Hz),
6.38 (1H, t, \( J = 2.5 \) Hz), 4.96 (2H, d, \( J = 2.5 \) Hz), 4.32 (2H, q, \( J = 7.1 \) Hz), 4.26 (2H, q, \( J
= 7.1 \) Hz), 3.77 (3H, s), 1.34 (3H, t, \( J = 7.1 \) Hz), 1.30 (3H, t, \( J = 7.1 \) Hz); \(^{13}\)C NMR (75
MHz, CDCl\(_3\)) 159.8 (C), 157.7 (C), 155.0 (C), 134.6 (C), 127.2 (2CH), 126.6 (C), 113.7
(2CH), 107.1 (CH), 62.6 (CH\(_2\)), 62.5 (CH\(_2\)), 57.8 (CH\(_2\)), 54.7 (CH\(_3\)), 13.8 (2CH\(_3\)); MS
(ES\(^+\)) \( m/z = 343 \) (M+Na\(^+\), 100); HRMS (ES\(^+\)) \( m/z \) calcld for C\(_{16}\)H\(_{21}\)N\(_2\)O\(_5\)Na (M+Na\(^+\)):
321.1445; found: 321.1448.
Dibenzyl 3-((3-chlorobenzoyloxy)methyl)-3-hydroxy-1,2-diazetidine-1,2-dicarboxylate (134β)/regioisomer (134α)

To a stirred mixture of dibenzyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (78) (100 mg, 0.30 mmol) and K$_2$CO$_3$ (53 mg, 0.38 mmol) in CH$_2$Cl$_2$ (2 mL) at 0 °C was added portionwise mCPBA (77% purity) (86 mg, 0.38 mmol). The reaction was allowed to warm to room temperature and stirred for 16 h. The reaction was then cooled to 0 °C, saturated aqueous Na$_2$S$_2$O$_3$ (2 mL) and saturated aqueous NaHCO$_3$ (2 mL) were added and the mixture extracted with CH$_2$Cl$_2$ (3 × 5 mL). The combined extracts were dried (MgSO$_4$), filtered, and concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate, 4:1) furnished 134 (57 mg, 38%) as a white semi-solid. IR (film) 3255, 2924, 1742, 1706, 1398, 1257, 1068, 695 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) 8.05 (1H, m), 7.95 (1H, t, $J = 7.5$ Hz), 7.58 (1H, m), 7.45-7.21 (11H, m), 7.03 (1H, m), 5.25-5.06 (4H, m), 5.01-4.82 (2H, m), 4.64-4.47 (2H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) 169.1 (C), 156.0 (C), 155.3 (C), 135.4 (C), 134.8 (C), 133.9 (C), 133.8 (CH), 130.5 (C), 130.0 (2CH), 128.6 (4CH), 128.5 (CH), 128.2 (3CH), 128.1 (2CH), 127.8 (CH), 69.1 (CH$_2$), 68.7 (C), 67.9 (CH$_2$), 67.3 (CH$_2$), 56.8 (CH$_2$); MS (ES$^+$) $m/z = 535$ ([M($^{37}$Cl)+Na]$^+$, 75), 533 ([M($^{35}$Cl)+Na]$^+$, 25); HRMS (ES$^+$) $m/z$ calcd for C$_{26}$H$_{23}$ClN$_2$O$_7$Na (M+Na)$^+$: 533.1086; found: 533.1087.
Dibenzyl 4,6-diazaspiro[2.4]heptane-4,6-dicarboxylate (136)

To a stirred solution of dibenzyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (78) (150 mg, 0.44 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C was added diethyl zinc (1.0M in hexanes, 2.22 mL, 2.22 mmol). Diiodomethane (179 µL, 2.22 mmol) was added immediately afterwards and the mixture stirred at 0 °C for 10 min, then allowed to warm to room temperature and stirred for a further 2.5 h. The reaction was cooled to 0 °C, quenched with saturated aqueous NH$_4$Cl (2 mL) then diluted with Et$_2$O (10 mL) and water (10 mL). The phases were separated and the aqueous layer extracted with Et$_2$O (3 × 10 mL). The combined extracts were washed with NaHCO$_3$ (10 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate, 6:1) furnished 136 (47 mg, 29%) as a colourless oil which crystallises slowly on standing. IR (film) 2959, 1698, 1401, 1360, 1094, 758, 736 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 7.41-7.18 (10H, m), 5.15 (2H, s), 5.08 (2H, s), 5.00-4.87 (2H, m), 3.56 (2H, br s), 1.66 (2H, br s), 0.66 (2H, br s); $^{13}$C NMR$^1$ (100 MHz, CDCl$_3$) 153.4 (C), 152.4 (C), 136.3 (C), 136.1 (C), 128.6 (4CH), 128.3 (2CH), 128.1 (4CH), 67.3 (CH$_2$), 67.0 (CH$_2$), 61.9 and 61.5 (CH$_2$), 52.6 (CH$_2$), 9.1 (2CH$_2$); MS (ES$^+$) m/z = 389 (M+Na)$^+$, 100; HRMS (ES$^+$) m/z calcd for C$_{21}$H$_{22}$N$_2$O$_4$Na (M+Na)$^+$: 389.1472; found: 389.1472.

$^1$ Quaternary carbon not observed.
**IV.X Reduction Chemistry**

*tert*-Butyl propane-1,2-diylicarbamate (141)

To a stirred solution of dibenzyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (78) (300 mg, 0.89 mmol) in MeOH (5 mL) was added 10% palladium on carbon (30 mg, 10% w/w) and the suspension stirred under a hydrogen atmosphere (1 atm) for 4 h. The reaction was filtered through celite (CH2Cl2) and concentrated to 2 mL *in vacuo*. The filtrate was cooled to 0 °C, di-*tert*-butyl dicarbonate (397 mg, 1.82 mmol) was added and the mixture allowed to warm to room temperature. After 16 h the reaction was concentrated *in vacuo* and triturated with petroleum ether (5 × 10 mL) to give 141 (214 mg, 88%) as a white crystalline solid. M.p. 121.0-122.0 °C (ethanol); IR (film) 3342, 2979, 1682, 1529, 1315, 1162, 1064 cm⁻¹; ¹H NMR (300 MHz, CDCl3) 4.96-4.51 (2H, m), 3.72 (1H, m), 3.14 (2H, br t, J = 5.4 Hz), 1.43 (18H, s), 1.12 (3H, d, J = 6.8 Hz); ¹³C NMR (100 MHz, C₆D₆) 156.0 (2C), 78.7 (2C), 47.5 (CH), 46.3 (CH₂), 28.5 (6CH₃), 18.3 (CH₃); MS (ES⁺) m/z = 297 ([M+Na]⁺, 100); HRMS (ES⁺) m/z calcd for C₁₃H₂₆N₂O₄Na (M+Na)⁺: 297.1785, found: 297.1787. Data in agreement with literature values.
(1R*, 6S*)-Diethyl 7,8-diazabicyclo[4.2.0]octane-7,8-dicarboxylate {(1R*, 6S*)-142}

EtO₂C₆N₇N₂CO₂Et  To a stirred solution of 105 (50 mg, 0.20 mmol) in ethyl acetate (5 mL) was added 10% palladium on carbon (5 mg, 10% w/w) and the suspension stirred under a hydrogen atmosphere (1 atm) until tlc showed complete consumption of starting material (0.5 h). The reaction was filtered through celite (ethyl acetate) and concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate, 5:1) gave (1R*, 6S*)-142 (46 mg, 92%) as a colourless oil. IR (neat) 2950, 1744, 1702, 1375, 1323, 1262, 1080, 769 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 4.53-4.49 (2H, m), 4.20 (4H, q, J = 7.1 Hz), 2.08-1.93 (2H, m) 1.80-1.60 (4H, m), 1.57-1.43 (2H, m), 1.26 (6H, t, J = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) 159.3 (2C), 61.6 (2CH₂), 59.4 (2CH), 22.7 (2CH₂), 15.7 (2CH₂), 13.9 (2CH₃); MS (ES⁺) m/z = 279 ([M+Na]⁺, 100); HRMS (ES⁺) m/z calcd for C₁₂H₂₀N₄O₄Na (M+Na)⁺: 279.1315; found: 279.1320.

(1R*, 2S*)-1,2-Diaminocyclohexane-N,N'-diethyl dicarbamate {(1R*, 2S*)-144}

EtO₂CHN₆NHCO₂Et  Firstly, a stock solution of LiDBB was prepared as follows. Small pellets of lithium (11 mg, 1.59 mmol) were placed in a Schlenk tube containing 4,4'-di-tert-butylbiphenyl (404 mg, 1.52 mmol) and some glass ‘anti-bumping’ granules. The tube was evacuated and purged with argon several times. The contents were stirred vigorously until a fresh surface of lithium was exposed. THF (5 mL) was added and stirring continued for 15 minutes whereupon the solution turned dark green. The vessel was cooled to -78 °C under an argon atmosphere and used directly. (1R*, 6S*)-142 (18 mg, 0.07 mmol) in THF (1 mL) was cooled to -78 °C under argon. LiDBB in THF (578 µL, approx. 0.18 mmol) was added dropwise via syringe
until the dark green colour persisted. The reaction mixture was stirred for a further 10 minutes and then quenched by the addition of saturated aqueous NH₄Cl (1 mL). After warming to room temperature, Et₂O (2 mL) was added. The layers were separated and the aqueous layer extracted with Et₂O (3 × 10 mL). The combined extracts were dried (MgSO₄), filtered, and concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate, 3.5:1) followed by crystallisation (Et₂O/petroleum ether) afforded (1R*, 2S*)-144 (16 mg, 86%) as a white crystalline solid. M.p. 73.0-74.5 (petrol) °C; IR (neat) 3272, 2943, 1684, 1530, 1241,1052, 780 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 5.25-4.75 (2H, m), 4.11 (4H, br q, J = 7.1 Hz), 3.90-3.78 (2H, m), 1.83-1.62 (2H, m), 1.60-1.40 (6H, m), 1.25 (6H, t, J = 7.1 Hz); ¹³C NMR (125 MHz, CDCl₃) 156.5 (2C), 60.9 (2CH₂), 50.9 (2CH), 29.1 (2CH₂), 22.0 (2CH₂), 14.6 (2CH₃); MS (ES⁺) m/z = 281 ([M+Na]⁺, 100); HRMS (ES⁺) m/z calcd for C₁₂H₂₂N₂O₄Na (M+Na)⁺: 281.1472, found: 281.1474.

Preparation of authentic samples of (1R*, 2S*)-144 and (1S, 2S)-144 for stereochemical assignment:

(1S, 2S)-1,2-Diaminocyclohexane-N,N'-diethyl dicarbamate {(1S, 2S)-144}

Ethyl chloroformate (176 µL, 1.84 mmol) in toluene (3 mL) was added to a stirred solution of (1S, 2S)-1,2-diaminocyclohexane (100 mg, 0.88 mmol) and NaOH (175 mg, 4.38 mmol) in water (3 mL) and the mixture stirred rapidly for 2 h. The resultant white precipitate was filtered, washed with toluene and dried under vacuum for 16 h. Recrystallization from ethanol gave (1S, 2S)-144 (179 mg, 79%) as white needles. M.p. 174.0-175.5 (ethanol) °C; IR (neat) 3310, 2930, 1677, 1532, 1236, 1060, 610 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 5.09-
4.63 (2H, m), 4.16-4.02 (4H, m), 3.41-3.12 (2H, m), 2.06 (2H, d, J = 12.1 Hz), 1.79-1.69 (2H, m), 1.35-1.26 (4H, m), 1.22 (6H, t, J = 7.1 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) 157.1 (2C), 60.8 (2CH$_2$), 55.4 (2CH), 32.9 (2CH$_2$), 24.8 (2CH$_2$), 14.6 (2CH$_3$); MS (ES$^+$) m/z = 281 ([M+Na]$^+$, 100); HRMS (ES$^+$) m/z calcd for C$_{12}$H$_{22}$N$_2$O$_4$Na (M+Na)$^+$: 281.1472, found: 281.1472. Spectroscopic data in agreement with published values.$^{201}$

(1$R^*$, 2$S^*$)-1,2-Diaminocyclohexane-$N,N'$-diethyl dicarbamate {((1$R^*$, 2$S^*$)-144)

Ethyl chloroformate (176 µL, 1.84 mmol) in toluene (3 mL) was added to a stirred solution of (1$R^*$, 2$S^*$)-1,2-diaminocyclohexane (103 µL, 0.87 mmol) and NaOH (175 mg, 4.37 mmol) in water (3 mL) and the mixture stirred rapidly for 2 h. The resultant mixture was extracted with Et$_2$O (3 × 10 mL). The combined extracts were dried (MgSO$_4$), filtered, and concentrated in vacuo. Precipitation from diethyl ether/petroleum ether furnished (1$R^*$, 2$S^*$)-144 (156 mg, 69%) as a white amorphous solid. M.p. 73.0-75.0 °C; IR (neat) 3273, 2951, 1684, 1530, 1241, 1104, 1051, 779 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 5.26-4.85 (2H, m), 4.11 (4H, br q, J = 7.1 Hz), 3.89-3.80 (2H, m), 1.83-1.65 (2H, m), 1.60-1.42 (6H, m), 1.25 (6H, t, J = 7.1 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) 156.5 (2C), 60.9 (2CH$_2$), 50.8 (2CH), 29.1 (2CH$_2$), 22.1 (2CH$_2$), 14.6 (2CH$_3$); MS (ES$^+$) m/z = 281 ([M+Na]$^+$, 100); HRMS (ES$^+$) m/z calcd for C$_{12}$H$_{22}$N$_2$O$_4$Na (M+Na)$^+$: 281.1472, found: 281.1471.
1,2-Diaminocyclohex-2-ene-$N,N'$-diethyl dicarbamate (143)

Diethyl 7,8-diazabicyclo[4.2.0]oct-1-ene-7,8-dicarboxylate 105 (22 mg, 0.09 mmol) in THF (1 mL) was cooled to -78 °C under argon. LiDBB, prepared according to method used above, in THF (685 μL, approx. 0.21 mmol) was added dropwise via syringe until the dark green colour of LiDBB persisted. The reaction mixture was stirred for a further 10 minutes and then quenched by the addition of saturated aqueous NH$_4$Cl (1 mL). After warming to room temperature, Et$_2$O (2 mL) was added. The layers were separated and the aqueous layer extracted with Et$_2$O (3 × 10 mL). The combined organic extracts were dried (MgSO$_4$), filtered, and concentrated in vacuo. Column chromatography (petroleum ether:ethyl acetate, 8:1) furnished 143 (19 mg, 86%) as an off-white solid. M.p. 76.5-78.0 °C; IR (neat) 3316, 2984, 1684, 1511, 1480, 1233, 1045, 777 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 6.56 (1H, s), 6.19 (1H, s), 4.86 (1H, m), 4.19-4.01 (5H, m), 2.19-1.79 (3H, m), 1.76-1.56 (2H, m), 1.48 (1H, m), 1.22 (6H, t, $J = 7.1$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) 157.3 (C), 154.3 (C), 132.3 (C), 112.3 (CH), 61.2 (CH$_2$), 60.7 (CH$_2$), 47.7 (CH), 29.7 (CH$_2$), 23.8 (CH$_2$), 18.5 (CH$_2$), 14.5 (2CH$_3$); MS (ES$^+$) $m/z = 279$ ([M+Na]$^+$, 100); HRMS (ES$^+$) $m/z$ calcd for C$_{12}$H$_{20}$N$_2$O$_4$Na (M+Na)$^+$: 279.1315; found: 279.1317.
IV.XI  LC conditions

IV.XI.1  Method A

**Method Description:** Formic Acid Generic Analytical UPLC Open Access LC/MS

2 Minute Method

**LC Conditions**

The UPLC analysis was conducted on an Acquity UPLC BEH C18 column (50mm x 2.1mm i.d. 1.7μm packing diameter) at 40 degrees centigrade.

The solvents employed were:

- A = 0.1% v/v solution of Formic Acid in Water.
- B = 0.1% v/v solution of Formic Acid in Acetonitrile.

The gradient employed was:

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The UV detection was a summed signal from wavelength of 210 nm to 350 nm.

**MS Conditions**

- MS : Waters ZQ
- Ionisation mode : Alternate-scan Positive and Negative Electrospray
- Scan Range : 100 to 1000 AMU
- Scan Time : 0.27 seconds
- Inter scan Delay : 0.10 seconds
IV.XI.II  Method B

Method Description:  Formic Acid Generic Analytical UPLC Open Access LC/MS
10 Minute Method

LC Conditions

The UPLC analysis was conducted on an Acquity UPLC BEH C18 column (50mm x 2.1mm
i.d. 1.7μm packing diameter) at 40 degrees centigrade.

The solvents employed were:

A = 0.1% v/v solution of Formic Acid in Water.
B = Acetonitrile.

The gradient employed was:

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The UV detection was a summed signal from wavelength of 200 nm to 320 nm.

MS Conditions

MS : Waters ZQ
Ionisation mode : Alternate-scan Positive and Negative Electrospray
Scan Range : 100 to 1000 AMU
Scan Time : 0.27 seconds
Inter scan Delay : 0.10 seconds.
IV.XI.III  HPLC conditions

Column : 5.0μm Waters Atlantis dC18 100x19.0mmID
Injection Volume : 200μl (12 injections at ~6.7mg loading)
Injection Vehicle : DMSO/DMF (1:1)
Flow Rate(mL/min) : 20
Temperature : Ambient
UV Detection : Diode-array 210-400nm (averaged)
Gradient Profile : 55-80%

The solvents employed were:

A = 0.1% v/v solution of Formic Acid in Water.
B = MeOH + 0.1%v/v of Formic Acid

The gradient employed was:

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MS Detection : Electrospray, +ve/-ve switching, 100-1000amu, centroid mode
Fraction Recovery : Nitrogen blow-down
REFERENCES


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## APPENDIX

### I Solvent/Base Studies

![Chemical structure](image)

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<td>100 : 0</td>
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<tr>
<td>7</td>
<td>8 eq Cs2CO3</td>
<td>acetone</td>
<td>42 : 32 : 26</td>
<td>55 : 44</td>
</tr>
<tr>
<td>8</td>
<td>8 eq Cs2CO3</td>
<td>DCM</td>
<td>36 : 36 : 29</td>
<td>55 : 44</td>
</tr>
<tr>
<td>9</td>
<td>8 eq Li2CO3</td>
<td>CH3CN</td>
<td>~100 : trace : trace</td>
<td>- : -</td>
</tr>
<tr>
<td>10</td>
<td>1.4 eq sec-BuLi</td>
<td>THF, -78 °C to rt, 3 h</td>
<td>0 : 72 : 0</td>
<td>100 : 0</td>
</tr>
<tr>
<td>11</td>
<td>1.7 eq KOtBu</td>
<td>THF, 0 °C to rt, 3 h</td>
<td>trace : 72 : 5</td>
<td>93 : 7</td>
</tr>
<tr>
<td>12</td>
<td>1.7 eq KOtBu</td>
<td>CH3CN, 0 °C to rt, 3 h</td>
<td>trace : 69 : 9</td>
<td>89 : 11</td>
</tr>
<tr>
<td>13</td>
<td>1.2 eq NaOtBu</td>
<td>THF, 0 °C to rt, 3 h</td>
<td>0 : 94 : 6</td>
<td>94 : 6</td>
</tr>
<tr>
<td>14</td>
<td>8 eq DBU</td>
<td>CH3CN</td>
<td>0 : 45 : 55</td>
<td>45 : 55</td>
</tr>
<tr>
<td>15</td>
<td>8 eq TBD</td>
<td>CH3CN</td>
<td>22 : 39 : 39</td>
<td>50 : 50</td>
</tr>
<tr>
<td>16</td>
<td>8 eq TMG</td>
<td>CH3CN</td>
<td>31 : 21 : 28</td>
<td>43 : 57</td>
</tr>
</tbody>
</table>

Table I.I.\(^a\) Determined by \(^1\)H NMR analysis of the crude reaction mixture; sm = starting material.
II Thermogravimetric Analysis of 53
IV Stereochemical Assignment of Diamine 144

144 $^1$H NMR (400 MHz, CDCl$_3$)

144 $^{13}$C NMR (125 MHz, CDCl$_3$)
(1$S,2S$)-144 (from diamine) $^{13}$C NMR (100 MHz, CDCl$_3$)

(1$R^*,2S^*$)-144 (from diamine) $^{13}$C NMR (100 MHz, CDCl$_3$)