

University of Warwick institutional repository: <http://go.warwick.ac.uk/wrap>

A Thesis Submitted for the Degree of PhD at the University of Warwick

<http://go.warwick.ac.uk/wrap/38106>

This thesis is made available online and is protected by original copyright.

Please scroll down to view the document itself.

Please refer to the repository record for this item for information to help you to cite it. Our policy information is available from the repository home page.

Synthesis, Structure and Functionalisation of 1,2-Diazetidines

by

Michael John Brown

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

CONTENTS

ACKNOWLEDGMENTS	iv
DECLARATION	v
ABSTRACT	vi
ABBREVIATIONS	vii
I Introduction	2
I.I 1,2-Diazetidines	2
I.II Thermodynamics of Four-Membered Ring Formation	3
I.III Prior Synthetic and Structural Studies	5
I.IV Purpose of Study	13
I.V Conclusions	16
II Synthesis of 1,2-Diazetidines	18
II.I Synthesis of 1,2-Dicarboxyalkyl-1,2-Diazetidines	19
II.II Synthesis of 1,2-Dialkyl-1,2-Diazetidines	35
II.III Synthesis of 1,2-Disulphonyl-1,2-Diazetidines	39
II.IV Attempted Synthesis of 1,2-Diazetidine	44
II.IV.I Via N–N Bond Formation	45
II.IV.II Via Deprotection of <i>N,N'</i> -Disubstituted-1,2-Diazetidines	47
II.V Synthesis of 3-Alkylidene-1,2-Diazetidines	52
II.VI Conclusions	64
III Structure and Functionalisation of 1,2-Diazetidines	67
III.I Structure	68
III.II Functionalisation of 1,2-Diazetidines	74
III.II.I Lithiation Chemistry	75
III.III Functionalisation of 3-Alkylidene-1,2-Diazetidines	83
III.III.I Cross-coupling chemistry	84

III.III.II Addition Chemistry	89
III.IV Reduction Chemistry	91
III.V Conclusions	95
IV Experimental	98
IV.I General	98
IV.II Synthesis of 1,2-Dicarboxyalkyl-1,2-Diazetidines	100
IV.III Synthesis of 1,2-Dialkyl-1,2-Diazetidines	117
IV.IV Synthesis of 1,2-Disulphonyl-1,2-Diazetidines	121
IV.V Attempted Synthesis of 1,2-Diazetidine	127
IV.VI Synthesis of 3-Alkylidene-1,2-Diazetidines	131
IV.VII Functionalisation of 1,2-Diazetidines	145
IV.VIII Lithiation Chemistry	146
IV.IX Functionalisation of 3-Alkylidene-1,2-Diazetidines	148
IV.X Reduction Chemistry.....	153
IV.XI LC conditions	158
IV.XI.I Method A.....	158
IV.XI.II Method B.....	159
IV.XI.III HPLC conditions.....	160
REFERENCES	161
APPENDIX	175
I Solvent/Base Studies	175
II Thermogravimetric Analysis of 53	176
III ¹⁵ N HMBC of 122	177
IV Stereochemical Assignment of Diamine 144	178

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:

1. *Critical importance of leaving group 'softness' in nucleophilic ring closure reactions of ambident anions to 1,2-diazetidines.* Brown, M. J.; Clarkson, G. J.; Fox, D. J.; Inglis, G. G.; Shipman, M. *Tetrahedron Lett.* **2010**, 51, 382.

2. *Synthesis and functionalisation of 3-alkylidene-1,2-diazetidines using transition metal catalysis.* Brown, M. J.; Clarkson, G. J.; Inglis, G. G.; Shipman, M. *Org. Lett.* **2011**, 13, 1686.

ABSTRACT

The four-membered cyclic hydrazine, 1,2-diazetidene, 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-diazetidene 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-diazetidene molecule ($C_2N_2H_6$) 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.

ABBREVIATIONS

atm	Atmosphere
Bn	benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
br	broad
Bus	<i>tert</i> -Butylsulphonyl
Calcd	calculated
CAN	Cerium(IV) ammonium nitrate
<i>cat.</i>	catalytic
Cbz	Carbobenzyloxy
COSY	Correlation Spectroscopy
d	day
DBB	4,4'-di- <i>tert</i> -Butylbiphenyl
DBU	1,3-Diazobicyclo[5.4.0]undecane
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DEAD	Diethyl azodicarboxylate
decomp.	decomposed
DIBAL	Di- <i>iso</i> -butylaluminium hydride
DMEDA	<i>N,N'</i> -Dimethylethylenediamine
DMF	<i>N,N'</i> -Dimethylformamide
DMPU	<i>N,N'</i> -Dimethylpropylene urea
DMSO	Dimethyl sulphoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	Electron Impact
equiv	equivalent
ES	Electrospray
FT	Fourier Transform
GCMS	Gas Chromatography Mass Spectroscopy

h	hour
HMBC	Heteronuclear Multiple Bond Coherence
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
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
<i>J</i>	Coupling constant
LCMS	Liquid chromatography-Mass Spectroscopy
LDA	Lithium Di- <i>iso</i> -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	<i>N</i> -Bromosuccinimide
NMR	Nuclear Magnetic Resonance
nOe	nuclear Overhauser effect
<i>p</i>	<i>para</i>
PMB	<i>para</i> -Methoxybenzyl
ppm	parts per million
<i>R_f</i>	Retention factor

rt	room temperature
SCF	Self-Consistent Field
S _N 2	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
tlc	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -Tetramethylethylenediamine
TMG	<i>N,N,N',N'</i> -Tetramethylguanidine
TMS	Trimethylsilyl
Ts	<i>para</i> -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.

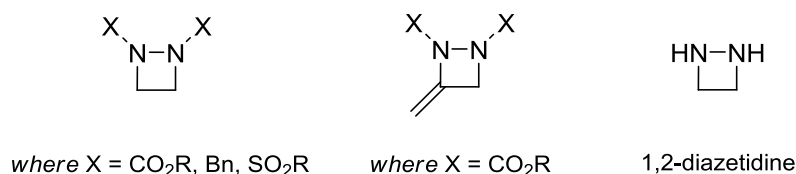


Figure 1.1

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





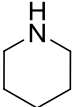





					
	ammonia	aziridine	azetidine	pyrrolidine	piperidine
bp/°C	-33	56-58	61-62	86-87	106
					
	hydrazine	diaziridine	diazetidine	pyrazolidine	piperazine
bp/°C	114	-	-	138	149

Figure 1.2 Parent cyclic amines and hydrazines with isolated boiling point.¹⁻⁶

Diaziridine can be reliably generated and reacted successfully *in situ*;⁷ several routes exist to mono- and di-substituted species, and simple and general methods to trisubstituted species are available.⁸ 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* (ΔH^\ddagger), *i.e.* energy is required to ‘bend’ the molecule into the reacting conformation. Such S_N2 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 ($\Delta H_f^\circ = 238 \pm 1$ kJ mol⁻¹) and diazetidine ($\Delta H_f^\circ = 242 \pm 1$ kJ mol⁻¹).¹⁰

Consideration of relative rates of ring closure is crucial. For a series of bromoalkylamines, the following data was obtained:¹¹

$$\text{H}_2\text{N}-(\text{CH}_2)_n\text{Br} \xrightarrow[25\text{ }^\circ\text{C}]{\text{NaOH}} \left(\begin{array}{c} \text{H} \\ | \\ \triangle \\ | \\ \text{N} \end{array} \right)_n$$

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 ΔG^\ddagger the *free energy of activation*, which is composed of enthalpic and entropic components:

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger \quad [1]$$

Three-membered rings form readily because the unfavourable ΔH^\ddagger change is offset by a favourable ΔS^\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 ΔS^\ddagger), this adds to the unfavourable ΔH^\ddagger change, resulting in a large ΔG^\ddagger and therefore a slow cyclisation.

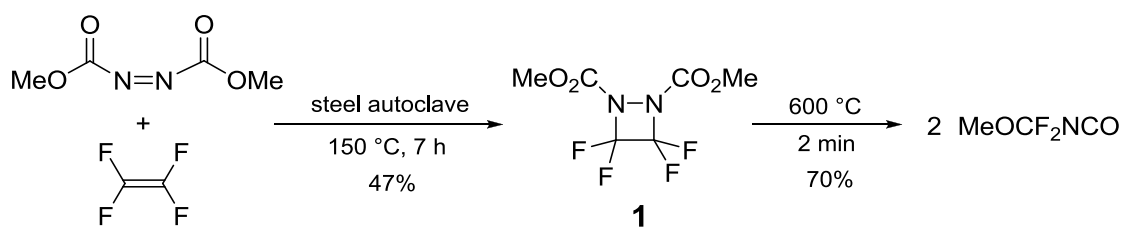
Ring closures to five- and six-membered rings do not suffer from such large ΔH^\ddagger values as the contribution from ring strain is small. This combined with a favourable ΔS^\ddagger term (reacting conformations are readily accessible) results in a smaller ΔG^\ddagger and faster ring closures. The 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.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

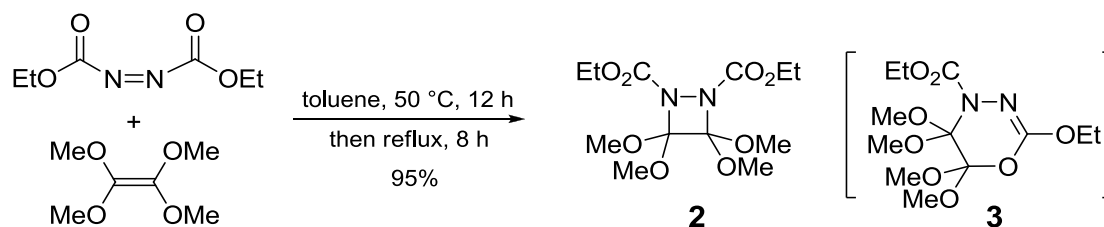
Although claims about the synthesis of diazetidines date back to the 1850's, most of the earlier reports were later found to be erroneous.^{13,14} It appears the first successful attempts at the synthesis of 1,2-diazetidines were recorded in the late 1940's.¹⁵ Only within the last five years or so have claims of efficient synthetic routes to these systems been made.^{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,^{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),²⁰ a method patented previously by the company in 1948.¹⁵ The authors further disclosed its flash pyrolysis to methoxydifluoromethyl isocyanate.



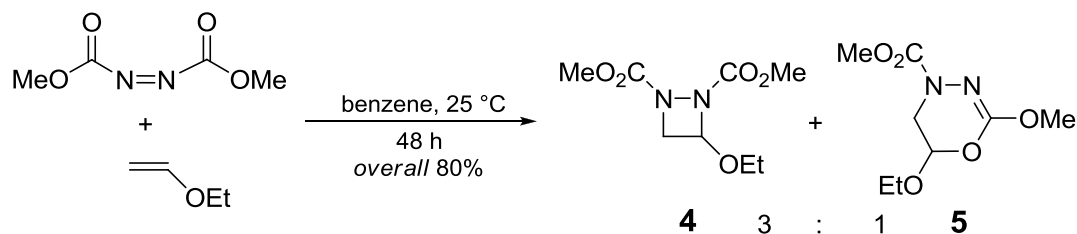
Scheme 1.1

In 1964, Hoffmann and Häuser reported an efficient thermal addition of tetramethoxyethylene to diethyl azodicarboxylate to give **2** (Scheme 1.2).²¹ In further work, they critically considered the possible [4+2] by-product, dihydrooxadiazine **3**.²² Based on IR analysis, and supported by earlier work on these six-membered rings from Gustorf,²³ they discounted the dihydrooxadiazine as the major reaction product.



Scheme 1.2

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).²⁴ These adducts were differentiated on the basis of IR and NMR analysis.^{23,25} Illumination of this reaction with ultraviolet light only accelerated the reaction and no change in product ratio was observed.²⁶ The authors attributed this rate increase to faster conversion of the normally *trans*-azodicarboxylate to the more reactive *cis*-azodicarboxylate conformer.

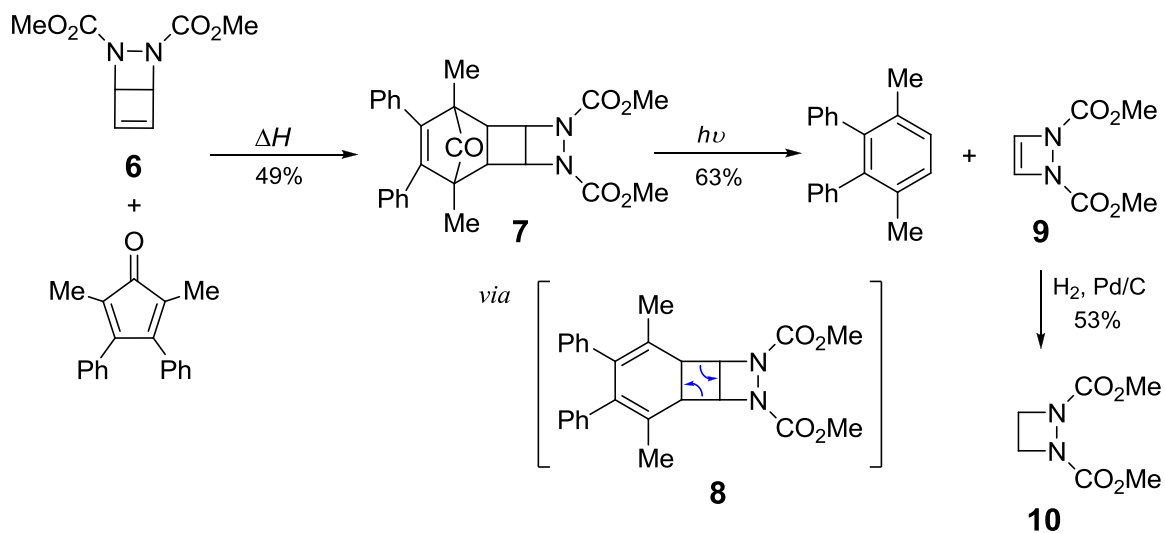


Scheme 1.3

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.²⁷ 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;²⁸ 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.²⁹

Determination of the mechanism of similar reactions has continued.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, Warrenner and Nunn first synthesised the unsaturated diazetidine analogue Δ^3 -1,2-diazetidine **9** (Scheme 1.4).³³ Reaction of cyclobutadiene with dimethyl azodicarboxylate furnished **6** (31% yield) which underwent a thermal cycloaddition with 2,5-dimethyl-3,4-diphenylcyclopenta-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 Δ^3 -1,2-diazetidine-1,2-dicarboxylate (**9**) (63% yield) and the corresponding aromatic hydrocarbon.

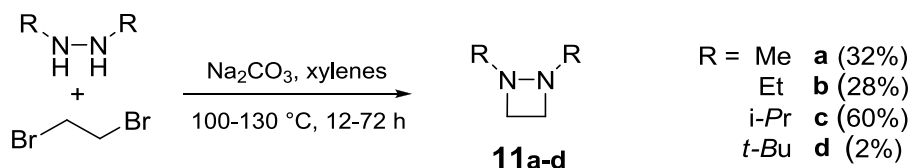


Scheme 1.4

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,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-diazetidines 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).³⁵ Hall and Bigard used this method to provide a range of simple dialkyl-1,2-diazetidines to study the ring conformation of these molecules.³⁶ 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.

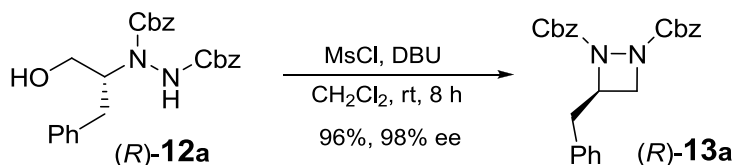


Scheme 1.5

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.³⁶

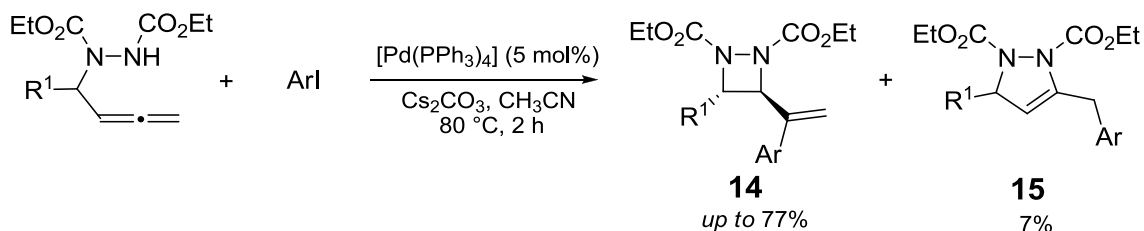
In 2006, Miao and co-workers reported the cyclisation of hydroxyethylhydrazine derivatives such as **12a** to give optically pure 1,2-diazetidines in excellent yields (Scheme 1.6).¹⁶ These alcohols could be produced in both enantiomeric forms *via* the catalytic α -amination of aldehydes as reported by List.³⁷ 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.³⁸



Scheme 1.6

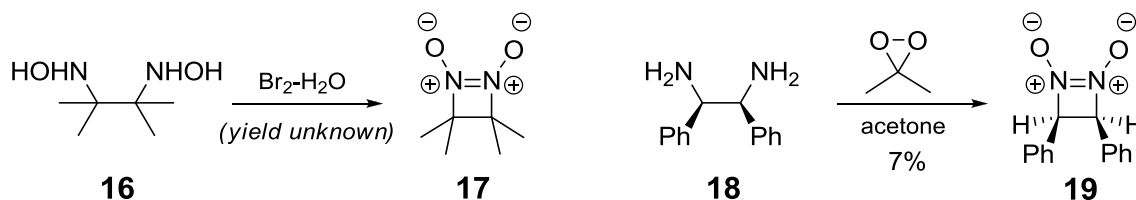
More recently, in 2008 Cheng and Ma provided a palladium catalysed coupling/cyclisation of aryl iodides with 2,3-allenyl hydrazines to yield *trans*-1,2-diazetidines (Scheme 1.7).¹⁷ Variation at the ring carbon was limited to *n*-alkyl or benzyl groups, and electron poor aryl iodides were preferred.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



Scheme 1.7

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 *via* N–N bond formation. The most important industrial method for the synthesis of hydrazine, the Raschig process,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,⁴¹ and importantly has been used with success to access the parent 1,2-pyrazolidine and 1,2-piperazine systems.⁶ There appear to be only two reports on the synthesis of four-membered rings *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- Δ^1 -1,2-diazetine-1,2-dioxide (**17**);⁴² and Breton and co-workers synthesised 3,4-diphenyl- Δ^1 -1,2-diazetine-1,2-dioxide (**19**) *via* oxidation of 2,3-diphenyl-1,2-ethylenediamine (**18**) with dioxirane.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.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.

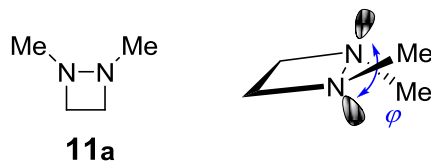


Figure 1.3 φ is the dihedral angle between the lone pairs.

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 ($C_{\text{methyl}}\text{NN}'C_{\text{methyl}}$) = 105°], in agreement with Rademacher.⁴⁵

Further studies of 1,2-dimethyl-1,2-diazetidines were undertaken by Hall and Bigard using NMR spectroscopy.³⁶ Low temperature ^1H 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 *trans eq-11*, where ($\text{H}^1=\text{H}^4$ and $\text{H}^2=\text{H}^3$).

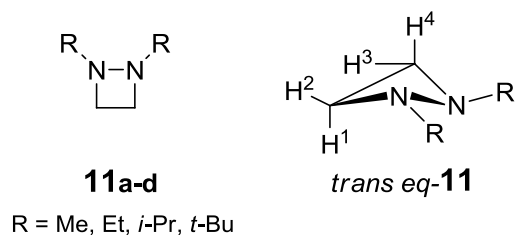
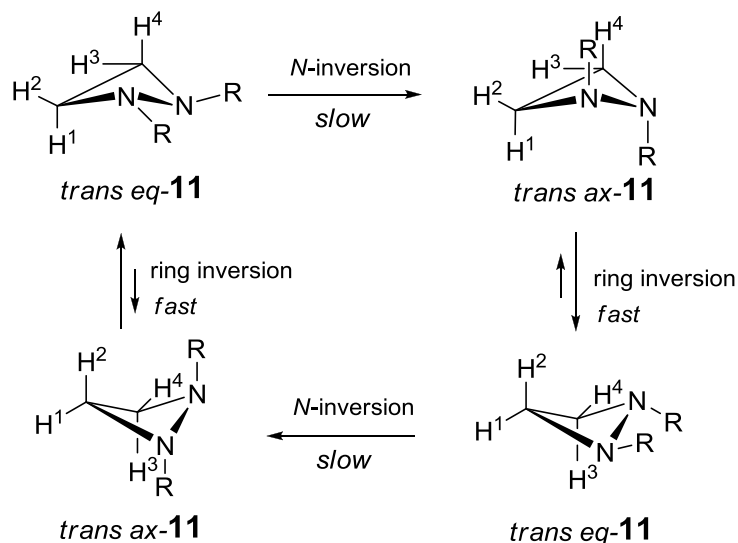


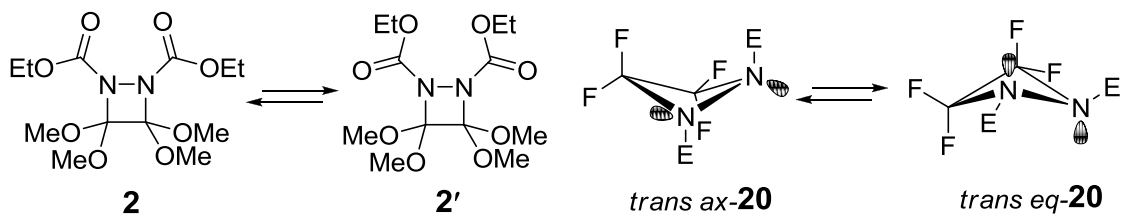
Figure 1.4

These signals coalesced to a singlet resonance when double inversion at nitrogen became rapid. Relative rates of this process at $T = 66\text{ }^\circ\text{C}$ were determined by line-shape analysis as $1.00 : 0.78 : 0.51 : 0.74 \times 10^{-3}$ for $\text{R} = \text{Me}, \text{Et}, i\text{-Pr}, t\text{-Bu}$ respectively, and the free energy of double nitrogen inversion for 1,2-dimethyl-1,2-diazetidines was calculated as $\Delta G_c^\ddagger = 68.6\text{ kJ mol}^{-1}$. The di-*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 *trans ax-11* with the alkyl groups *trans*-diaxial (Scheme 1.9) until coalescence of the ring methylene signals at $155\text{ }^\circ\text{C}$.



Scheme 1.9 Slow nitrogen inversion in **11** as illustrated by Hall and Bigard.³⁶

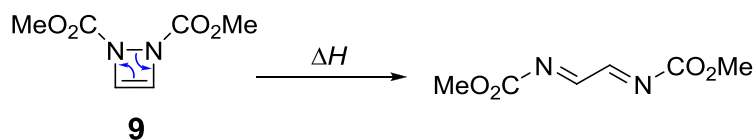
Similar dynamic NMR studies of **2** (Scheme 1.10) showed that restricted rotation about the amide bond ($\mathbf{2} \leftrightarrow \mathbf{2}'$) was responsible for a barrier of $\Delta G_c^\ddagger = 56.9 \text{ kJ mol}^{-1}$ ($T_c = -27^\circ \text{C}$ in d_6 -acetone d_8 -toluene solution),⁴⁶ as 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** ($\Delta G_c^\ddagger = 43.9 \text{ kJ mol}^{-1}$), 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. Lehn⁴⁸ and other workers.^{49,50}



Scheme 1.10 Isomerisation *via* rotation around N-(CO)R bond in **2**. Ring inversion in **20** (E = CO₂Et).

Δ^3 -1,2-diazetidine **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 stabilisation.



Scheme 1.11

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.

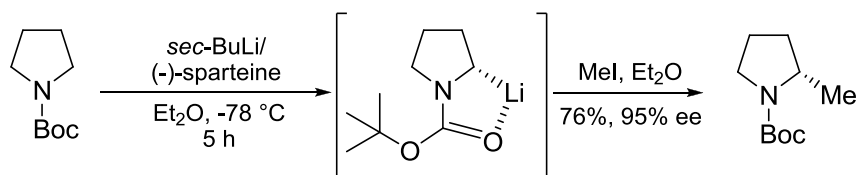
Four-membered heterocycles are emerging as useful tools in medicinal chemistry. The physicochemical properties of these systems offer new opportunities for drug discovery. For example, the conformationally restricted nature of functionalised azetidine rings^{52,53,54,55} has seen their development into a new class of nicotinic acetylcholine receptor agonists.⁵⁶ Recently, oxetanes have been explored as surrogates for *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.⁵⁷ 1,2-Diazetidines have already been explored computationally as components of β -turn mimetics,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.⁵⁹ 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.⁶⁰ 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.

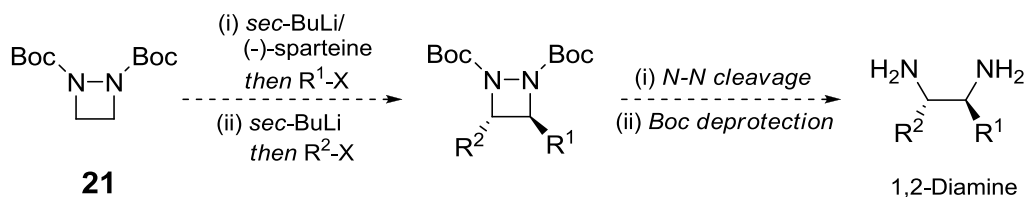
We were particularly interested in the use of 1,2-diazetidines to act as scaffolds for the introduction of the 1,2-diamine moiety into larger organic molecules. Functionalisation of simple systems (*those unsubstituted at the ring carbons*) via C–H activation; or functionalisation of those bearing an 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.^{61,62} 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.⁶³ Chiral diamine ligands such as, but not exclusively,⁶⁴ (–)-sparteine, have been used extensively to induce stereoselective deprotonation. Seminal work by Beak on the asymmetric deprotonation of *N*-Boc pyrrolidine⁶⁵ (Scheme 1.12) has been elaborated by several groups to other *N*-Boc heterocycles including oxa-, thia- and imidazolidines⁶⁶ and piperidines,⁶⁷ generally with reasonable levels of enantioselectivity. Deprotonation/substitution adjacent to nitrogen in aziridines,⁶⁸ methyleneaziridines,⁶⁹ azetidines⁷⁰ and pyrazoles⁷¹ have also been successful.



Scheme 1.12 Enantioselective deprotonation of *N*-Boc-pyrrolidine.

We envisaged that di-*tert*-butyl-1,2-diazetidene-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 sp^3 carbons. As such, this would represent a novel, divergent route to chiral diamines.⁷²



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,¹⁶ 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.

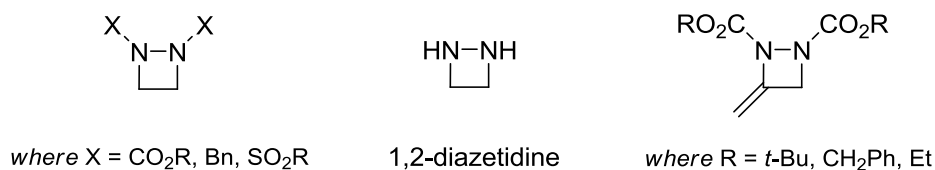
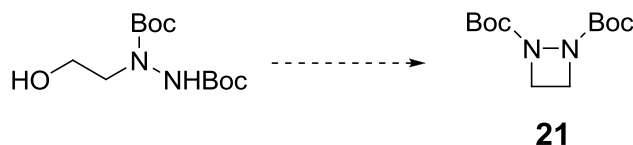


Figure 2.1

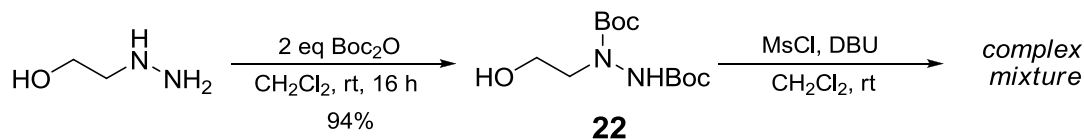
II.I Synthesis of 1,2-Dicarboxyalkyl-1,2-Diazetidines

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



Scheme 2.1

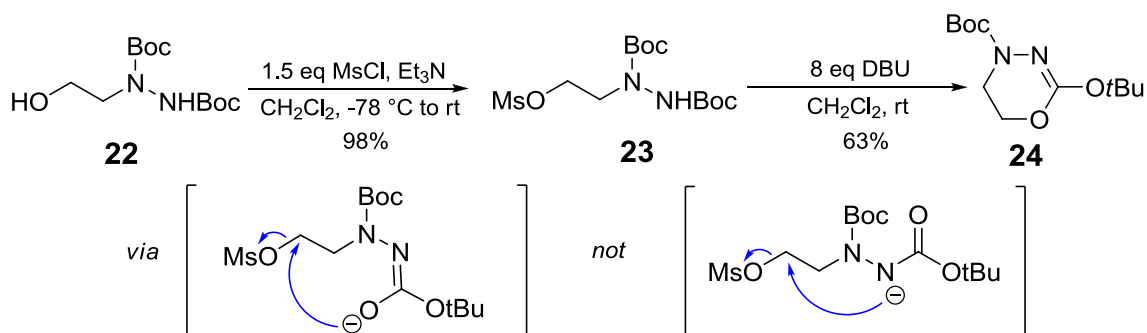
2-Hydroxyethyl hydrazine is commercially available. Boc protection of the hydrazine nitrogens proceeded smoothly to give **22** in excellent yield (Scheme 2.2).⁷³ However, treatment of this alcohol under Miao's best cyclisation conditions (1.5 eq MsCl, 8 eq DBU, CH_2Cl_2 , rt) led to a complex mixture of products.



Scheme 2.2

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 ^1H 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.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.



Scheme 2.3

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).

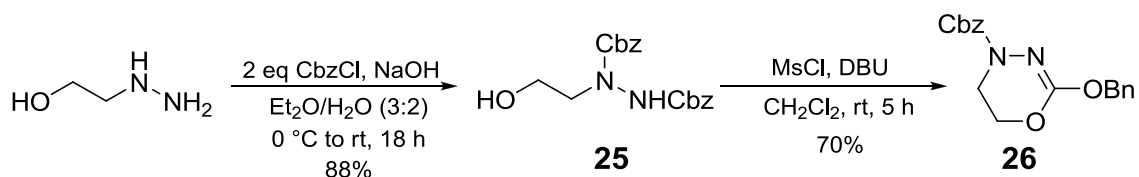
entry	conditions	yield (%)
1	8 eq DBU, CH ₂ Cl ₂	63
2	1.3 eq NaH, DMF	80
3	1.5 eq LiHMDS, toluene	24
4	8 eq Cs ₂ CO ₃ , CH ₃ CN	93

Table 2.1

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

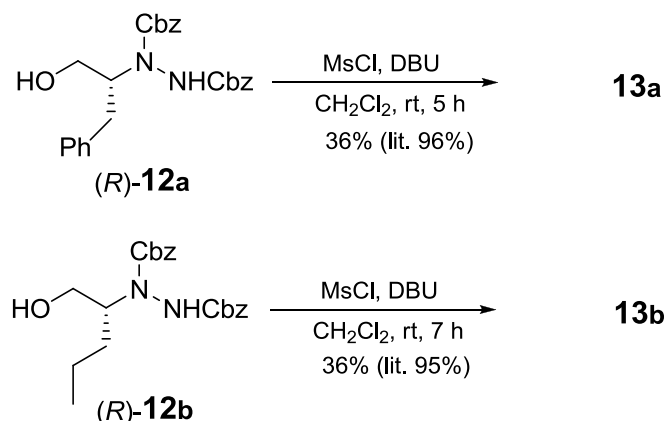
cyclisation outcome, we elected to prepare the corresponding substrate bearing Cbz groups.

Treatment of hydroxyethyl hydrazine with benzyl chloroformate under *Schotten-Baumann* conditions⁷⁴ 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.



Scheme 2.4

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.³⁷ 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.¹⁶ 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.



Scheme 2.5

Based on our earlier results (Schemes 2.2-2.4) we were very concerned about Miao's structural assignments. Indeed only ^1H 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).

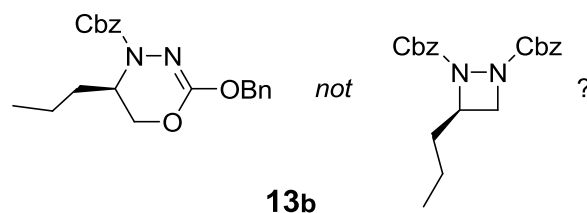


Figure 2.2

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 ^1H 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 $\nu = 1800\text{--}1600\text{ cm}^{-1}$ 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).

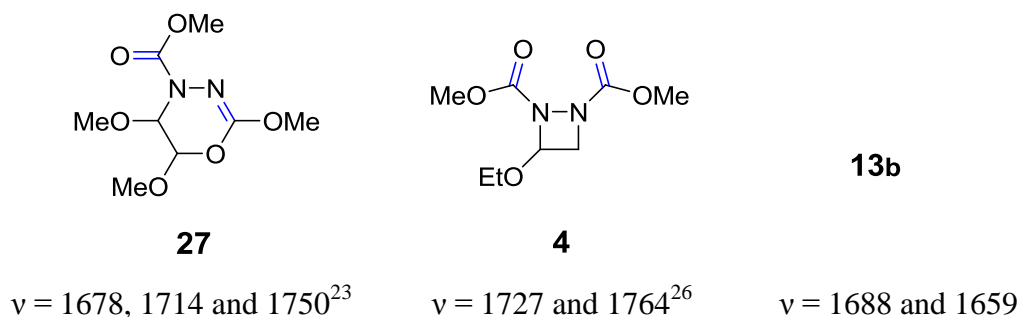
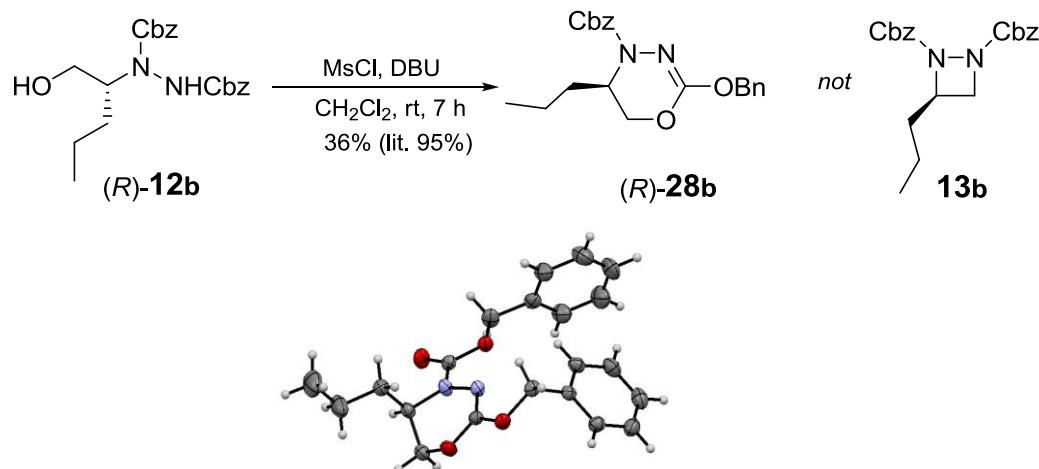


Figure 2.3 Absorptions measured in $\text{CCl}_4/\text{cm}^{-1}$.

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** (H_2 , 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.

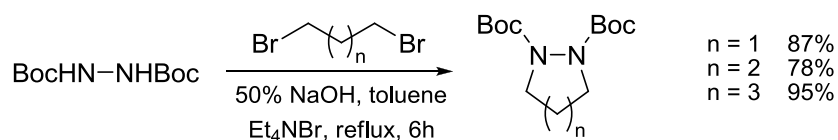
Although taken together the evidence points to the dihydrooxadiazine isomer, this was not conclusive. Fortunately, analysis of a single crystal *via* X-ray diffraction confirmed our suspicions that indeed the dihydrooxadiazine was the product formed, contrary to the assignment made by Miao (Scheme 2.6). 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}

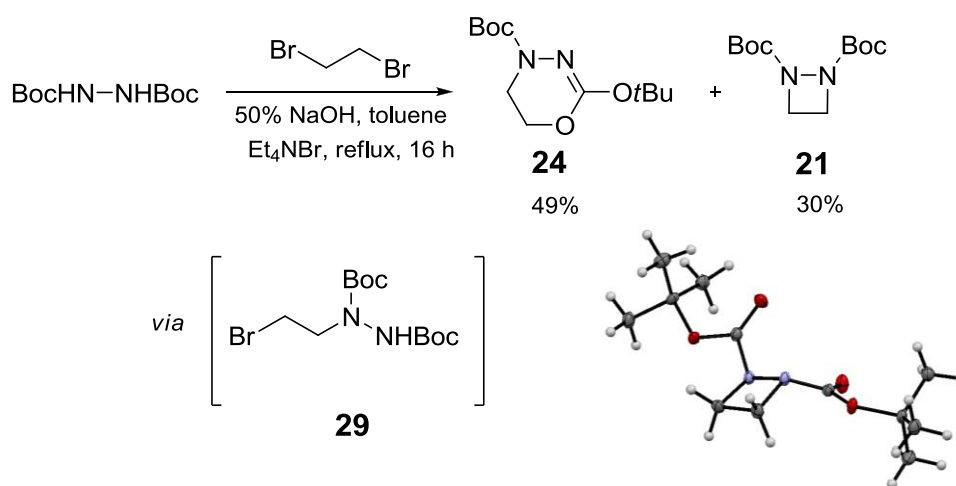
Undeterred by these difficulties, we explored other potential routes to the *bis*-Boc diazetidine. Several groups have routinely synthesised *bis*-Boc protected cyclic hydrazines *via* the reaction of *bis*-Boc hydrazine with the corresponding dibromoalkane under strongly basic or phase transfer conditions.^{77,78}



Scheme 2.7

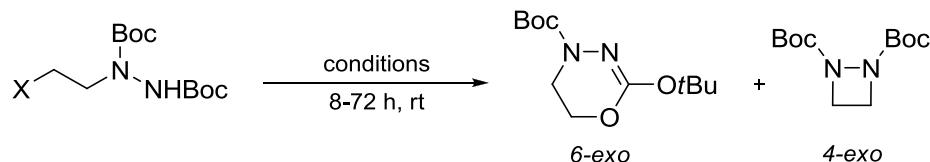
An alternative approach based on this method was tested. Reaction of *bis*-Boc hydrazine with dibromoethane under weakly basic conditions (Na₂CO₃, DMF, 100 °C, 1 h) returned only starting material (*cf.* Scheme 1.5).³⁶ However, under more forcing phase

transfer conditions, in addition to the dihydrooxadiazine **24**, we were delighted to observe two singlets in the crude ^1H 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 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.⁷⁹ Tabulated cyclisation results are shown in Table 2.2.



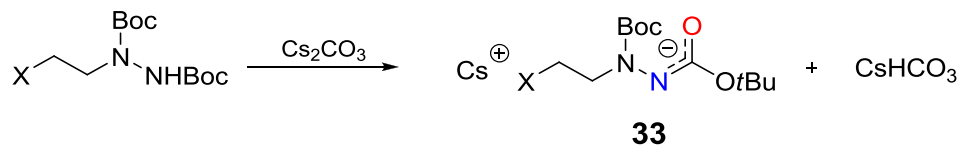
entry	substrate	X	conditions	6- <i>exo</i> (24) : 4- <i>exo</i> (21) ^a	yield ^b
1	22	OH	PPh ₃ , DEAD, THF, 0 °C	100 : 0	64% (24)
2	23	OMs	Cs ₂ CO ₃ , CH ₃ CN	97 : 3	96% (24)
3	30	Cl	Cs ₂ CO ₃ , CH ₃ CN	73 : 27	<i>n.d.</i>
4	31	Br	Cs ₂ CO ₃ , CH ₃ CN	60 : 40	<i>n.d.</i>
5	32	I	Cs ₂ CO ₃ , CH ₃ CN	46 : 54	53% (21)

Table 2.2 ^a Determined by ¹H NMR analysis of the crude reaction mixture; ^b Yield after silica gel chromatography. *n.d.* = not determined.

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.⁸⁰ Why does this ambident anion react through oxygen when presented with a C–OSO₂Me 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 Klopman⁸⁸ rationalised the HSAB observations in physical terms, based on the charge-charge and molecular orbital interactions:

$$\Delta E = -q_r q_s \frac{\Gamma}{\epsilon} + \Delta solv + \sum_{\substack{m \\ \text{occ}}} \sum_{\substack{n \\ \text{unocc}}} \left[\frac{2(c_r^m)^2 (c_s^n)^2 \beta^2}{E_m^* - E_n^*} \right] \quad [2]$$

Klopman equation: For species r and s with frontier molecular orbitals m and n respectively, where: ΔE = energy change on interaction; q = total initial charges including core electrons; Γ = Coulomb repulsion term; ϵ = local dielectric constant; $\Delta solv$ = solvation and desolvation change; c = orbital coefficient; E = energy of frontier molecular orbital and β = 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.^{89,90,91,92,i}

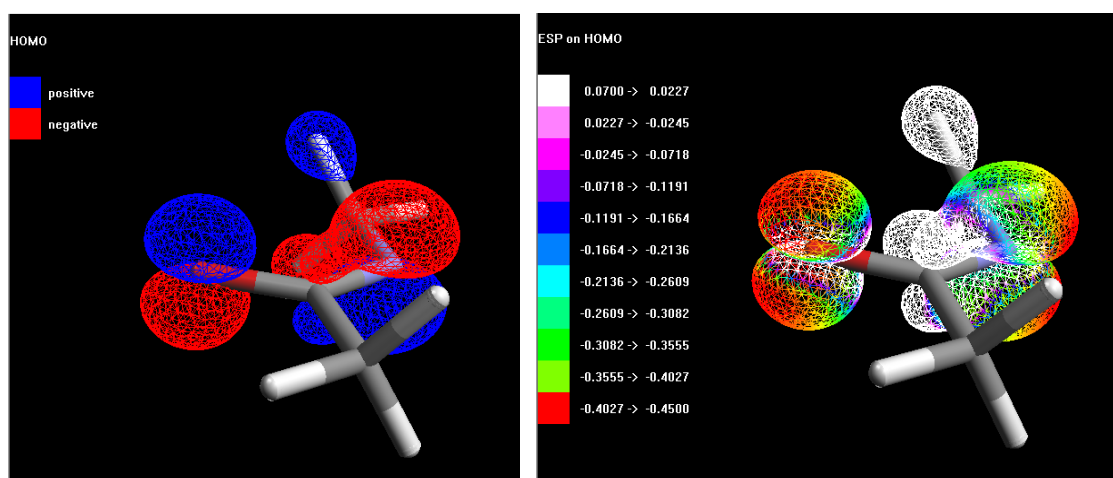


Figure 2.4 Model of the carboxamide anion system: $[\text{CH}_3\text{C}(\text{O})\text{NCH}_3]^-$.

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.

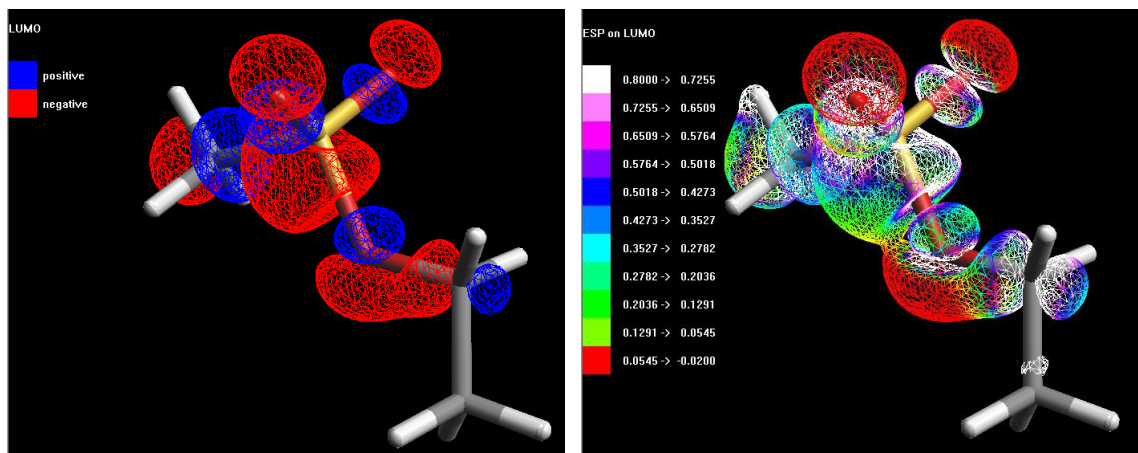


Figure 2.5 Model of the carbon-methanesulphonyl system: $\text{CH}_3\text{CH}_2\text{OSO}_2\text{CH}_3$.

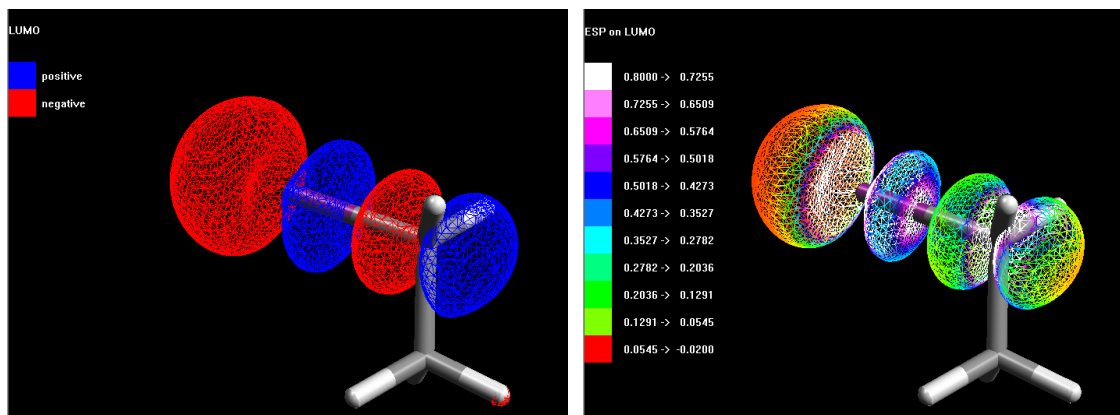
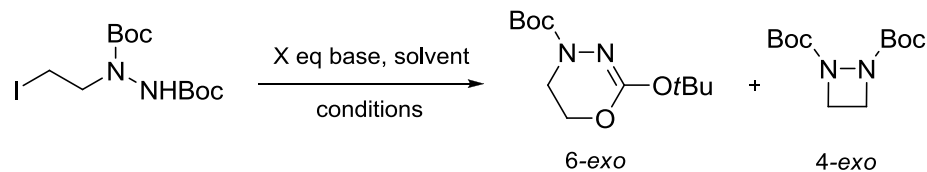


Figure 2.6 Model of the carbon-iodine system: $\text{CH}_3\text{CH}_2\text{I}$.

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.



entry		base	solvent	conditions	6- <i>exo</i> (24) : 4- <i>exo</i> (21) ^a
1	1.4 eq	<i>sec</i> -BuLi	THF	−78 °C → rt, 3 h	100 : 0
2	1.2 eq	NaOtBu	THF	0 °C → rt, 3 h	94 : 6
3	1.7 eq	KOtBu	THF	0 °C → rt, 3 h	93 : 7 ^b
4	8 eq	TBD	CH ₃ CN	rt, 48 h	50 : 50 ^c
5	8 eq	DBU	CH ₃ CN	rt, 48 h	45 : 55
6	8 eq	Cs ₂ CO ₃	CH ₃ CN	rt, 8 h	45 : 55
7	8 eq	TMG	CH ₃ CN	rt, 48 h	43 : 57 ^c

Table 2.3 ^aDetermined by ¹H NMR analysis of the crude reaction mixture. Complete consumption of starting material unless otherwise stated; ^bA ratio of 89:11 was observed for KOtBu in CH₃CN. ^c Reaction did not reach completion.

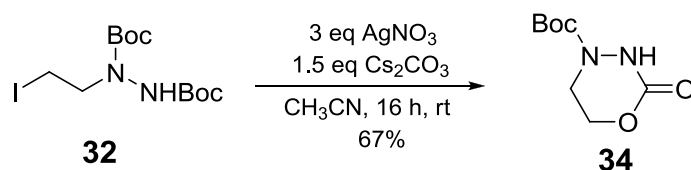
Studies on the alkylation of metal enolates have shown that the structure of the ambident ion-pair is important in controlling the site of alkylation.^{93,94} Reaction at carbon (*Soft* terminus) is favoured by highly oxophilic counterions (*e.g.* Li⁺), in poorly coordinating solvents which allow this ion-pair (or aggregate) to be tightly bound. Increasing solvent polarity disrupts this arrangement and increases *O*-alkylation. However, in the alkylation of metallated indoles and pyrroles (carbon *Hard*, nitrogen *Soft*), more azaphilic counterions (*e.g.* K⁺) favour alkylation at the nitrogen terminus.⁹⁵ Also in this case, increasing solvent polarity favours *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

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.⁸² 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.

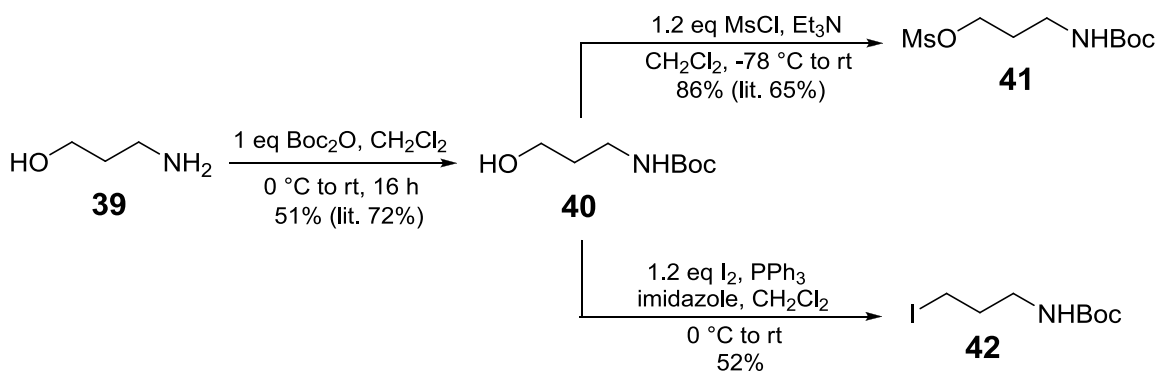


Scheme 2.10

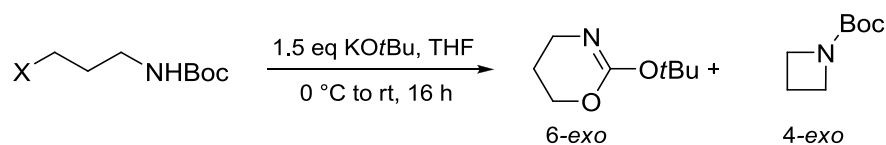
The use of iodide as a leaving group to encourage ring closures to diazetidines was extended to the synthesis of various 3-substituted-1,2-diazetidines. Alcohol **25** (Scheme 2.11) was prepared as described in Scheme 2.4 and alcohols **12a-c** were prepared according to the procedure of List.³⁷ Mesylation 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

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 δ -activated propylamines to *N*-Boc azetidine was studied. Aminopropanol **39** underwent facile Boc protection to give **40**⁹⁷ (Scheme 2.12). Conversion of the protected amine to mesylate **41**,⁹⁸ and direct iodination to **42**⁹⁹ using I₂/PPh₃/imidazole both proceeded well.



A range of conditions were studied for the cyclisation of **42**. The use of Cs₂CO₃ 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).



entry	substrate	X	6- <i>exo</i> (43) : 4- <i>exo</i> (44) ^a
1	41	OMs	100 : 0
2	42	I	90 : 9 ^b

Table 2.5 ^aDetermined by ¹H 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 prepared¹⁰⁰ 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-*exo* product does still improve when switching to iodide. This system does not benefit from increased nucleophilicity at nitrogen *via* the α -effect which may have improved four-membered ring formation in the diazetidine/dihydrooxadiazine system.^{101,102,103} It is worthy of note, however, that the use of potassium *tert*-butoxide in both systems produced very similar ratios of products (*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).¹⁰⁴ 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.

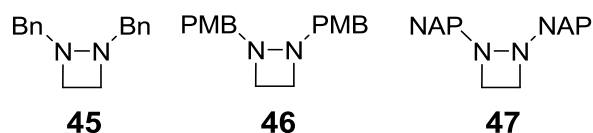
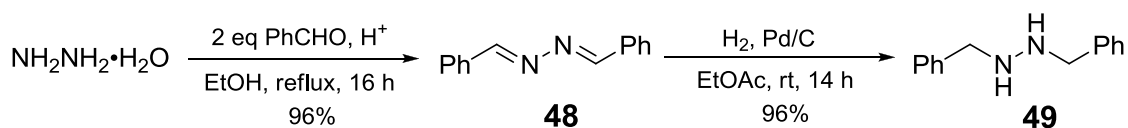


Figure 2.7

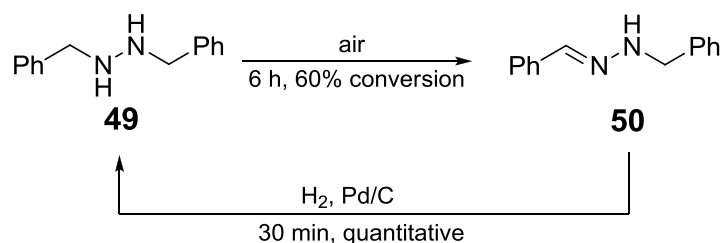
Our initial studies were directed toward the synthesis of **45**. We turned to an approach based on two successive alkylation reactions of a 1,2-dialkylhydrazine with 1,2-dibromoethane,³⁵ which was used by Hall and Bigard to produce a range of simple dialkyl-1,2-diazetidines in moderate to low yields (Scheme 1.5).³⁶

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).¹⁰⁵ Hydrogenation over Pd/C (1 atm) proceeded well in anhydrous ethyl acetate at room temperature to give 1,2-dibenzylhydrazine.¹⁰⁶



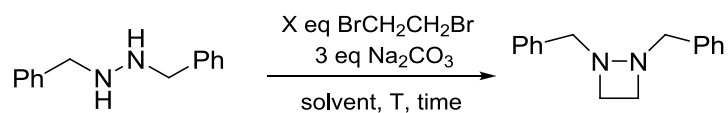
Scheme 2.13

Like other dialkyl hydrazines,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

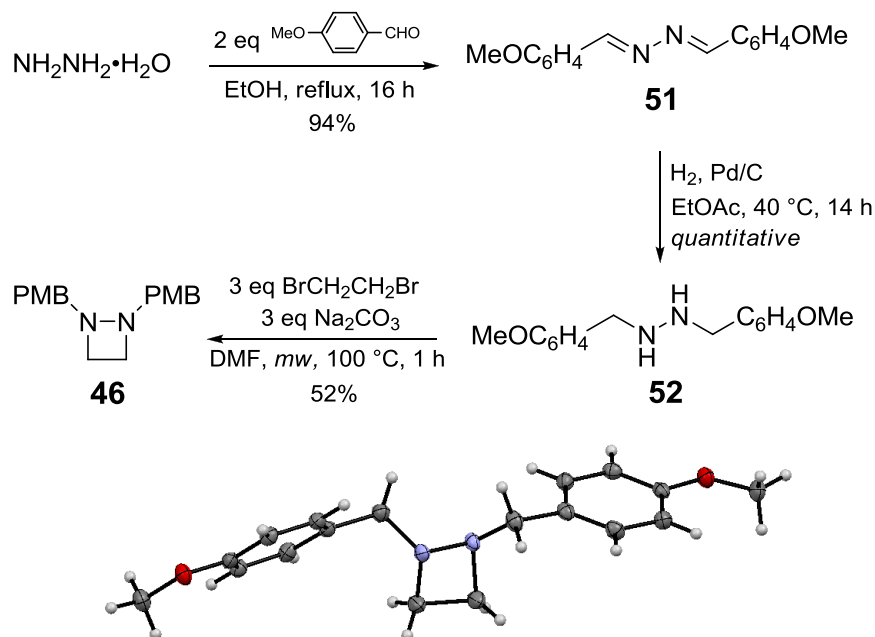
Reaction of 1,2-dibenzylhydrazine **49** with dibromoethane under the published conditions gave only a poor yield of 1,2-dibenzyl-1,2-diazetidine **45** (Table 2.6, entry 1).³⁶ Optimisation of the *bis*-alkylation was conducted in a sealed tube and in a CEM Discover microwave to prevent loss of the electrophile 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.



entry	eq dibromide	solvent	T/°C	time/h	method ^a	yield % (conversion % ^b)
1	10	xylenes	120	24	reflux	4 (5)
2	10	toluene	180	1	mw	n.d. (12)
3	10	DMF	160	1	mw	n.d. (0)
4	10	DMF	100	1	mw	n.d. (22)
5	3	DMF	100	1	mw	62 (65)
6	3	DMF	100	1	st	55 (59)

Table 2.6 ^a mw = microwave, st = sealed tube, traditional heating; ^b conversion determined by ¹H 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-diazetidene (**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.

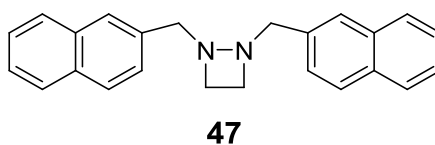


Figure 2.8

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.¹⁰⁸ 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.

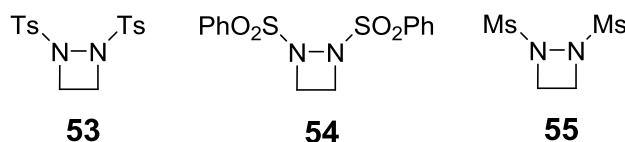
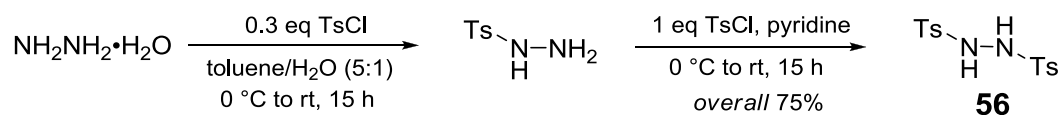


Figure 2.9

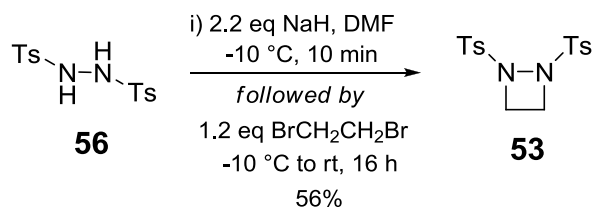
The preparation of 1,2-*bis*(arylsulphonyl)hydrazines has been well documented. Our studies began with preparation of 1,2-*bis*(tosyl)hydrazine (**56**) *via* the two-step method reported by Bartmann.¹⁰⁹



Scheme 2.16

Treatment of this hydrazine with dibromoethane in DMF at 0 °C using Cs₂CO₃ 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.



Scheme 2.17

Temperature control during the addition of the hydrazine to the sodium hydride suspension was found to be crucial to the success of the reaction. Below -10°C , the hydrazine precipitated from solution; but above 0°C the resultant anion decomposed liberating the toluenesulphonate ion which reacted with dibromoethane to give 1,2-ditosylethane (**57**) (identified by a single resonance for the methylene protons at 3.40 ppm) for which an X-ray crystal structure was also obtained (Figure 2.10). At higher addition temperatures, or when the exotherm on hydride addition was not carefully controlled, **57** became the major reaction product.

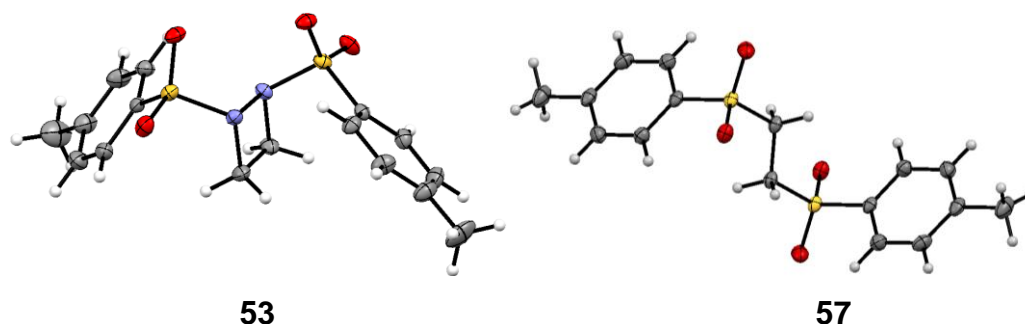
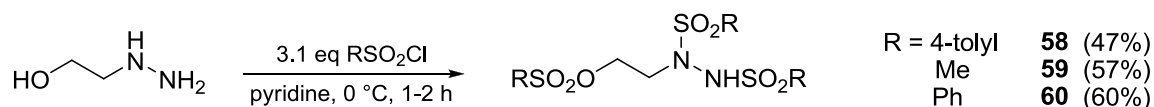


Figure 2.10 X-ray structures of 1,2-bis(tosyl)-1,2-diazetidine **53** and 1,2-ditosylethane **57**.

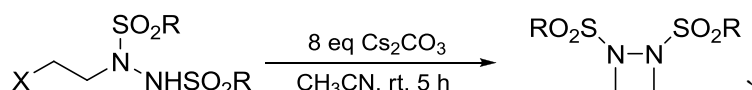
Reaction of 1,2-bis(phenylsulphonyl)hydrazine¹⁰⁹ with sodium hydride and dibromoethane proved more difficult to control. Even at -20°C , a mixture of diazetidine and elimination products were obtained.

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.¹¹⁰ This reaction was found to proceed well with several sulphonyl chlorides to give the *tris*-sulphonylated species **58-60**.



Scheme 2.17

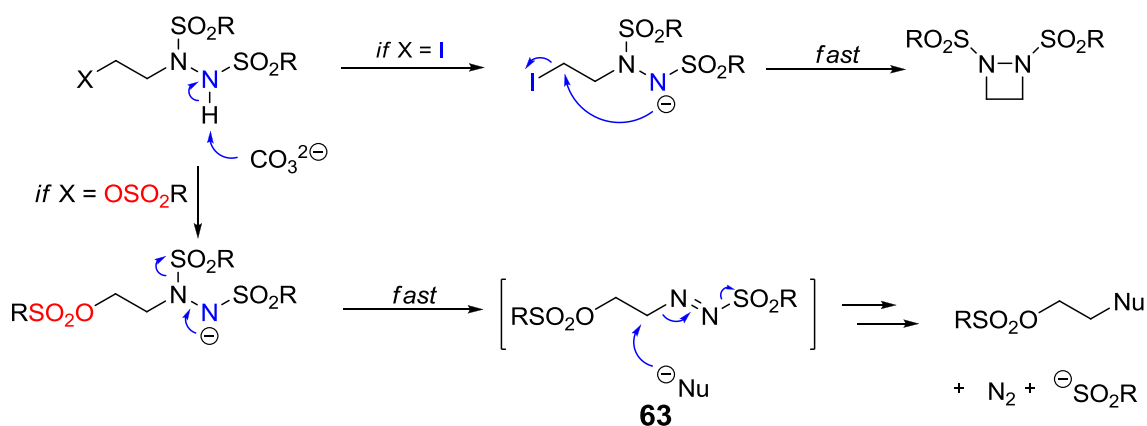
Treatment of tosylate **58** with NaH in DMF gave a disappointing 25% yield of diazetidine. We sought to determine if this unfavourable ring closure could be encouraged by consideration of the *Hard and Soft Acids and Bases* principle (Chapter II.I). The sulphonate esters were converted to the respective 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.



entry	substrate	X	SO ₂ R	yield
1	58	OTs	Ts	0% ^a
2	59	OMs	Ms	13% (55)
3	61	I	Ms	73% (55)
4	60	OSO ₂ Ph	SO ₂ Ph	0% ^{a,b}
5	62	I	SO ₂ Ph	98% (54)

Table 2.7 ^aA poor mass balance was obtained. An alternative aqueous workup returned a poor mass balance. ^bNo diazetidine was observed between 10 and 100% conversion when the reaction was performed in CD₃CN and monitored *in situ* by ¹H 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

The *tert*-butylsulphonyl (Bus) group¹¹² 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*(*tert*-butylsulphonyl)hydrazine (**64**) or the *tris*-sulphonylated **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

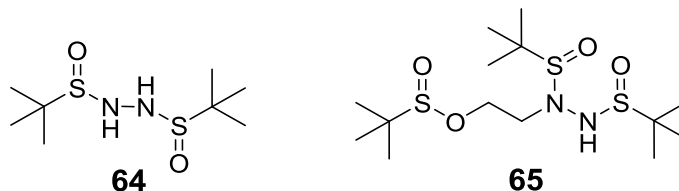
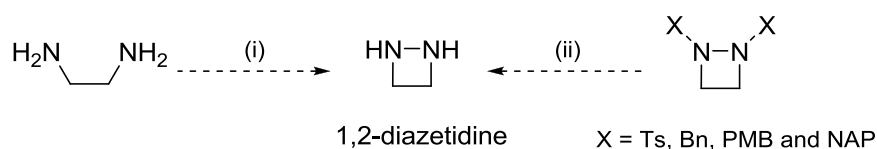


Figure 2.11

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-Diazetidines

Access to the parent 1,2-diazetidines 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-diazetidines 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.

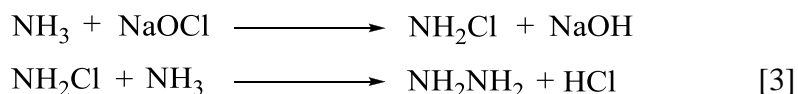


Scheme 2.19

Through comparison with its structural analogues, 1,2-diazetidines 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

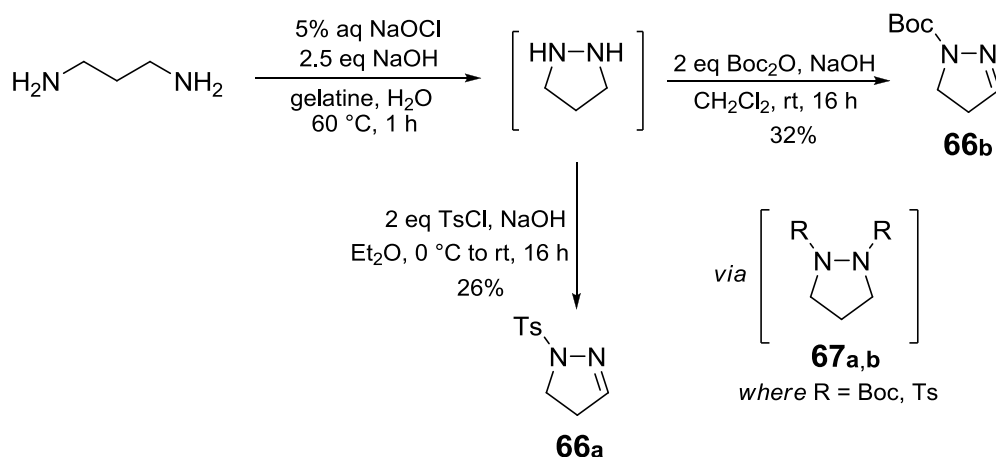
When ammonia is treated with an equimolar amount of hypochlorite in alkaline aqueous solution, chloramine (NH₂Cl) is formed. This reagent was shown by Raschig to react with further quantities of ammonia to produce hydrazine.⁴⁰ N–N bond formation in this way forms the basis of hydrazine manufacture.¹¹⁴



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.

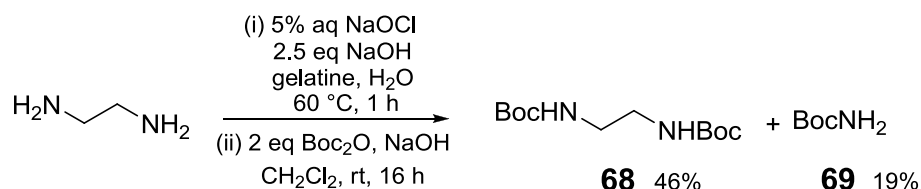
Chloramines are known to disproportionate, and poly-chlorinated organic amines, although normally stable substances, have been known to deflagrate or detonate on heating under ordinary pressure. For example, *tetrachloroethylenediamine* is a powerful explosive and its hazards have been well documented.^{116,117} 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**¹¹⁸ 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%).



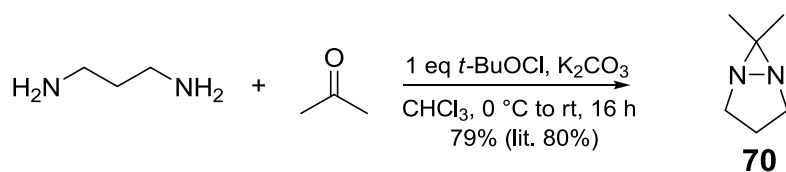
Scheme 2.20

After demonstrating the validity of this method to access 1,2-pyrazolidines, our attention turned to 1,2-diazetidines (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 hypochlorite¹¹⁹ in place of commercial bleach. In each case, no diazetidine was observed.



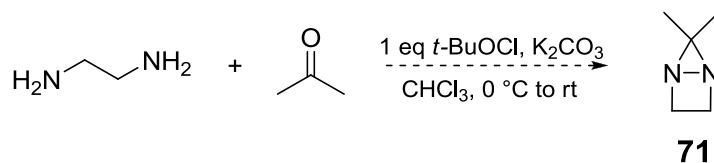
Scheme 2.21 Attempted cyclisation of 1,2-diaminoethane.

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



Scheme 2.22

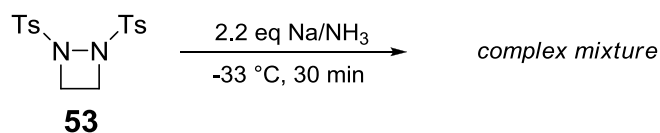
However, attempted formation of the analogous bicyclic diazetidine **71** using acetone in this way to encourage ring closure led only to a complex mixture of products with mass spectroscopy suggesting polymeric species (repeating unit $M_n = 14$).



Scheme 2.23

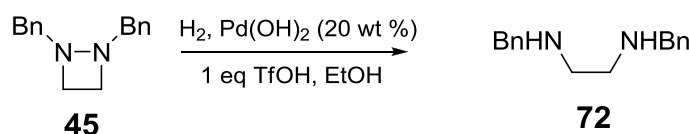
II.IV.II Via Deprotection of N,N' -Disubstituted-1,2-Diazetidines

Our attention turned to the double deprotection of N,N' -disubstituted 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_2O , 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.



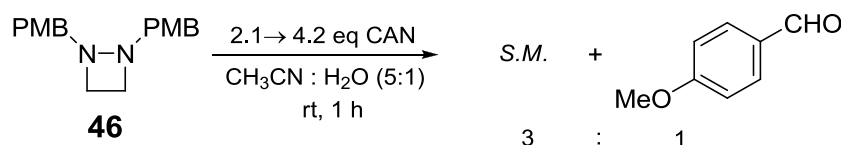
Scheme 2.24

As an alternative route, we considered deprotection of diazetidines bearing benzylic groups. *bis*-Benzyl diazetidine **45** was found to be stable under standard hydrogenation conditions [H_2 (1 atm), Pd/C, MeOH]. No reaction occurred when $\text{Pd}(\text{OH})_2/\text{C}$ 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 ^1H NMR and mass spectroscopy [$m/z = 241 (\text{MH}^+)$] (Scheme 2.25).



Scheme 2.25

We next considered methods for oxidative cleavage of protecting groups from diazetidines **46** and **47**. Cerium(IV) ammonium nitrate (CAN)¹²² is a single electron oxidant commonly used for debenzylation of amines.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 , *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 ^1H NMR spectroscopy (Scheme 2.26). The presence of *p*-methoxybenzaldehyde was confirmed by derivatisation with 2,4-dinitrophenylhydrazine.¹²⁴



Scheme 2.26

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

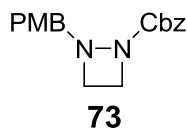
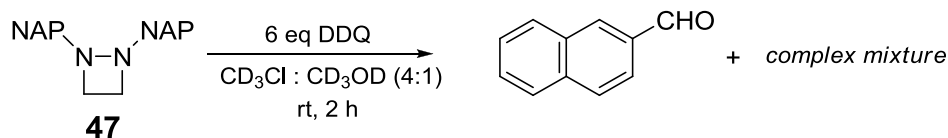


Figure 2.12

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.

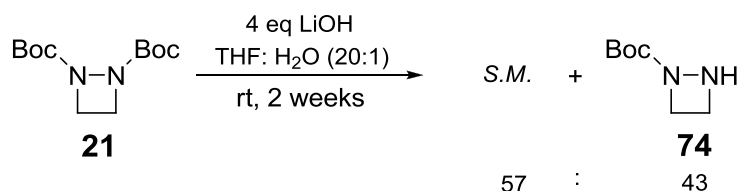
The strong oxidizing power of CAN [$\text{Ce}^{4+} \rightarrow \text{Ce}^{3+}$, $E^\circ = -1.42\text{ V}$; *cf.* $\frac{1}{2} \text{Cl}_2 \rightarrow \text{Cl}^-$, $E^\circ = -1.36\text{ V}$ (standard hydrogen electrode)]¹²⁵ led us to investigate milder methods for this transformation. The 2-naphthylmethyl 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 ^1H NMR) with this oxidant, significant amounts of 2-naphthaldehyde were formed, along with ring opened products as suggested by ^1H NMR spectroscopy. Methoxybenzyl diazetidine **46** reacted more slowly with DDQ but with equally poor selectivity.



Scheme 2.27

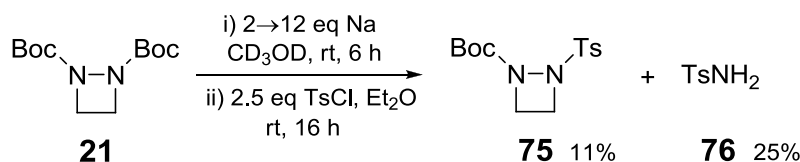
Later studies on the functionalisation of *bis*-Boc diazetidine **21** revealed that the Boc group carbonyls were susceptible to nucleophilic attack (Chapter III.II.I). Treatment of

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 ^1H NMR). Pieces of sodium were added until the starting diazetidine was completely consumed, then excess *p*-toluenesulphonyl chloride was added.



Scheme 2.29

^1H NMR spectroscopy of the crude reaction mixture indicated the presence of unsymmetrical diazetidine **75** alongside tosylamine¹²⁸ 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**.

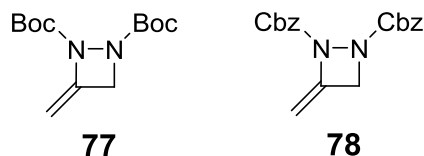
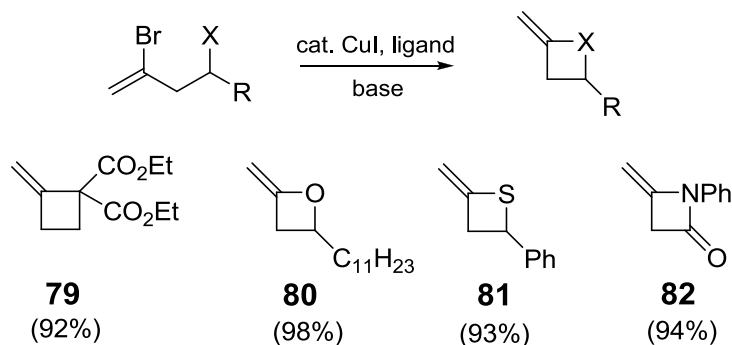


Figure 2.13

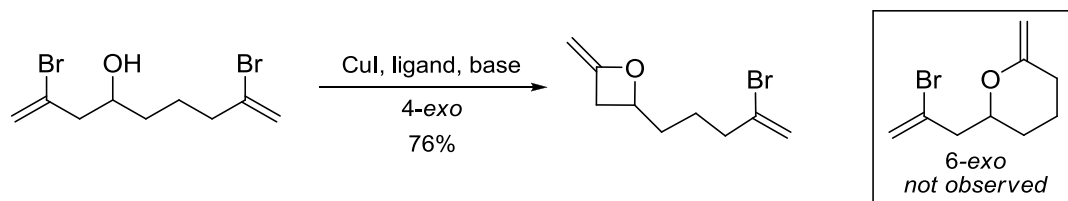
This new class of 1,2-diazetidine bearing an exocyclic double bond may offer greater potential for functionalisation and elaboration of the diazetidine ring system *via* cross-coupling, cycloaddition, or simple addition reactions of the double bond to provide highly functionalised nitrogen containing 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.³⁹ 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.^{129,130,131,132}



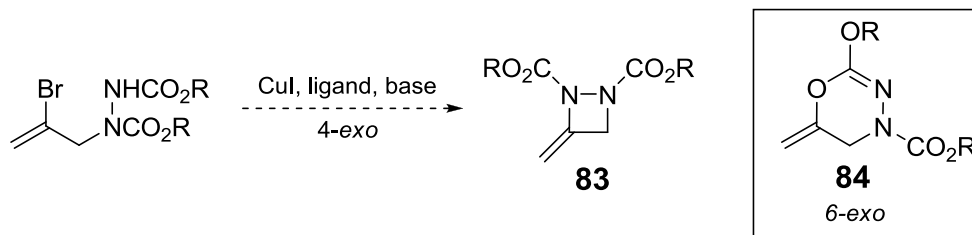
Scheme 2.30

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-*exo* product was observed over 5-*exo*, 6-*exo*, 6-*endo* cyclisation products.¹³⁰



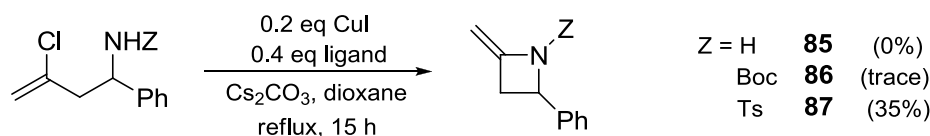
Scheme 2.31

Based upon these observations, we wished to establish if a similar copper-catalysed method could be developed for cyclisations to 3-alkylidene-1,2-diazetidines **83**, avoiding or minimising competitive formation of the 6-*exo* product **84** (Scheme 2.32).



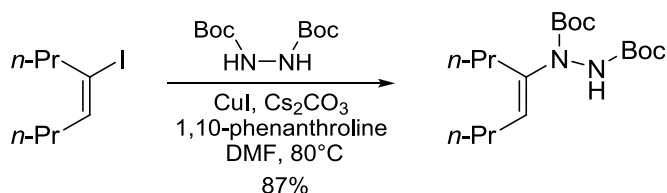
Scheme 2.32

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.¹³³



Scheme 2.33 Ligand: $\text{Me}_2\text{NCH}_2\text{CO}_2\text{H}\cdot\text{HCl}$.

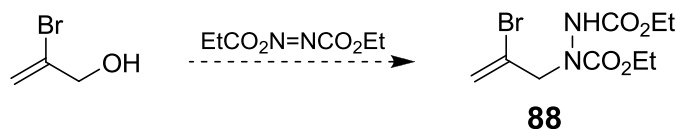
However, there are reports of *intermolecular* copper catalysed vinylations onto *bis*-Boc-protected hydrazine under similar copper-catalysed conditions (for example, Scheme 2.34).^{134,135}



Scheme 2.34

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

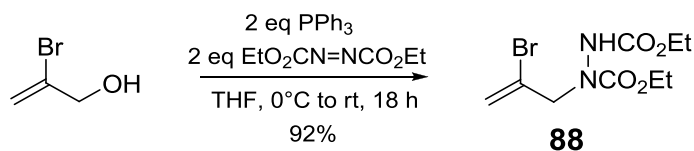
attractive route to these molecules involving the direct coupling of commercially available 2-bromoallyl alcohol with diethyl azodicarboxylate (DEAD).



Scheme 2.35

Reductive couplings of azodicarboxylates with aryl boronic acids¹³⁶ and silyl enol ethers¹³⁷ 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

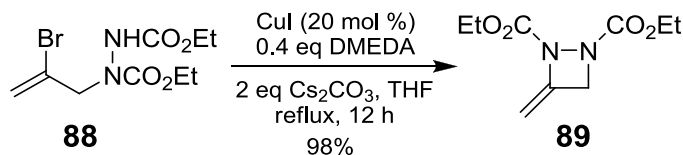
We proposed that in the absence of an external nucleophile, treatment of these alcohols with triphenylphosphine and an excess of azodicarboxylate would yield the hydrazine adduct. Under our first attempted conditions, the hydrazodicarboxylate derivative **88** of 2-bromoallyl alcohol was accessed in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



Scheme 2.36

We next focused on determining suitable ring closure conditions. Conditions that closely parallel those developed by Li for ring closures to β -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'*-dimethylethylenediamine (DMEDA) and caesium

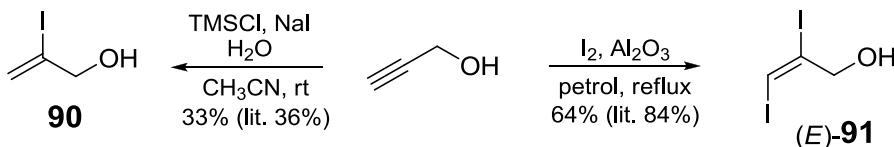
carbonate promoted ring closure to 3-methylene-1,2-diazetidine **89** as the only observable product in excellent yield.



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.

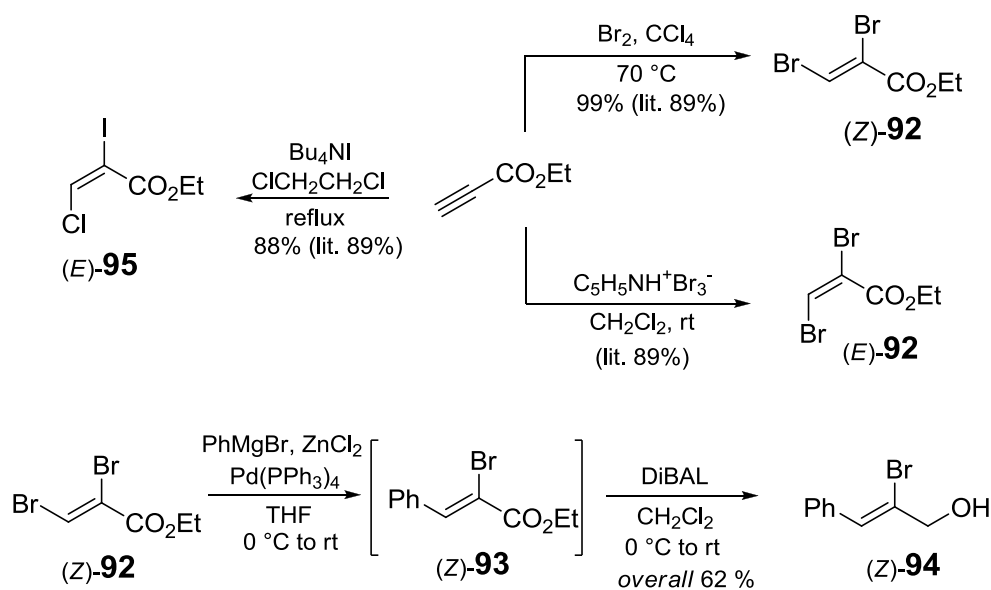
Encouraged by this result, we sought to establish the generality of this new method. A range of suitable alcohols were prepared from commercially available starting materials. As an alternative to the expensive 2-bromoallyl alcohol, **90** was prepared in one step from propargyl alcohol using a mixture 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 Larson¹⁴³ in moderate yield.



Scheme 2.38

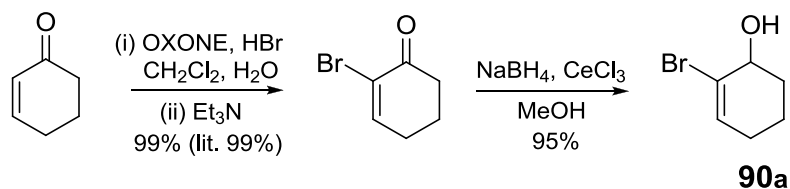
In addition, dibromides (*Z*)-**92** and (*E*)-**92** are readily accessible *via* selective bromination of ethyl propiolate¹⁴⁴ (Scheme 2.39), and have been shown by Rossi *et al.* to undergo efficient Negishi couplings of the terminal bromide,¹⁴⁵ presenting opportunity

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**.^{145,146} 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.¹⁴⁷



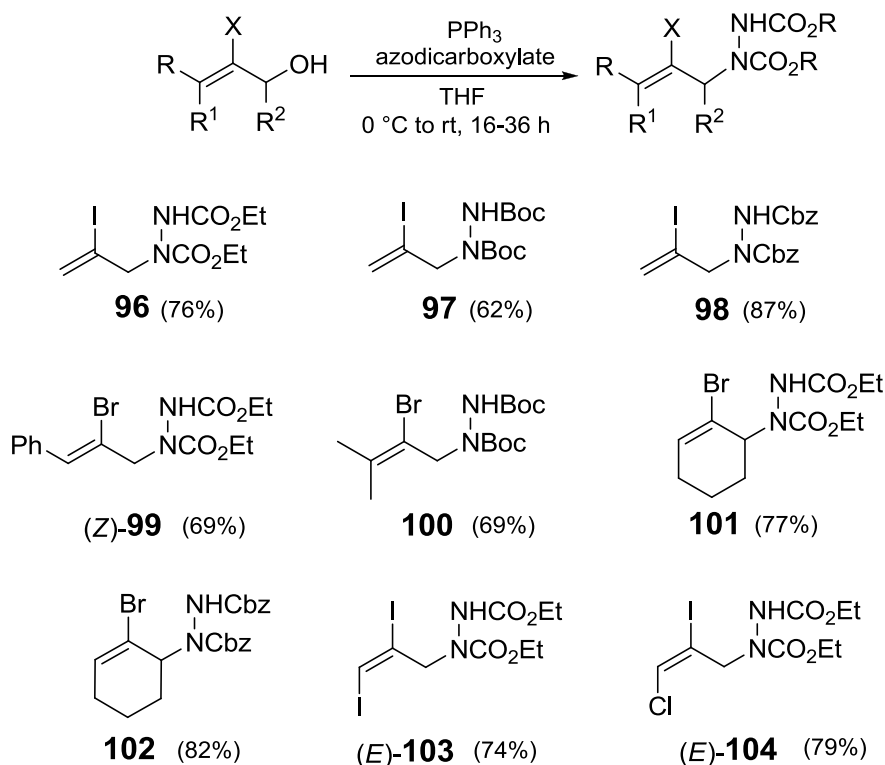
Scheme 2.39

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/HBr¹⁴⁸ and subsequent Luche reduction.¹⁴⁹ This alcohol would test the ability of the cyclisation chemistry to produce highly strained, bicyclic 1,2-diazetidene systems.



Scheme 2.40

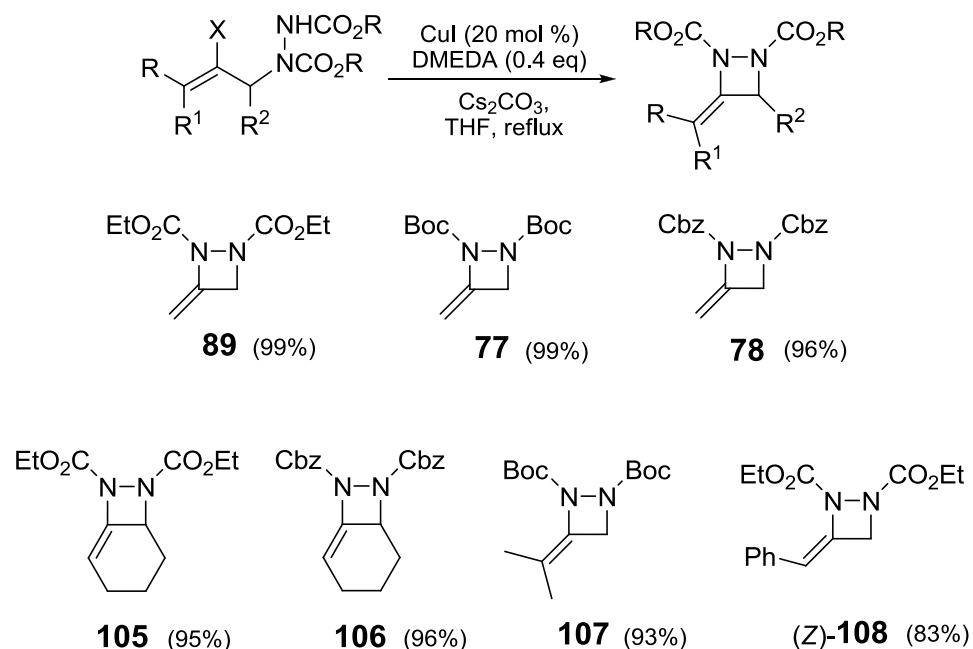
Reductive coupling of these alcohols with a range of commercially available azodicarboxylates proceeded in good to excellent yields (Scheme 2.41). DEAD, di-*tert*-butyl azodicarboxylate and dibenzyl azodicarboxylate all performed well. Phenyl substituted (*Z*)-**94** coupled with DEAD with retention 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.



Scheme 2.41

Ring closures of **96-102** gave the 1,2-diazetidines 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

Substitution of the alkene double bond was possible as established by the ring closure of *gem*-dimethyl substituted **100** to 3-isopropylidene-1,2-diazetidene **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 sp^2 -hybridised carbon, as evidenced by nOe measurements.

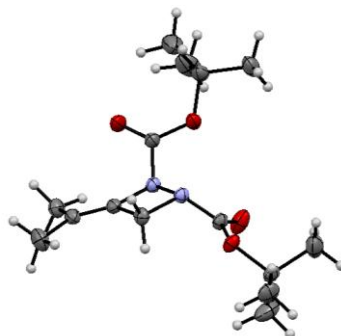
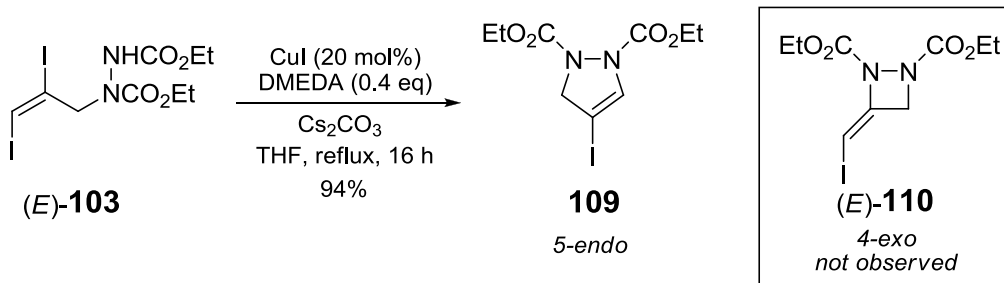


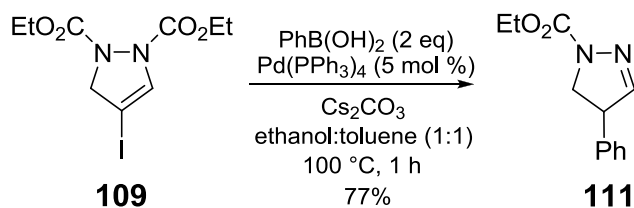
Figure 2.14 Single crystal X-ray structure of **107**.

In each of the cyclisations reported above, and to the best of our knowledge in all literature examples of such copper-catalysed ring closures,^{129,131,130,133,132} the reaction proceeds to give *exclusively* the 4-*exo* 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 ¹H NMR.



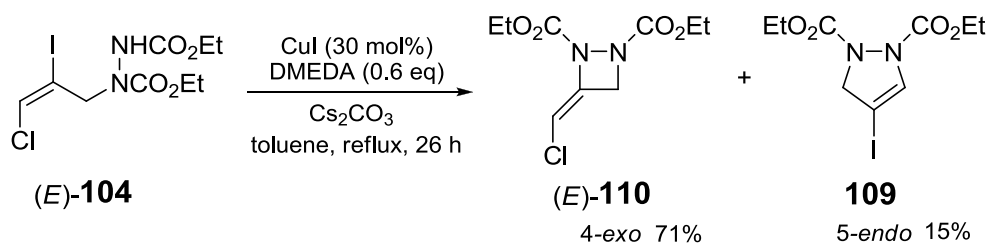
Scheme 2.43

HMBC and HMQC NMR correlation experiments confirmed the expected connectivity through the ring carbons at 60.2 (CH₂), 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).



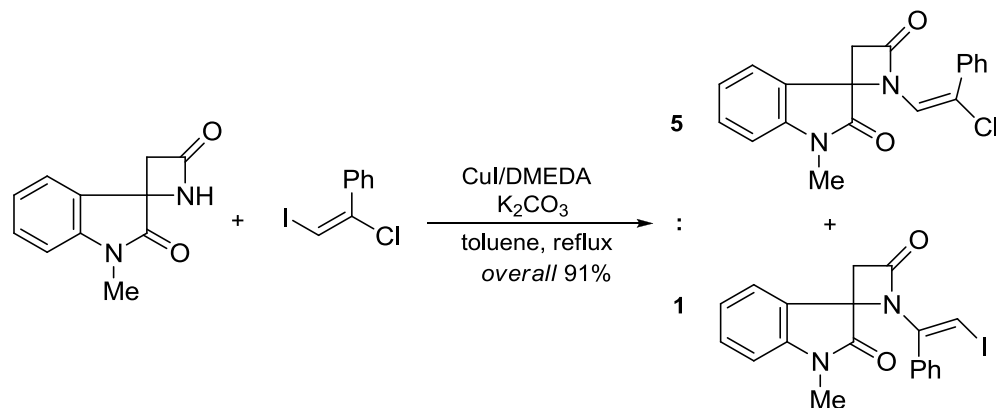
Scheme 2.44

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.



Scheme 2.45

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.¹⁵⁰



Scheme 2.46

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.

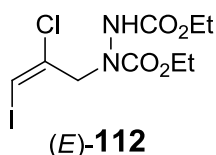


Figure 2.14

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*.¹³⁰

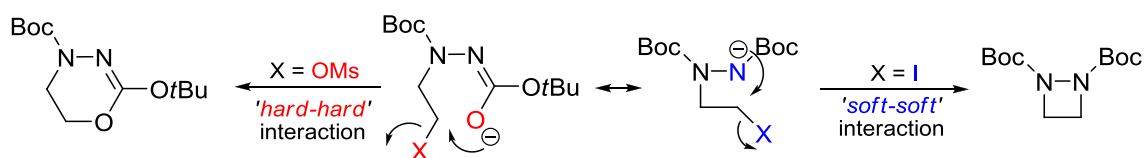
In each of the examples presented above, ring closure through nitrogen was clearly preferred over closure through the carbamate oxygen. There are several examples in the literature where reaction at nitrogen is preferred over reaction at oxygen in

intermolecular vinylations by similar copper-catalysed systems.^{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 *softer* lewis acid under the *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.^{155,156,157} It is likely therefore, considering the collected evidence that copper may display a *fundamental* preference for reaction at nitrogen rather than a *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-dicarboxyalkyl-1,2-diazetidines. This work was published in *Tetrahedron Letters* in 2010.¹⁵⁸

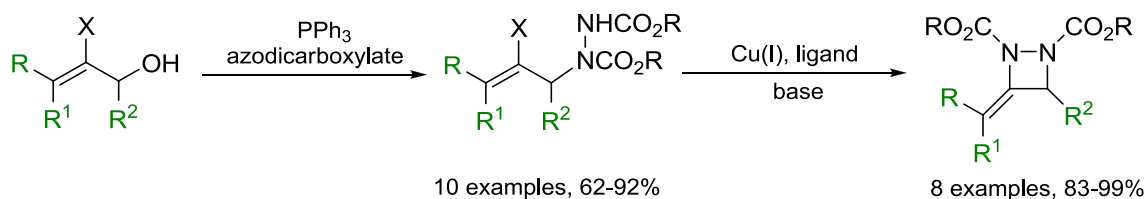


Scheme 2.47

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.



Scheme 2.48

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.

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 diazetine **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-diazetine 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

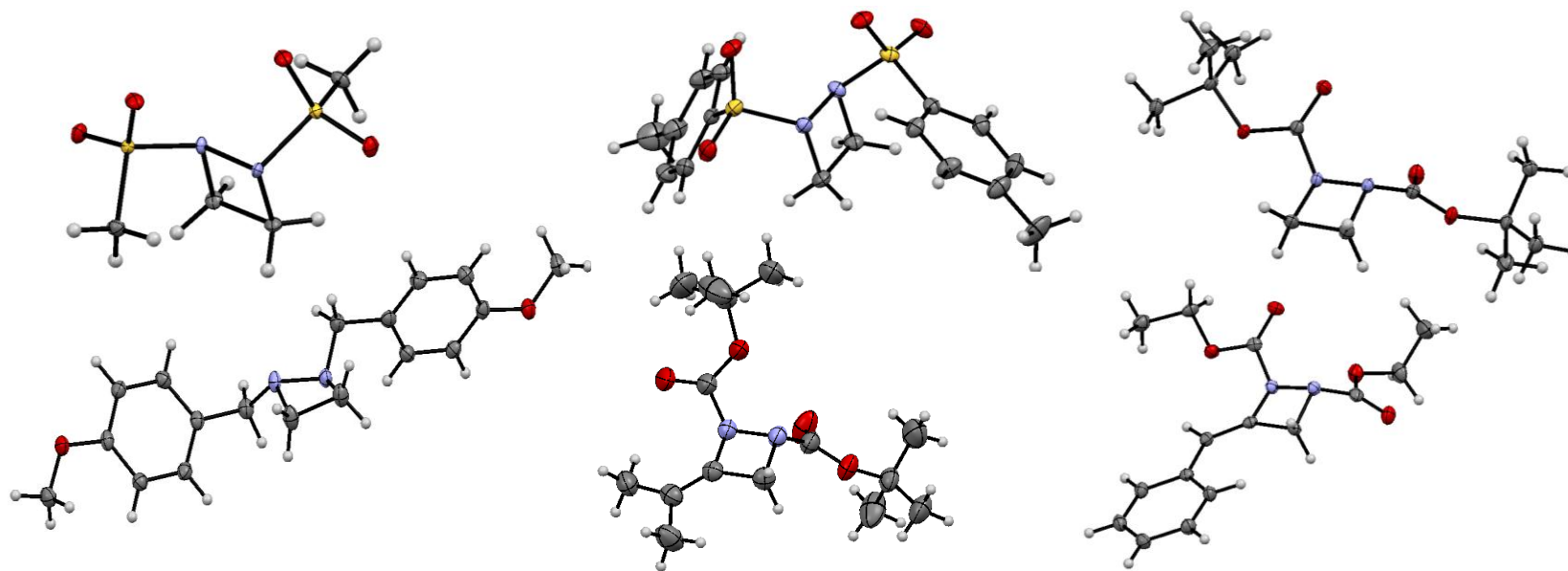
The synthesised 1,2-diazetidines were found to be stable, highly crystalline solids. For example, 1,2-*bis*(tosyl) diazetidine **53** was stable up to 200 °C as evidenced by thermogravimetric analysis (Appendix II). Collected physical and X-ray crystallographic data for six representative types of 1,2-diazetidine 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 *N*-substituents.

The N–N bonds of diazetidines **53** and (*E*)-**131** were found to be 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-*bis*(tosyl)hydrazine (1.413 Å).¹⁵⁹ Also, a significantly longer bond is observed in (*E*)-**131** (1.4521 Å) *cf.* 1,2-diethylhydrazine-1,2-dicarboxylate (1.379 Å).¹⁶⁰

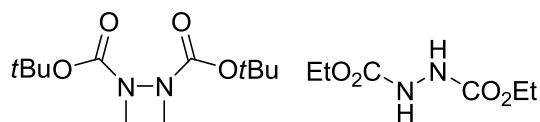
The extent of pyramidalisation at nitrogen in *N*-carboxyalkyl diazetidines can be determined by quantifying the deviation of the amide unit from planarity. Amide twist angles (τ) for **21**, **107** and (*E*)-**131** as defined by Winkler and Dunitz,¹⁶¹ and modified by Yamada,¹⁶² are shown in Table 3.1. A slight flattening of the nitrogen *syn*- to the exocyclic double bond is clearly observed in (*E*)-**131**. This may be due to a stabilising effect brought about by (*p-p*) π conjugation with the exocyclic benzyldiene 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 *syn*- to the exocyclic double bond is observed, suggesting a poorer stabilising contribution from the exocyclic isopropylidene unit.

	55	53	21	46	107	(E)-131
M.p./°C	229-232	199.5-200.5	93.5-94	84-86	79-80	88-89.5
N-N length/Å	1.485(2)	1.475(3)	1.4505(2)	1.5028(2)	1.4620(16)	1.4521(13)
ring C-C length/Å	1.538(3)	1.532(4)	1.536(2)	1.527(2)	1.509(2)	1.5104(16)
Substituent torsion (X-N-N'-X')/°	118	124	102	108	110	93.9
Amide twist (τ)/°	-	-	33.4	-	36.4 (<i>syn</i>), 35.1	27.1 (<i>syn</i>), 35.5
Ring torsion (C-N-N'-C')/°	1.57	2.40	4.67	20.27	1.42	5.71

Table 3.1 & Figure 3.1 Selected physical data and X-ray structures of 1,2-diazetidines. Ellipsoids drawn at 50% probability.



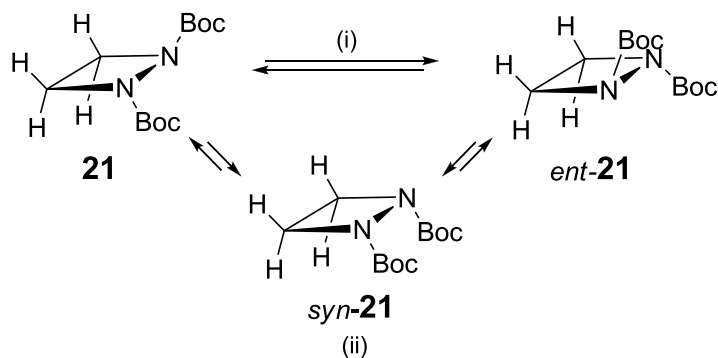
It is also useful to compare selected data from **21** against that of the acyclic analogue such as 1,2-diethylhydrazine-1,2-dicarboxylate (**113**) (Table 3.2).^{160,163} The nitrogen atoms within **21** are more highly pyramidal, displaying significant amide twist angles (τ). The infrared carbonyl 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.



	21	113
(N-N')/Å	1.4505	1.379
(N-C _(C=O))/Å	1.3915	1.352
(C _(C=O) -N-N'-C _{(C=O)'})/°	101.51	83.92
τ /°	33.4	4.3
IR (C=O)/cm ⁻¹	1739	1712
NMR (C=O)/ppm ^a	160.2	158.7

Table 3.2 ^a In CDCl₃.

The ¹H 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;⁴⁸ 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.



Scheme 3.1

No changes were observed in the ^1H 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 $\text{C}=\text{O}$) or $(p-d)_\pi$ conjugation (with the sulphur atom)¹⁶⁴ are known to stabilise the transition state and reduce the barrier to inversion.¹⁶⁵

bis-Methoxybenzyl diazetidine **46** exhibits a more interesting ring structure. The ring is significantly puckered [ring torsion ($\text{C}-\text{N}-\text{N}'-\text{C}'$) = 20.27°]. The ambient temperature ^1H 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°C (in CDCl_3). Signals for the benzylic hydrogens coalesce on cooling to -50°C .

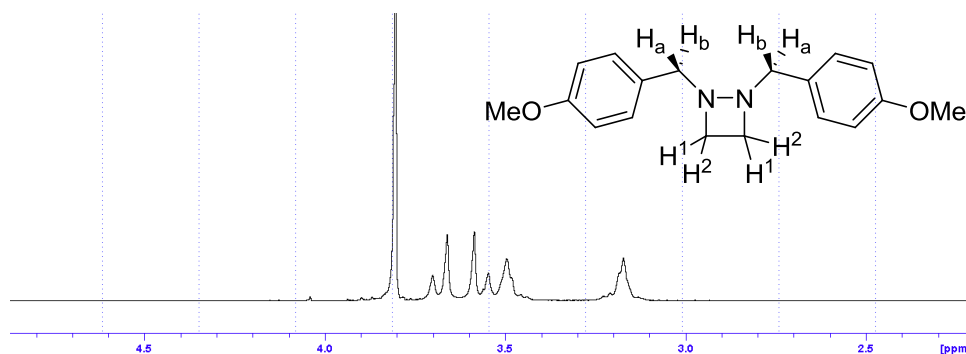
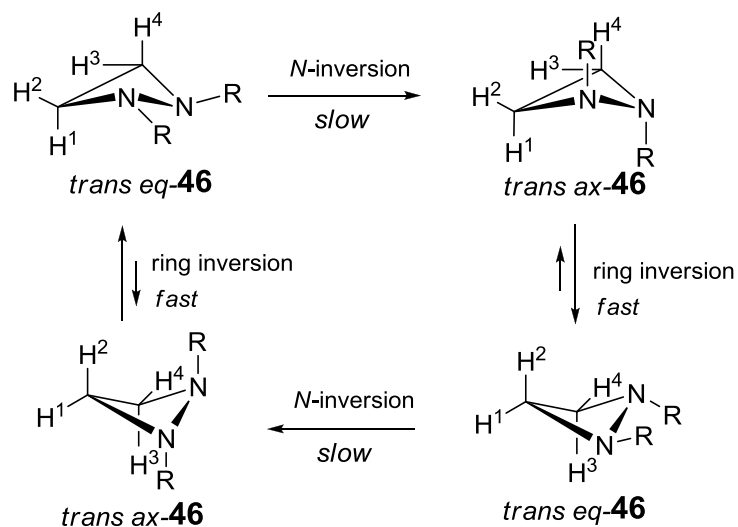


Figure 3.2 ^1H NMR (298 K) of **46** of the region 4.50–2.50 ppm.

Assuming that motion of the ring is un-coupled with the observed behaviour of the benzylic groups, an energy barrier of $\Delta G_c^\ddagger = 67.5 \text{ kJ mol}^{-1}$ may be calculated from the coalescence of the ring hydrogen signals ($T_c = 73 \text{ }^\circ\text{C}$ in d_6 -DMSO, 600 MHz).ⁱ 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 ($\Delta G_c^\ddagger = 68.6 \text{ kJ mol}^{-1}$).³⁶ 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 $\Delta G_c^\ddagger = 65.9 \text{ kJ mol}^{-1}$ ($T_c = 60 \text{ }^\circ\text{C}$, 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).



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

ⁱ 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 $k = \pi\Delta\nu/\sqrt{2}$ where $\Delta\nu$ is the signal separation at slow exchange. The uncertainty presented in the measurement of $\Delta\nu$ gives rise to an uncertainty in ΔG_c^\ddagger of $\pm 2.3 \text{ kJ mol}^{-1}$.

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).

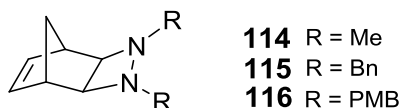


Figure 3.3

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

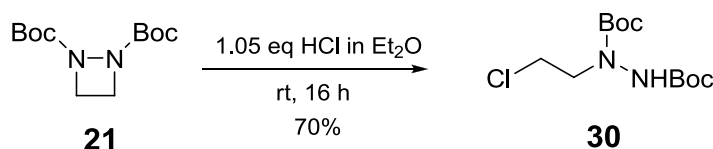
The significant ring distortion and long N–N bond observed in **46** suggest the difficulty the ring has in accommodating the opposing nitrogen lone pairs. As a result, these lone pairs are likely to exhibit enhanced basic character. In addition, the nature of the bonding observed in *bis*-Boc diazetidine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

III.II Functionalisation 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.³⁶ These species were found to be remarkably inert. 1,2-Diethyl-1,2-diazetidine was found to be unreactive toward 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

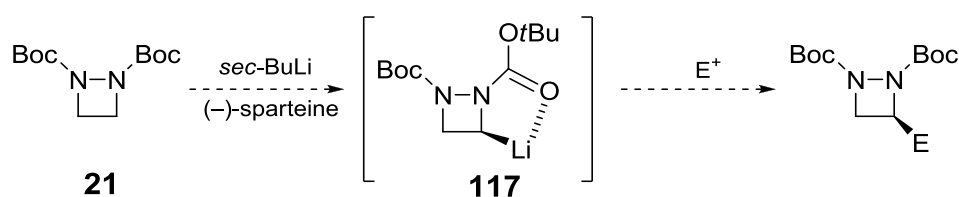
However, **21** showed no reactivity toward the potent electrophile ethyl triflate at room temperature in either acetonitrile or DMF, suggesting that the nitrogen lone pairs are partially deactivated by the Boc groups.

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 pyrrolidine⁶⁵ and *N*-(triphenylacetyl)azetidine⁷⁰ 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 Me_3Si^+).



Scheme 3.4

Diazetidine **21** was found to be inert to treatment with LDA or LiHMDS in the presence of Me_3SiCl as an *in situ* quench. Conditions that in our hands promoted deuteration of pyrrolidine **118** [83% yield, 92 (± 2)% D] (Figure 3.4),⁶⁵ and complete deuteration of **119** (86% yield)⁶⁹ 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)⁷⁰ 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 ¹H NMR) along with several decomposition products in small amounts.

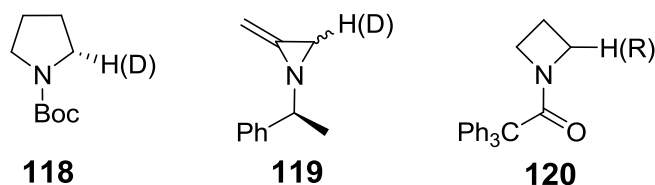
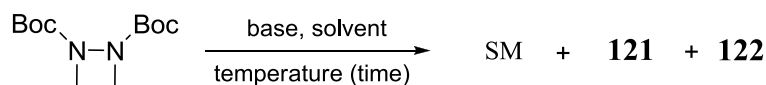


Figure 3.4

LCMS (UV/TIC) analysis of the crude material showed a similar product distribution in each case. By correlation of these results with ¹H 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 ¹H 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).



entry		base	solvent, ligand ^a	temperature (time)	SM : 121 : 122 ^e
1	1.3 eq	<i>sec</i> -BuLi	Et ₂ O, (–)-sparteine ^b	–78 °C (2 h)	78 : 19 : 3
2	1.9 eq	<i>sec</i> -BuLi	THF	–78 °C (6 h)	84 : 7 : 9
3	1.2 eq	<i>tert</i> -BuLi	THF	–78 °C → –40 °C (2 h) → –15 °C (10 min)	84 : 10 : 6
4	1.0 eq	<i>sec</i> -BuLi	THF	–78 °C (3 h)	84 : 16 : 0
5	1.5 eq	<i>sec</i> -BuLi	THF	–78 → –40 °C (2 h)	62 : 34 : 4
6	3.1 eq	<i>sec</i> -BuLi	THF	–78 °C (3 h)	30 : 67 : 3
7	4.0 eq	<i>sec</i> -BuLi	THF	–78 °C (3 h)	14 : 81 : 5
8	1.2 eq	<i>sec</i> -BuLi	THF, TMEDA ^c	–78 °C (1 h)	9 : 88 : 3
9	1.2 eq	<i>sec</i> -BuLi	THF, HMPA ^d	–78 °C (3 h)	83 : 10 : 6
10	1.2 eq	<i>sec</i> -BuLi	THF, HMPA ^d	–78 → –40 °C (3 h)	67 : 14 : 19

Table 3.3 ^a Ligand was added to the reaction prior to addition of the butyllithium. ^b 1.3 eq (–)-sparteine. ^c 1.3 eq. ^d 2.0 eq. ^e Determined by ¹H 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 ¹H NMR spectrum displayed a triplet at 4.32 ppm (*J* = 8.0 Hz), and a broad singlet at 3.76 ppm for the ring hydrogens. HRMS and ¹H 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, ¹H 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.

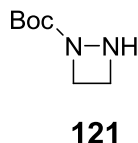


Figure 3.5

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.^{168,169} 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, ¹H, ¹³C and ¹⁵N NMR spectroscopy (Figure 3.6). Two slightly inequivalent resonances for the ring methylene units were observed in the ¹H NMR [4.30 (4H, t, *J* = 2.1 Hz), 4.23 (4H, t, *J* = 2.1 Hz)] and ¹³C NMR spectra [50.6 (2CH₂) and 50.1 (2CH₂)]. In addition, the presence of a quaternary ¹³C 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 ¹⁵H HMBC spectrum (Appendix III) were entirely consistent with this structure, which may result from attack of lithiated **121** on *bis*-Boc diazetidine **21**.

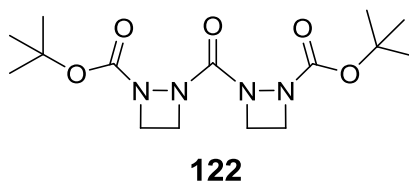


Figure 3.6

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).^{65,100,70} 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.

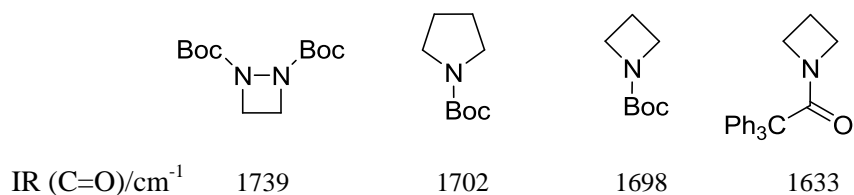
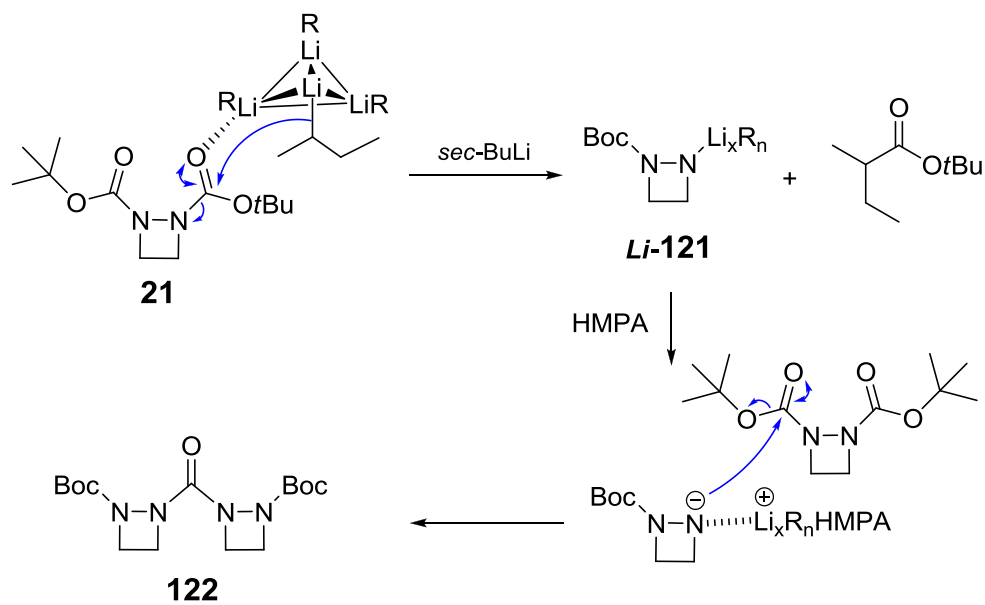


Figure 3.7

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.¹⁷⁰ The carbonyl of the Boc group is likely to coordinate to such a lithium species in solution,¹⁷¹ 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**.



Scheme 3.5

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 $-78\text{ }^{\circ}\text{C}$ (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 $-78\text{ }^{\circ}\text{C}$. Treatment with *sec*-butyllithium returned only starting diazetidine. Performing the reaction in $\text{Et}_2\text{O}:\text{DMPU}$ (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}

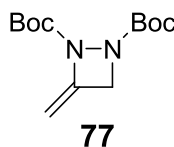
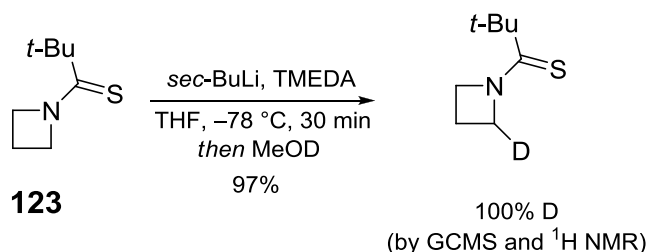


Figure 3.8

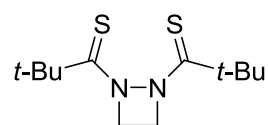
Sec-BuLi, *sec*-BuLi/TMEDA, and *tert*-BuLi were tested for the lithiation of **77** under the conditions described in entries 3, 5 and 8 of Table 3.3. In the crude reaction material, no deuterated diazetidine was observed. A complex mixture of **77** and multiple decomposition products were seen in 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*.¹⁷³ Under conditions of *sec*-butyllithium, TMEDA in THF at $-78\text{ }^{\circ}\text{C}$ they demonstrated complete deuteration after 30 minutes and were able to obtain modest levels of enantioselectivity with (–)-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.

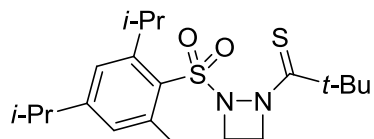


Scheme 3.6

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.



124

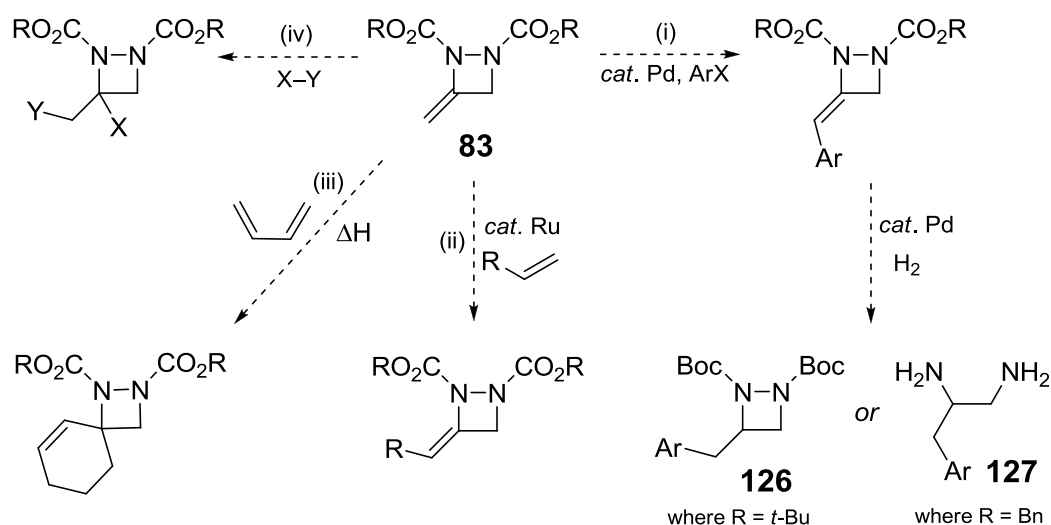


125

Figure 3.9

III.III Functionalisation of 3-Alkylidene-1,2-Diazetidines

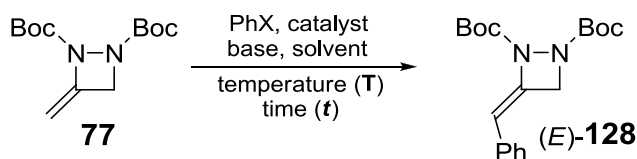
Although our attempts at lithiation of simple 1,2-diazetidines met with no success, we expected that the exocyclic double bond of 3-methylene-1,2-diazetidines could be used to functionalise these readily available 1,2-diazetidines into a range of nitrogen containing molecules (Scheme 3.7). For example, (i) palladium-catalysed Heck couplings with aryl or alkenyl halides;^{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 **126**, or further reduction to vicinal diamines (**127**).



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 substates 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.¹⁷⁶ However, under these conditions, no reaction occurred (entry 2). Replacing the base with dicyclohexylmethylamine¹⁷⁷ 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.



entry	PhX ^a	base ^b	catalyst ^c	solvent ^f	T, t	outcome
1	PhI	Cs ₂ CO ₃	Pd(OAc) ₂ , PPh ₃ ^d	CH ₃ CN	reflux, 16 h	no reaction
2	PhI	Cs ₂ CO ₃	Pd(OAc) ₂ , Bu ₄ NCl ^e	DMAc	100 °C, 16 h	no reaction
3	PhI	Cy ₂ NMe	Pd(OAc) ₂ , Bu ₄ NCl ^e	DMAc	100 °C, 16 h	trace 128
4	PhI	Cy ₂ NMe	Pd(OAc) ₂ , Bu ₄ NCl ^e	DMAc	80 °C, 48 h	23% 128 ^{g,h}
6	PhBr	Cy ₂ NMe	Pd ₂ (dba) ₃ , P(<i>t</i> -Bu) ^d	dioxane	80 °C, 16 h	no reaction
7	PhBr	Cy ₂ NMe	Pd ₂ (dba) ₃ , [P(<i>t</i> -Bu) ₃ H]BF ₄ ^d	dioxane	80 °C, 16 h	trace 128

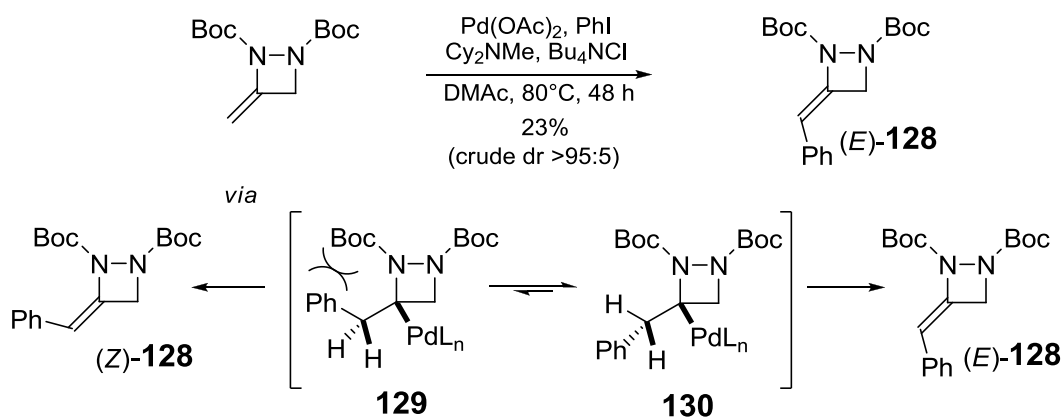
Table 3.4 ^a1.5 eq PhX. ^b1.5 eq base. ^c5 mol % Pd. ^d15 mol % PR₃. ^e1 eq Bu₄NCl. ^fsolvent 0.18-0.20 M.

^gIsolated yield after column chromatography; ^h25% starting material was recovered.

The electron rich and bulky phosphane P(*t*-Bu)₃ has been shown to form extremely active palladium catalyst systems.^{178,179,180,181} However, for the formation of **128**, use of this phosphane directly or from its more stable tetrafluoroborate salt,¹⁸² 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),¹⁸³ cleaner transformations to product were observed, but in each case the mass balance of the crude product mixture was poor.

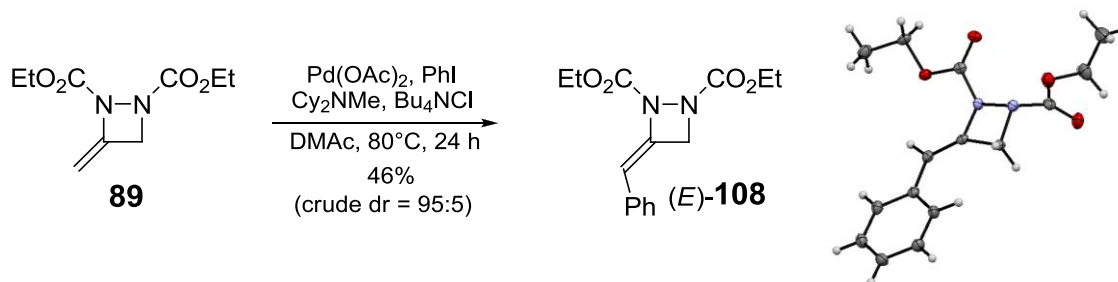
The stereochemistry of (*E*)-**128** was confirmed by nOe measurements. The high degree of diastereoselectivity (crude dr >95:5) observed in this transformation can be rationalized through consideration of the presumed organopalladium intermediate prior to *syn*-elimination of the β -hydride (Scheme 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 CO₂*t*-Bu groups are minimised.



Scheme 3.8

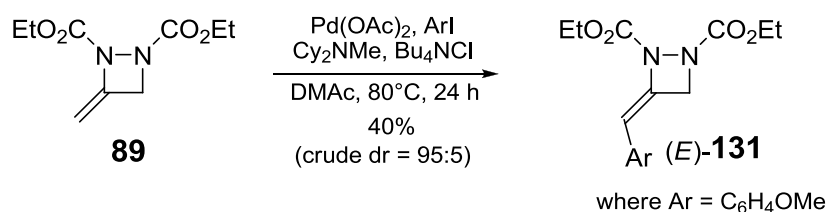
In order to improve the yield of this transformation, we investigated the coupling of the less sterically encumbered methylenediazetidene **89** bearing *N*-carboxyethyl substituents. When **89** was treated under our best conditions (Scheme 3.9), (*E*)-**108** was formed in much higher yield and in 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*

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**.

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.



Scheme 3.10

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 *via* the same methodology used to provide **89** (Chapter II.V).

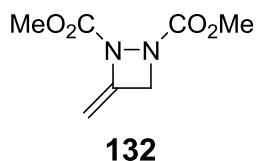


Figure 3.10

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-octene¹⁸⁴ with Grubbs first and second generation catalysts.^{185,186} Under conditions which promoted the metathesis of α -methylene- β -lactams¹⁸⁷ and 3-methyleneoxetan-2-ones¹⁸⁸ 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 ¹H 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.

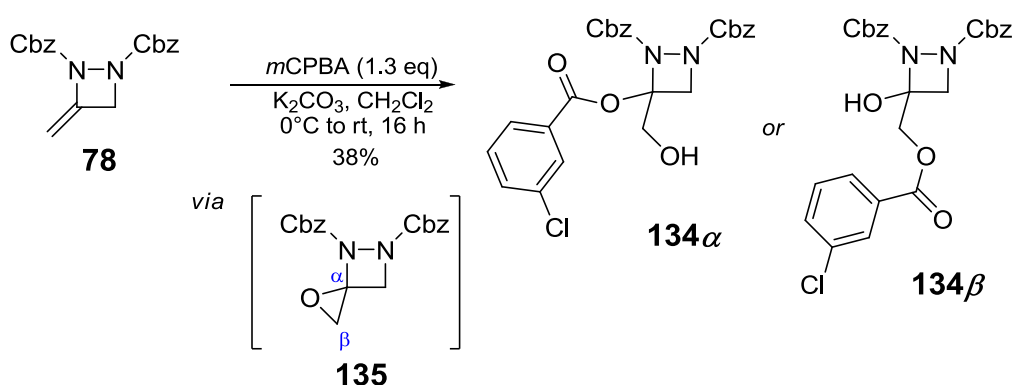


Scheme 3.11

Ready access to halogen substituted methylenediazetidine (*E*)-**110** invited attempts at functionalisation *via* Negishi and Suzuki¹⁸⁹ 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 $\text{P}(t\text{-Bu})_3$.^{181,180} Attempted reaction of (*E*)-**110** under these conditions failed presumably due in part to the strength of the C–Cl 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 *m*CPBA resulted in the formation of a single 1:1 adduct in moderate yield, presumably *via* epoxide **135**, followed by ring opening at the α - or β -carbon to give either **134 α** or **134 β** respectively.

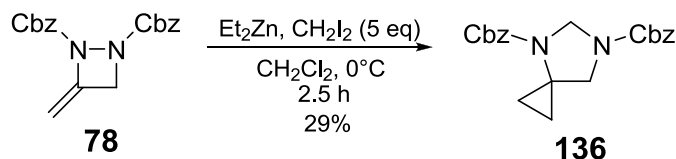


Scheme 3.13

1H 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 α** or **134 β** . A methylene resonance in the 1H 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 β** , resulting from ring opening at the least hindered carbon of the epoxide by *m*-chlorobenzoic acid, however, ring opening at the α -carbon might be expected on the basis of a stepwise mechanism. The use of a less nucleophilic and less acidic epoxidising agent such as dimethyldioxirane¹⁹⁰ (DMDO) may allow isolation of epoxide **135**.

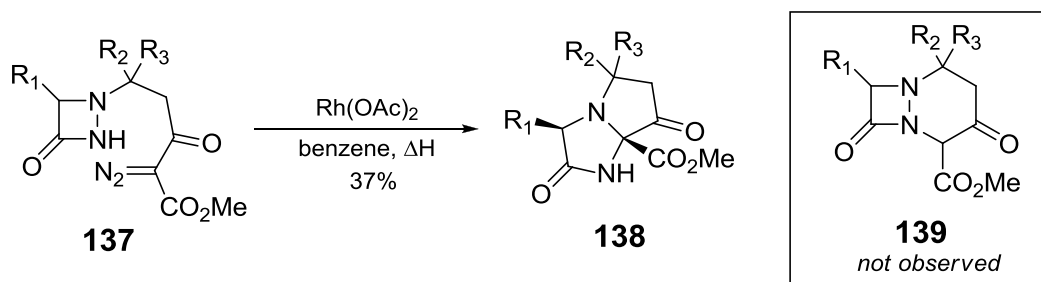
On attempting Simmons-Smith cyclopropanation¹⁹¹ of the double bond with 5 equivalents of Et_2Zn and CH_2I_2 , imidazolidine **136** was isolated in moderate yield, from ring expansion of the diazetidine by insertion into the N–N bond, and concomitant

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

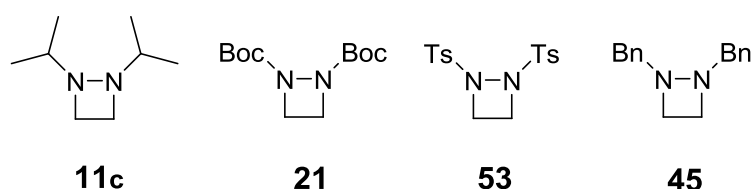
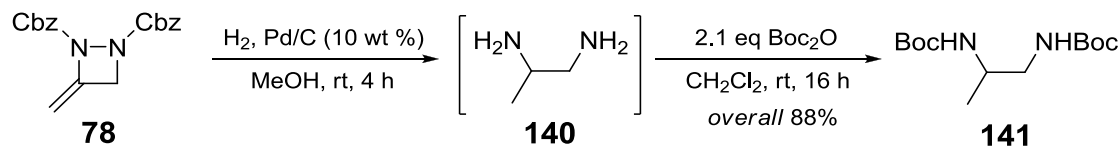


Figure 3.12 Simple 1,2-diazetidines studied under reducing conditions.

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).

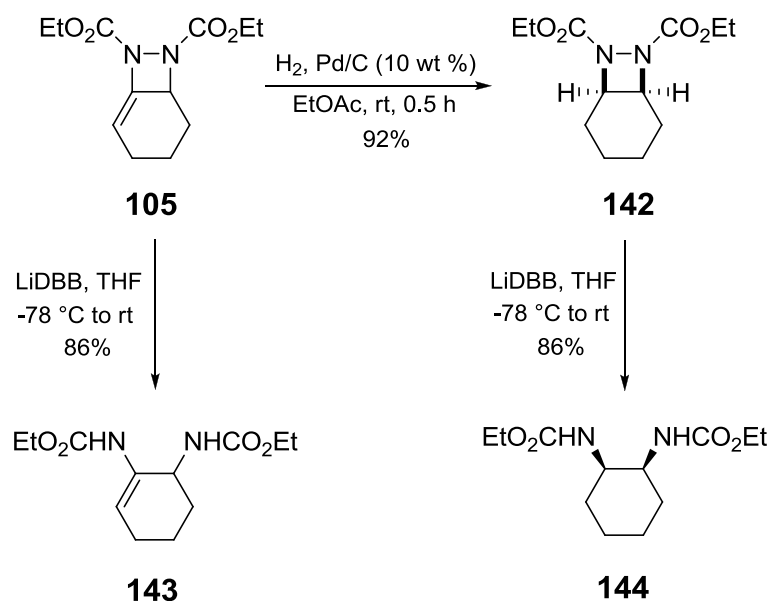
Our attention moved to *bis*-Cbz methylenediazetidine **78**. As expected, this was much more readily reduced by catalytic hydrogenation (Scheme 3.16). Exhaustive reduction occurred rapidly in methanol to the vicinal diamine **140** which was isolated by *bis*-Boc protection for comparison to the literature data for this known compound.¹⁹³



Scheme 3.16

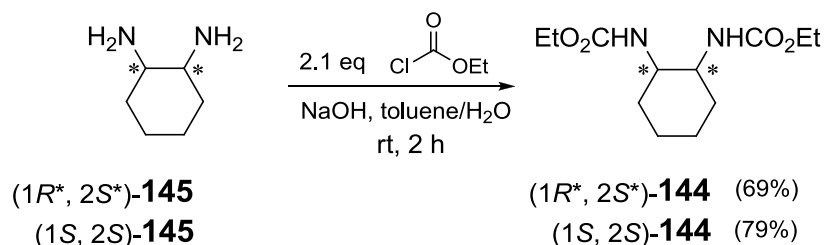
Comparing this result with our previous observations on *bis*-Boc diazetidine **21** suggests that deprotection of one or both Cbz groups occurs before reduction of the N–N bond. If the diazetidine ring remains intact before reduction of the exocyclic double bond, **78** could be good potential substrate 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_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 solvent¹⁹⁴ slowed this reduction, and after 30 minutes, we obtained *cis*-1,2-diazetidine **142** as the only observable product by ^1H and ^{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.



Scheme 3.17

Cleavage of the N–N bond of **105** was investigated using lithium di-*tert*-butylbiphenyl (LiDBB).¹⁹⁵ 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 (1*R**, 2*S**)-**144** (*cis*) and (1*S*, 2*S*)-**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.

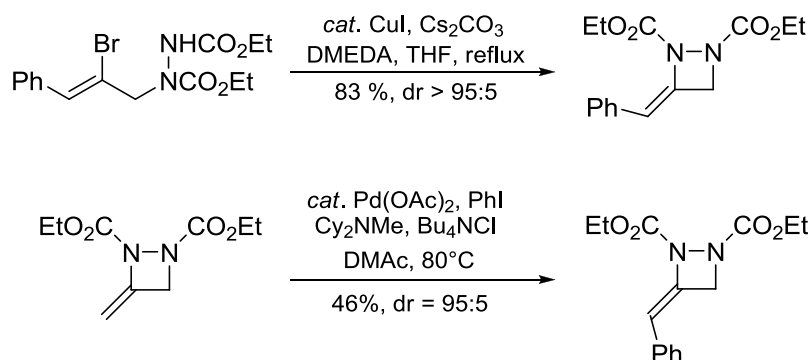
A diastereocontrolled reduction in this way highlights the potential for 1,2-diazetidines to act as precursors to vicinal diamines. Future work may explore the incorporation of the alkylidenediazetidine unit into the synthesis of larger organic molecules, where a late-stage cleavage of the N–N bond is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

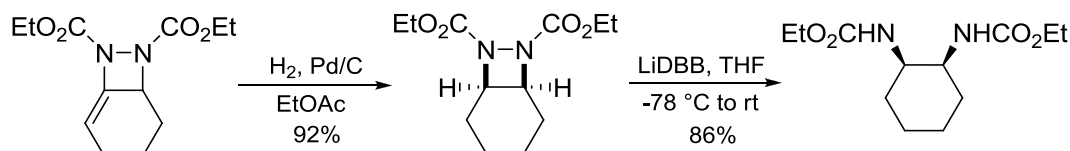
Functionalisation reactions of 3-alkylidene-1,2-diazetidines have been explored. 3-Methylene-1,2-diazetidines have been shown to undergo highly stereoselective palladium-catalysed Heck cross-coupling reactions. The origin of this selectivity has been rationalised in terms of steric interactions with 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

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 through 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 F₂₅₄), 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.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 cm² g⁻¹.

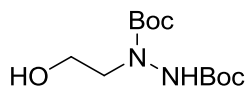
Nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX (300, 400, 500 or 600 MHz) spectrometers. NOe measurements were performed on a 600 MHz spectrometer. Chemical shifts are reported in parts per million relative to the standard tetramethylsilane for ¹H NMR and to the centre line of the chloroform triplet at 77.2 ppm for ¹³C 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 ^1H 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.

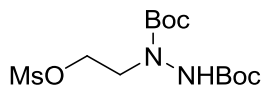
IV.II Synthesis of 1,2-Dicarboxyalkyl-1,2-Diazetidines

Di-*tert*-butyl 1-(2-hydroxyethyl)-hydrazine-1,2-dicarboxylate⁷³ (**22**)



To a solution of 2-hydroxyethylhydrazine (98% purity, 3.00 mL, 43.4 mmol) in CH₂Cl₂ (45 mL) at 0 °C was added dropwise a solution of di-*tert*-butyl dicarbonate (19.9 g, 91.1 mmol) in CH₂Cl₂ (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 MgSO₄, 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; ¹H NMR (400 MHz, CDCl₃) 6.42 (1H, m), 3.98 (1H, m), 3.70 (2H, br s), 3.57 (2H, br s), 1.49-1.47 (18H, m); ¹³C NMR (125 MHz, CDCl₃) 157.2 (C), 155.1 (C), 82.2 (C), 81.6 (C), 59.5 (CH₂), 54.0 and 52.7 (CH₂), 27.8 (6CH₃); MS (ES⁺) *m/z* = 299 ([M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₂H₂₄N₂O₅Na (M+Na)⁺: 299.1577; found: 299.1582.

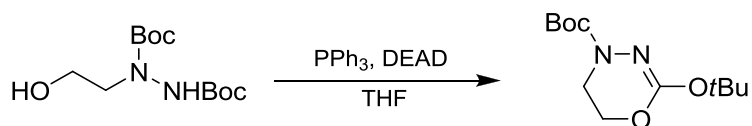
Di-*tert*-butyl 1-(2-(methylsulphonyloxy)ethyl)-hydrazine-1,2-dicarboxylate (**23**)



To a solution of MsCl (1.35 mL, 17.4 mmol) in CH₂Cl₂ (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 Et₃N (4.86 mL, 34.9 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (3 × 40 mL). The combined organic phases were washed with brine, dried over MgSO₄, 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; ¹H NMR (400 MHz, CDCl₃) 6.41 (1H, m), 4.39 (2H, br s), 3.81 (2H, br s), 3.04 (3H, s), 1.48 (18H, br s); ¹³C NMR (125 MHz, CDCl₃) 155.1 (2C), 81.8 (C), 81.5 (C), 66.6 and 66.0 (CH₂), 45.0 and 48.8 (CH₂), 37.7 (CH₃), 28.2 (6CH₃); MS (ES⁺) *m/z* = 377 ([M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₃H₃₀N₃O₇S (M+NH₄)⁺: 372.1799; found: 372.1796.

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

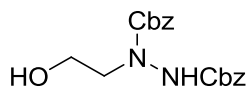


Diethyl azodicarboxylate (111 μL, 0.71 mmol) was added dropwise to a stirred solution of di-*tert*-butyl 1-(2-hydroxyethyl)-hydrazine-1,2-dicarboxylate (**22**) (150 mg, 0.54 mmol) and triphenylphosphine (186 mg, 0.71 mmol) in THF (5 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 48 h then concentrated *in vacuo*. ¹H 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; ¹H NMR (400 MHz, CDCl₃) 4.30 (2H, t, *J* = 4.8 Hz), 3.72 (2H, t, *J* = 4.8 Hz); 1.52-1.49 (18H, m); ¹³C NMRⁱ (75 MHz, CDCl₃) 146.6 (C), 82.4 (CH₂), 80.5 (CH₂), 65.0 (CH₂), 39.2 (CH₂), 28.4 (3CH₃), 28.0 (3CH₃); MS (ES⁺) *m/z* = 539 ([2M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₂H₂₂N₂O₄Na (M+Na)⁺: 281.1472; found:

ⁱ Quaternary carbon not observed.

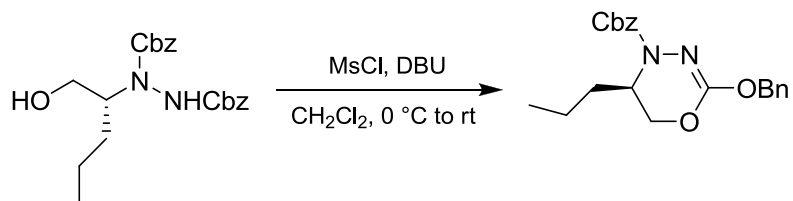
281.1476. Crystals suitable for X-ray diffraction were grown from CH₂Cl₂/hexane by solvent diffusion.

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



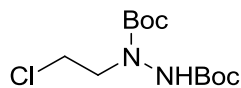
Benzyl chloroformate (2.01 mL, 14.0 mmol) was added dropwise to a rapidly stirred mixture of 2-hydroxyethylhydrazine (500 μ L, 6.6 mmol) and NaHCO₃ (2.25 g, 33.2 mmol) in diethyl ether (10 mL) and water (15 mL) at 0 °C. The heterogeneous mixture was allowed to warm to room temperature and stirred rapidly 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 \times 25 mL). The combined organic phases were washed with brine, dried over MgSO₄, 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; ¹H NMR (400 MHz, CDCl₃) 7.53-7.02 (11H, m), 5.14 (4H, br s), 3.84-3.44 (5H, m); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 68.3 (CH₂), 59.2 (CH₂), 53.6, 53.3 and 52.8 (CH₂); MS (ES⁺) *m/z* = 367 ([M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₈H₂₀N₂O₅Na (M+Na)⁺: 367.1264; found: 367.1278.

Benzyl 2-(benzyloxy)-5-propyl-5,6-dihydro-4H-1,3,4-oxadiazine-4-carboxylate {(R)-28b}



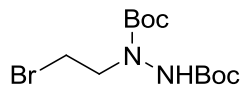
To (R)-dibenzyl 1-(1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate³⁷ (1.00 g, 2.59 mmol) in CH₂Cl₂ (25 mL) was added DBU (3.10 mL, 20.73 mmol). This solution was cooled to 0 °C then MsCl (301 μ L, 3.89 mmol) was added dropwise. After the addition, the mixture was allowed to warm to room temperature 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 CH₂Cl₂ (3 \times 25 mL). The combined organic phases were washed with saturated aqueous NaHCO₃ (20 mL), brine (30 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Column chromatography [petroleum ether:ethyl acetate, 6:1 with 1% Et₃N (v/v)] gave (R)-**28b** (342 mg, 36%) as a colourless crystalline solid. M.p. 81-83 °C; IR (CCl₄) 2958, 1688, 1659, 1298 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 67.8 (CH₂), 67.6 (CH₂), 48.4 (CH), 31.1 (CH₂), 19.0 (CH₂), 13.7 (CH₃); MS (ES⁺) *m/z* = 391 ([M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₂₁H₂₅N₂O₄ (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**) (1g, 3.62 mmol) and CCl₄ (700 μ L, 7.25 mmol) in CH₃CN (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; ¹H NMR (300 MHz, CDCl₃) 6.37 (1H, m), 3.83-3.62 (4H, m), 1.48 (18H, br s); ¹³C NMR (125 MHz, CDCl₃) 154.7 (C), 154.6 (C), 81.0 (broad, 2C), 51.7 and 50.8 (CH₂), 40.5 (CH₂), 27.5 (6CH₃); MS (ES⁺) *m/z* = 319 ([M(³⁷Cl)+Na]⁺, 25), 317 ([M(³⁵Cl)+Na]⁺, 75); HRMS (ES⁺) *m/z* calcd for C₁₂H₂₃³⁵ClN₂O₄Na (M+Na)⁺: 317.1239; found: 317.1244.

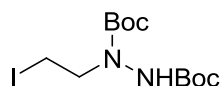
Di-*tert*-butyl 1-(2-bromoethyl)-hydrazine-1,2-dicarboxylate (**31**)



Bromine (668 μ L, 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 CH₂Cl₂ (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 CH₂Cl₂ (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; ¹H NMR (300 MHz, CDCl₃) 6.41

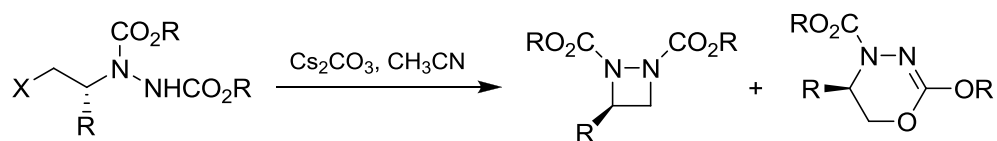
(1H, m), 3.82-3.69 (2H, m), 3.44 (2H, br s), 1.41 (18H, br s); ^{13}C NMR (75 MHz, CDCl_3) 155.2 (C), 154.9 (C), 82.2 (C), 81.6 (C), 52.3 and 51.4 (CH_2), 29.1 (CH_2), 28.2 (6 CH_3); MS (ES^+) m/z = 363 ($[\text{M}(^{81}\text{Br})+\text{H}]^+$, 50), 361 ($[\text{M}(^{79}\text{Br})+\text{H}]^+$, 50); HRMS (ES^+) m/z calcd for $\text{C}_{12}\text{H}_{23}^{79}\text{BrN}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 361.0733; found: 361.0719.

Di-*tert*-butyl 1-(2-iodoethyl)-hydrazine-1,2-dicarboxylate (**32**)



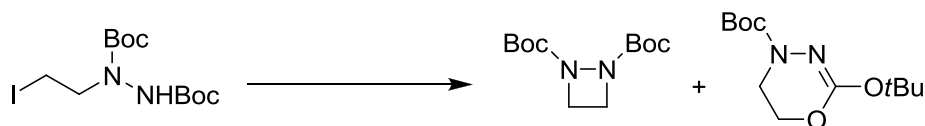
Iodine (3.31g, 13.0 mmol) was added portionwise to a solution of triphenylphosphine (3.42 g, 13.0 mmol) and imidazole (888 mg, 13.0 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The resultant yellow suspension was allowed to warm to room temperature and di-*tert*-butyl 1-(2-hydroxyethyl)-hydrazine-1,2-dicarboxylate (**22**) (3 g, 10.9 mmol) in CH_2Cl_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} ; ^1H 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 (6 CH_3), 0.0 and -0.7 (CH_2); MS (ES^+) m/z = 409 ($[\text{M}+\text{Na}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{12}\text{H}_{23}\text{IN}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 409.0595; found: 409.0609.

Cyclisation: General Procedure 1



To a solution of the substrate (1.0 molar equiv) in CH₃CN at room temperature was added in one portion Cs₂CO₃ (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 Cs₂CO₃ (885 mg, 2.72 mmol) in CH₃CN (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 ¹H 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; ¹H NMR (300 MHz, CDCl₃) 4.12 (4H, s), 1.48 (18H, s); ¹³C NMR (100 MHz, CDCl₃) 160.2 (2C), 81.9 (2C), 48.8 (2CH₂), 28.1 (6CH₃); MS (ES⁺) *m/z* = 539 ([2M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₂H₂₂N₂O₄Na (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.

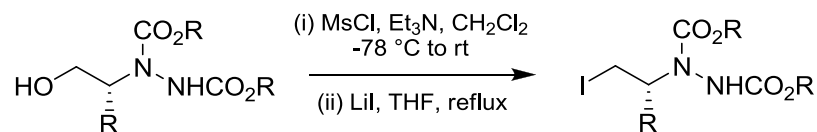
***tert*-Butyl 2-oxo-1,3,4-oxadiazinane-4-carboxylate (**34**)**



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*

vacuo 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



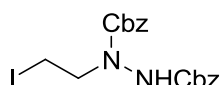
To a solution of MsCl (1.2 molar equiv) in CH₂Cl₂ at -78 °C was added dropwise a solution of the alcohol (1.0 molar equiv) and triethylamine (1.2 molar equiv) in CH₂Cl₂. After 10 min, the reaction was allowed to warm to room temperature and stirred overnight. The reaction was brought to pH 7 by the addition 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 iodideⁱ (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

ⁱ Wet lithium iodide or lithium iodide hydrate gave substantially lower yields.

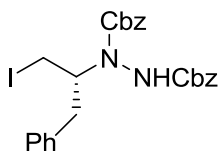
organic phases were washed with 10% aqueous Na₂S₂O₃ solution, brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification of the iodide was achieved by column chromatography or recrystallisation.

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



Iodide **35** was prepared from alcohol **25** (380 mg, 1.10 mmol), MsCl (111 μ L, 1.44 mmol), Et₃N (400 μ L, 2.87 mmol) in CH₂Cl₂ (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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 68.0 (CH₂), 53.0 and 52.7 (CH₂), 1.16 and 0.71 (CH₂); MS (ES⁺) *m/z* = 472 ([M+NH₄]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₈H₁₉IN₂O₄Na (M+Na)⁺: 477.0282; found: 477.0299.

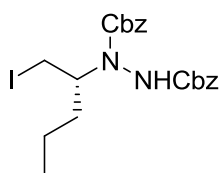
(*R*)-Dibenzyl 1-(1-benzyl-2-iodo-ethyl) hydrazine-1,2-dicarboxylate {(*R*)-**36a**}



Iodide (*R*)-**36a** was prepared from the corresponding alcohol³⁷ (366 mg, 0.84 mmol), MsCl (85 μ L, 1.10 mmol), Et₃N (306 μ L, 2.20 mmol) in CH₂Cl₂ (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

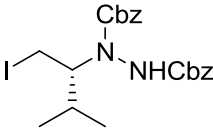
solid. M.p. 115.5-116.5 °C (methanol); $[\alpha]_D^{21} +5.1$ (c 0.45, CHCl₃); IR (neat) 3263, 3038, 1740, 1678, 1416, 1230, 695 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.60-7.04 (15H, m), 6.46 (1H, m), 5.38-4.97 (4H, m), 4.77-4.46 (1H, m), 3.64-2.53 (4H, m); ¹³C NMR (125 MHz, CDCl₃) 157.2 and 156.6 (C), 156.6 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 C₂₅H₂₅IN₂O₄Na (M+Na)⁺: 567.0751; found: 567.0768.

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

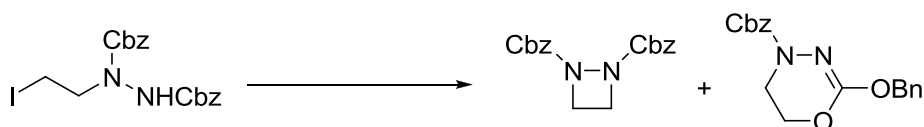


Iodide (*R*)-**36b** was prepared from the corresponding alcohol³⁷ (869 mg, 2.25 mmol), MsCl (226 μL, 2.93 mmol), Et₃N (816 μL, 5.85 mmol) in CH₂Cl₂ (15 mL) then LiI (3.02 g, 22.5 mmol) in THF (15 mL) according to general procedure **2**. Work-up followed by column chromatography (petroleum ether:ethyl acetate, 8:1) afforded (*R*)-**36b** (404 mg, 36% from (*R*)-**12b**) as a colourless crystalline solid. M.p. 83.5-84 °C (methanol); $[\alpha]_D^{21} -4.0$ (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 C₂₁H₂₅IN₂O₄Na (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 alcohol³⁷ (1.79 g, 4.64 mmol), MsCl (467 μ L, 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]_D²¹ -12.3 (c 0.4, CHCl₃) [racemate [α]_D²¹ -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* calcd for C₂₁H₂₅IN₂O₄Na (M+Na)⁺: 519.0751; found: 519.0746.

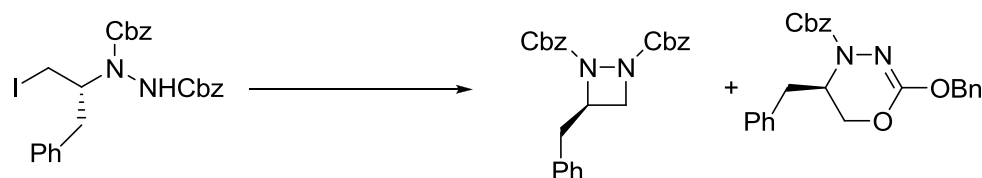
Dibenzyl 1,2-diazetidine-1,2-dicarboxylate (38**) and Benzyl 2-(benzyloxy)-5,6-dihydro-4H-1,3,4-oxadiazine-4-carboxylate (**37**)**



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} ; ^1H 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); ^{13}C NMRⁱ (125 MHz, CDCl_3) 136.4 (C), 135.4 (C), 128.7 (2CH), 128.6 (2CH), 128.4 (3CH), 128.2 (3CH), 69.9 (CH_2), 67.8 (CH_2), 65.4 (CH_2), 39.6 (CH_2); MS (ES^+) $m/z = 349$ ($[\text{M}+\text{Na}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$)⁺: 327.1339; found: 327.1340. Further elution gave **38** (54 mg, 53%) as a colourless crystalline solid. M.p. 93.5-94.5 $^\circ\text{C}$; IR (neat) 3032, 2910, 1745, 1718, 1393, 1282, 1266, 1019, 691 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) 7.24 (10H, s), 5.11 (4H, s), 4.16 (4H, s); ^{13}C NMR (100 MHz, CDCl_3) 160.8 (2C), 135.5 (2C), 128.6 (4CH), 128.3 (2CH), 128.1 (4CH), 68.2 (2 CH_2), 49.6 (2 CH_2); MS (ES^+) $m/z = 327$ ($\text{M}+\text{H}^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$)⁺: 349.1159; found: 349.1161.

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

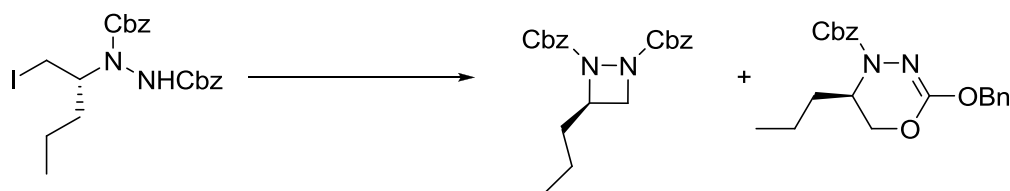


Iodide (*R*)-**36a** (138 mg, 0.25 mmol) was cyclised according to general procedure **1** with Cs_2CO_3 (885 mg, 2.0 mmol) in CH_3CN (10 mL) to give a mixture of diazetidine (*R*)-**13a** and dihydrooxadiazine (*R*)-**28a** (overall yield 103 mg, 98%) in the ratio 35:65 as judged by crude ^1H NMR. Separation by multiple column chromatography (petroleum ether:ethyl acetate, 6:1) gave (*R*)-**13a** (30 mg, 29%) as a colourless oil. $[\alpha]_{\text{D}}^{21} -36.1$ (c 1.70, CHCl_3); IR (film) 3031, 2956, 1710, 1390, 1328, 1276, 699 cm^{-1} ; ^1H 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),

ⁱ Quaternary carbons seen at -40°C (125 MHz, CDCl_3) 153.6 and 152.7 (C), 150.2 and 148.8 (C).

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), 68.0 (2CH₂), 62.4 (CH), 53.9 (CH₂), 40.0 (CH₂); MS (ES^+) $m/z = 417$ ($[\text{M}+\text{H}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$)⁺: 439.1628; found: 439.1641. Further elution gave (*R*)-**28a** (67 mg, 64%) as white solid. $[\alpha]_{\text{D}}^{21} +4.0$ (c 0.21, CHCl_3); M.p. 92.5-94 °C; IR (film) 3030, 1721, 1690, 1651, 1421, 1296, 1140, 693 cm^{-1} ; ^1H 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 NMRⁱ (75 MHz, CDCl_3) 136.7 (C), 136.3 (C), 135.5 (C), 129.5 (3CH), 128.8 (4CH), 128.6 (2CH), 128.5 (3CH), 128.2 (2CH), 127.0 (CH), 70.0 (CH₂), 67.7 (CH₂), 65.9 (CH₂), 50.3 (CH), 34.7 (CH₂); MS (ES^+) $m/z = 439$ ($[\text{M}+\text{Na}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{25}\text{H}_{28}\text{N}_3\text{O}_4$ ($\text{M}+\text{NH}_4$)⁺: 434.2074; found: 434.2071.

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

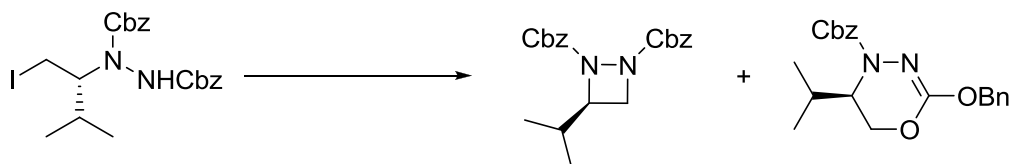


Iodide (*R*)-**36b** (321 mg, 0.65 mmol) was cyclised according to general procedure **1** with Cs_2CO_3 (1.69 g, 5.2 mmol) in CH_3CN (15 mL) to give a mixture of diazetidine (*R*)-**13b** and dihydrooxadiazine (*R*)-**28b** (overall yield 233 mg, 98%) as one spot by tlc (petroleum ether:ethyl acetate, 4:1, $R_f = 0.67$) in the ratio 41:59 as judged by crude ^1H

ⁱ Quaternary carbons not observed.

NMR. Analysis of mixture (assignments made where possible: **A** denotes diazetidine; **B** denotes dihydrooxadiazine): ^1H 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), 127.8 (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 ($[\text{M}+\text{H}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 391.1628; found: 391.1643.

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

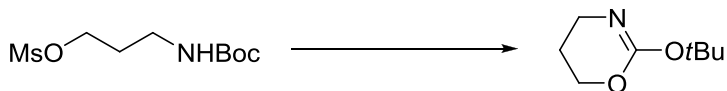


Iodide (*R*)-**36c** (179 mg, 0.36 mmol) was cyclised according to general procedure **1** with Cs_2CO_3 (941 mg, 2.9 mmol) in CH_3CN (10 mL) to give a mixture of diazetidine (*R*)-**13c** and dihydrooxadiazine (*R*)-**28c** (overall yield 129 mg, 97%) as one spot by tlc (petroleum ether:ethyl acetate, 6:1, R_f = 0.25) in the ratio 40:60 as judged by crude ^1H NMR. Separation was achieved by preparative HPLCⁱ. (*R*)-**13c**: ^1H 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

ⁱ 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⁺) t_r = 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⁺) t_r = 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-4*H*-1,3-oxazine (**43**)

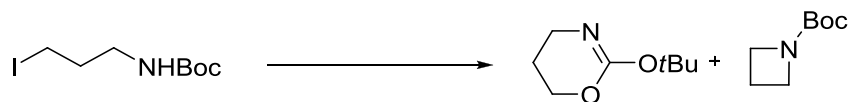


N-*tert*-Butoxycarbonyl-3-aminopropyl methanesulfonate⁹⁸ (**41**) (100 mg, 0.40 mmol) in THF (3 mL) was cooled to 0 °C and 95% potassium *tert*-butoxide (70 mg, 0.60 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stirred for 16 h, after which time volatile components 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 azetidine¹⁰⁰ (44)**

 To a mixture of di-*tert*-butyl dicarbonate (1.17 g, 5.36 mmol) and triethylamine (746 μ L, 5.36 mmol) in CH_2Cl_2 (10 mL) was added dropwise azetidine (300 μ L, 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_2Cl_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} ; ^1H 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 2 CH_2), 28.2 (3 CH_3), 15.1 (CH_2); HRMS (ES^+) m/z calcd for $\text{C}_8\text{H}_{15}\text{NO}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 180.0995; found: 180.1001.

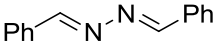
2-*tert*-Butoxy-5,6-dihydro-4*H*-1,3-oxazine (43) and *N*-tert-Butoxycarbonyl azetidine (44)



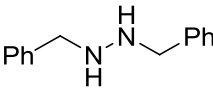
N-*tert*-butoxycarbonyl-3-aminopropyl iodide⁹⁹ (**42**) (101 mg, 0.35 mmol) in THF (3 mL) was cooled to 0 $^{\circ}\text{C}$ and 95% potassium *tert*-butoxide (63 mg, 0.53 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stirred for 16 h, after which time the reaction 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 ^1H NMR.

IV.III Synthesis of 1,2-Dialkyl-1,2-Diazetidines

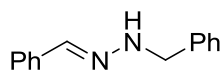
1,2-Dibenzylidenehydrazine¹⁰⁵ (**48**)

 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); ¹H NMR (300 MHz, CDCl₃) 8.71 (2H, s), 7.90-7.88 (4H, m), 7.51-7.47 (6H, m); ¹³C NMR (75 MHz, CDCl₃) 162.1 (2CH), 134.1 (2C), 131.3 (2CH), 128.8 (4CH), 128.6 (4CH); MS (ES⁺) *m/z* = 209 ([M+H]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₄H₁₃N₂ (M+H)⁺: 209.1073; found: 209.1076.

1,2-Dibenzylhydrazine¹⁰⁶ (**49**)

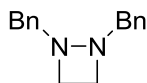
 To a stirred solution of 1,2-dibenzylidenehydrazine (**48**) (753 mg, 3.62 mmol) in ethyl acetate (20 mL) was added 10% palladium on carbon (75 mg, 10% w/w) and the suspension stirred under a hydrogen atmosphere (1 atm) for 16 h. The reaction was filtered through celite (ethyl acetate) and concentrated *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. ¹H NMR (300 MHz, CDCl₃) 7.37-7.21 (10H, m), 3.94 (4H, s), 3.38 (2H, br s); ¹³C NMR (75 MHz, CDCl₃) 138.0 (2C), 128.1 (4CH), 128.0 (4CH), 126.7 (2CH), 54.3 (2CH₂); MS (ES⁺) *m/z* = 213 ([M+H]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₄H₁₇N₂ (M+H)⁺: 213.1386; found: 213.1377.

Proposed structure: 1-Benzyl-2-benzylidenehydrazine (50)



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} ; ^1H 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^+) $m/z = 211$ ($\text{M}+\text{H}$) $^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{14}\text{H}_{15}\text{N}_2$ ($\text{M}+\text{H}$) $^+$: 211.1230; found: 211.1238.

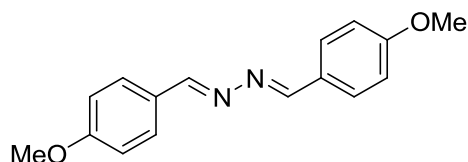
1,2-Dibenzyl-1,2-diazetidene (45)



To a mixture of Na_2CO_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 μL , 1.42 mmol). The reaction vessel was sealed then subjected to microwave irradiation (100 W, 100 $^\circ\text{C}$) 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, 6:1) furnished **45** (70 mg, 62%) as a colourless oil. IR (film) 2860, 1675, 1495, 1453, 1351, 733, 696 cm^{-1} ; ^1H 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),

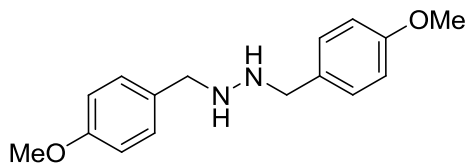
66.3 (2CH₂), 51.1 (2CH₂); MS (ES⁺) m/z = 239 ([M+H]⁺, 100); HRMS (ES⁺) m/z calcd for C₁₆H₁₉N₂ (M+H)⁺: 239.1543; found: 239.1545.

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.

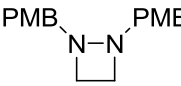
1,2-bis(4-Methoxybenzyl)hydrazine¹⁰⁶ (52)



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,

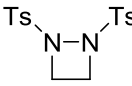
CDCl₃) 7.24 (4H, d, $J = 8.6$ Hz), 6.88 (4H, d, $J = 8.6$ Hz), 3.92 (4H, s), 3.81 (6H, s), 3.14 (2H, br s); ¹³C NMR (75 MHz, CDCl₃) 158.9 (2C), 130.6 (2C), 129.8 (4CH), 113.9 (4CH), 55.3 (2CH₃), 54.2 (2CH₂); MS (ES⁺) $m/z = 273$ ([M+H]⁺, 100); HRMS (ES⁺) m/z calcd for C₁₆H₂₁N₂O₂ (M+H)⁺: 273.1598; found: 273.1581.

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


 To a mixture of Na₂CO₃ (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 (MgSO₄), 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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 158.9 (2C), 130.6 (4CH), 129.0 (2C), 113.7 (4CH), 65.7 (2CH₂), 55.2 (2CH₃), 50.9 (2CH₂); MS (ES⁺) $m/z = 299$ ([M+H]⁺, 100); HRMS (ES⁺) m/z calcd for C₁₈H₂₅N₂O₂ (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

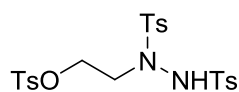
1,2-*bis*(Tosyl)-1,2-diazetidine (**53**)

 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)hydrazine¹⁰⁹ (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 MgSO₄, 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)ⁱ (diethyl ether); UV-Vis (CHCl₃) λ_{max} 241 nm; IR (neat) 2941, 1597, 1401, 1313, 1211, 1147, 1079, 812, 751 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.91 (4H, d, *J* = 8.1 Hz), 7.41 (4H, d, *J* = 8.1 Hz), 3.66 (4H, s), 2.49 (6H, s); ¹³C NMR (100 MHz, CDCl₃) 145.7 (2C), 130.3 (4CH), 129.7 (4CH), 129.2 (2C), 47.9 (2CH₂), 21.8 (2CH₃); MS (ES⁺) *m/z* = 389 ([M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₆H₁₈N₂O₄S₂Na (M+Na)⁺: 389.0600; found: 389.0600. Crystals suitable for X-ray diffraction were grown from ethanol/chloroform (95:5) by slow evaporation.

ⁱ 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); ¹H NMR (400 MHz, CHCl₃) 7.75 (4H, d, *J* = 8.2 Hz), 7.39 (4H, d, *J* = 8.2 Hz), 3.40 (4H, s), 2.48 (6H, s); ¹³C NMR (100 MHz, CHCl₃) 145.8 (2C), 135.1 (2C), 130.3 (4CH), 128.1 (4CH), 49.7 (2CH₂), 21.7 (2CH₃); MS (ES⁺) *m/z* = 339 ([M+H]⁺, 100). Crystals suitable for X-ray diffraction were grown from ethanol/chloroform (95:5) by slow cooling.

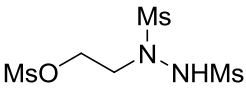
1-(2-(4-Tolylsulphonyl)oxyethyl)-1,2-bis(4-tolylsulphonyl) hydrazine (**58**)



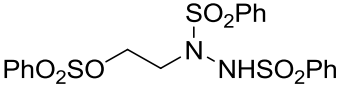
To a stirred solution of 2-hydroxyethyl hydrazine (90% purity) (1.00 mL, 13.3 mmol) in pyridine (15 mL) at 0 °C was added portionwise TsCl (7.86 g, 41.2 mmol) maintaining the temperature between 0 and 10 °C. The reaction was stirred at 0 °C for 2 h then poured into a mixture of ice and concentrated HCl (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 (MgSO₄), filtered, and concentrated *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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 calcd for C₂₃H₃₀N₃O₇S₃ (M+NH₄)⁺: 556.1240; found: 556.1244.

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

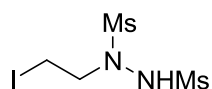

 To a stirred solution of 2-hydroxyethyl hydrazine (90% purity) (1.00 mL, 13.3 mmol) in pyridine (15 mL) at 0 °C was added dropwise MsCl (3.19 mL, 41.2 mmol) maintaining the temperature between 0 and 10 °C. The reaction was stirred at 0 °C for 1 h then poured into a mixture of ice and concentrated HCl (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, *d*₆-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, *d*₆-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 calcd 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, 1088, 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.

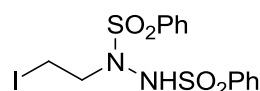
1-(2-Iodoethyl)-1,2-bis(methylsulphonyl) hydrazine (**61**)



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, *d*₆-DMSO) 9.91 (1H, s), 3.69 (2H, br s), 3.37 (2H, t, *J* = 8.2 Hz), 3.13 (3H, s), 3.06

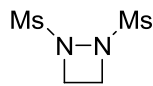
(3H, s); ^{13}C NMR (75 MHz, d_6 -DMSO) 55.0 (CH_2), 34.9 (2CH_3), 0.00 (CH_2); MS (ES^+) m/z = 365 ($[\text{M}+\text{Na}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_4\text{H}_{11}\text{IN}_2\text{O}_4\text{S}_2$ ($\text{M}+\text{Na}$) $^+$: 364.9097; found: 364.9110.

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 Et_2O and water were added. The phases were separated and the aqueous phase extracted three times with Et_2O . The combined organic phases were washed with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution, brine, dried over MgSO_4 , filtered, and concentrated *in vacuo*. Recrystallisation from MeOH/water furnished **62** (480 mg, 68%) as white needles. M.p. 115 $^\circ\text{C}$ (MeOH) (decomp.); IR (film) 3250, 1449, 1351, 1339, 1173, 1159, 1086, 687 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 137.9 (C), 136.1 (C), 134.8 (CH), 134.6 (CH), 130.0 (2CH), 129.8 (2CH), 129.1 (4CH), 57.3 (CH_2), 0.15 (CH_2); MS (ES^+) m/z = 489 ($\text{M}+\text{Na}$) $^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{14}\text{H}_{15}\text{IN}_2\text{O}_4\text{S}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 488.9410; found: 488.9423.

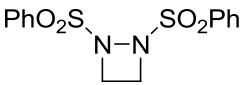
1,2-bis(Methylsulfonyl)-1,2-diazetidene (**55**)



To iodide **61** (116 mg, 0.34 mmol) in CH_3CN (10 mL) was added Cs_2CO_3 (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

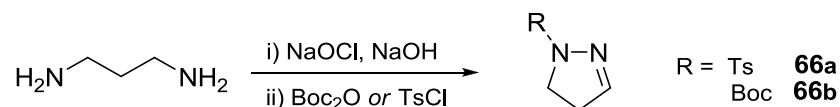
mL). These washings were discarded and the residue washed again with hot CH₃CN (4 × 5 mL). These washings were collected and concentrated *in vacuo*. Crystallisation from DMSO/water removed any remaining inorganic material to give **55** (53 mg, 73%) as a colourless crystalline solid. M.p. 229-232 °C (DMSO); IR (neat) 2941, 1346, 1170, 1151, 1030, 949, 755 cm⁻¹; ¹H NMR (300 MHz, *d*₆-DMSO) 4.29 (4H, s), 3.31 (6H, s); ¹³C NMR (75 MHz, *d*₆-DMSO) 47.2 (2CH₂), 33.1 (2CH₃); MS (ES⁺) *m/z* = 237 ([M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₄H₁₀N₂O₄S₂Na (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-diazetidene (**54**)


 To iodide **62** (163 mg, 0.35 mmol) in CH₃CN (10 mL) was added Cs₂CO₃ (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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 134.6 (2CH), 132.3 (2C), 130.3 (4CH), 129.1 (4CH), 47.8 (2CH₂); MS (ES⁺) *m/z* = 361 ([M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₄H₁₄N₂O₄S₂Na (M+Na)⁺: 361.0287; found: 361.0294.

IV.V Attempted Synthesis of 1,2-Diazetidine

1-Tosyl-4,5-dihydro-1H-pyrazole¹¹⁸ (**66a**) and *tert*-Butyl 4,5-dihydro-1H-pyrazole-1-carboxylate (**66b**)



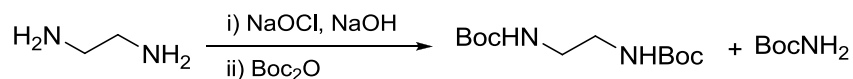
1,3-Diaminopropane (75 μL , 0.90 mmol) in water (10 mL) was brought to pH 7 with 2M HCl. An additional 75 μL of diamine was added. The solution, which now contained 1.80 mmol of 1,3-diaminopropane monohydrochloride, was cooled to 0 $^{\circ}\text{C}$ and commercial bleach (~5% NaOCl) (2.80 mL, approx. 1.89 mmol) was added over 15 min under vigorous stirring, ensuring the reaction temperature did not rise above 5 $^{\circ}\text{C}$. 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 $^{\circ}\text{C}$ 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 $^{\circ}\text{C}$, and NaOH (72 mg, 1.80 mmol), and TsCl (343 mg, 1.80 mmol) in Et₂O (10 mL) were added successively. After stirring for 16 h, the organic layer was separated and the aqueous layer extracted with Et₂O (3 \times 10 mL). The combined extracts were washed water (3 \times 10 mL), brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification by recrystallisation (ethanol) furnished 1-tosyl-4,5-dihydro-1H-pyrazole (**66a**)¹¹⁸ (50 mg, 26% corrected yield) as white needles. M.p. 162-163 $^{\circ}\text{C}$ (decomp.); IR (film) 2919, 1594, 1348, 1290, 1163, 1098, 641 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) 7.77 (2H, dd, *J* = 8.3, 1.7 Hz), 7.32 (2H, d, *J* = 8.3 Hz), 7.00 (1H, d, *J* = 1.6 Hz), 3.50 (2H, dt, *J* = 1.6, 9.5 Hz), 2.74 (2H, t, *J* = 9.5 Hz), 2.43 (3H, s); ¹³C

NMR (100 MHz, CDCl₃) 149.9 (CH), 144.4 (C), 139.8 (C), 129.5 (2CH), 128.9 (2CH), 46.5 (CH₂), 34.1 (CH₂), 21.6 (CH₃); MS (ES⁺) m/z = 225 (M+H)⁺, 100; HRMS (ES⁺) m/z calcd for C₁₀H₁₂N₂O₂SNa (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 CH₂Cl₂ (10 mL) and the mixture stirred at room temperature for 16 h. The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 × 10 mL). The combined extracts were washed with brine, dried (MgSO₄), 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 152.4 (C), 146.1 (CH), 81.3 (C), 43.3 (CH₂), 33.3 (CH₂), 28.4 (3CH₃); MS (ES⁺) m/z = 363 ([2M+Na]⁺, 100); HRMS (ES⁺) m/z calcd for C₈H₁₄N₂O₂Na (M+Na)⁺: 193.0947; found: 193.0940.

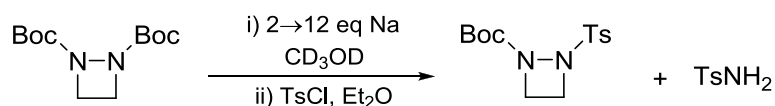
Attempted cyclisation of 1,2-diaminoethane



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

CH₂Cl₂ (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-diazetidene-1,2-dicarboxylate

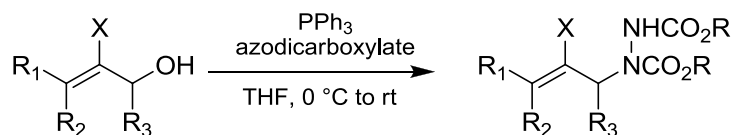


Sodium (10 mg, 0.43 mmol) was added to *d*₄-MeOH (2 mL) under strong stirring. After the metal had dissolved, di-*tert*-butyl 1,2-diazetidene-1,2-dicarboxylate (55 mg, 0.21 mmol) in *d*₄-MeOH (1 mL) was added dropwise. The reaction was sampled every hour for six hours by withdrawing 100 µL of the reaction 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*). Et₂O (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 tosylamide¹²⁸ (**76**) (18 mg, 25% based on starting material nitrogen content) as a colourless solid. M.p. 132-133 °C; ¹H NMR (400 MHz, CDCl₃) 7.73 (2H, d, *J* = 8.3 Hz), 7.36 (2H, d, *J* = 8.3 Hz), 7.28 (2H, s), 2.38 (3H, s); ¹³C NMR (75 MHz, CDCl₃) 141.9 (C), 141.5 (C), 129.3 (CH), 125.7 (CH), 20.9 (CH₃); MS (ES⁺) *m/z* = 194 (M+Na)⁺, 100; HRMS (ES⁺) *m/z* calcd for C₇H₁₀NO₂S (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. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 159.1 (C), 145.1 (C), 131.9 (2CH), 129.6 (2CH), 119.6 (C), 82.9 (C), 48.9 (CH₂), 47.5 (CH₂), 27.9 (3CH₃), 21.7 (CH₃); MS (ES⁺) *m/z* = 355 ([M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₄H₂₀N₂O₄SNa (M+Na)⁺: 335.1036; found: 335.1040.

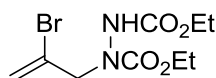
IV.VI Synthesis of 3-Alkylidene-1,2-Diazetidines

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).

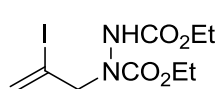
Diethyl 1-(2-bromoallyl)hydrazine-1,2-dicarboxylate (**88**)



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, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 155.9 (C), 155.8 (C), 127.9 (C), 120.2 and 119.6 (CH_2), 64.3

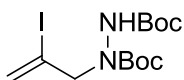
and 64.0 (CH₂), 62.9 and 62.2 (CH₂), 58.0 and 57.2 (CH₂), 14.4 (2CH₃); MS (ES⁺) *m/z* = 319 ([M(⁸¹Br)+Na]⁺, 50), 317 ([M(⁷⁹Br)+Na]⁺, 50); HRMS (ES⁺) *m/z* calcd for C₉H₁₆⁷⁹BrN₂O₄ (M+H)⁺: 295.0288; found: 295.0290.

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 diethylazodicarboxylate (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.

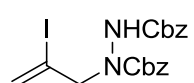
Di-*tert*-butyl 1-(2-iodoallyl)hydrazine-1,2-dicarboxylate (**97**)



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*-butylazodicarboxylate (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,

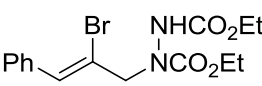
10:1) afforded **97** (2.66 g, 62%) as a colourless oil. IR (film) 3323, 2978, 1708, 1478, 1366, 1143 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) 6.53-6.11 (2H, m), 5.86 (1H, s), 4.24 (2H, br s), 1.49-1.38 (18H, m); ^{13}C NMR (75 MHz, CDCl_3) 154.5 (C), 154.0 (C), 127.3 and 127.0 (CH_2), 105.5 (C), 81.2 (CH_2), 80.9 (CH_2), 61.0 and 59.8 (CH_2), 27.6 (6 CH_3); MS (ES^+) m/z = 421 ($[\text{M}+\text{Na}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{13}\text{H}_{23}\text{IN}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 421.0595; found: 421.0604.

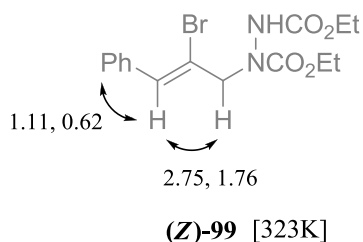
Dibenzyl 1-(2-iodoallyl)hydrazine-1,2-dicarboxylate (**98**)



To a solution of 2-iodoallyl alcohol¹⁴² (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} ; ^1H 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 ($[\text{M}+\text{Na}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{19}\text{H}_{19}\text{IN}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 489.0282; found: 489.0287.

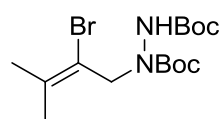
(Z)-Diethyl 1-(2-bromo-3-phenylallyl)hydrazine-1,2-dicarboxylate {(Z)-99}

 To a solution of (Z)-2-bromo-3-phenylprop-2-en-1-ol¹⁴⁵ (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 *in vacuo*. Column chromatography (petroleum ether:ethyl acetate, 10:1) afforded (Z)-99ⁱ (188 mg, 69%) as a colourless oil. IR (film) 3290, 2987, 1702, 1382, 1255, 1216, 1058, 735 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 (CH₂), 62.2 (CH₂), 59.8 and 59.1 (CH₂), 14.5 (2CH₃); MS (ES⁺) *m/z* = 395 ([M(⁸¹Br)+Na]⁺, 50), 393 ([M(⁷⁹Br)+Na]⁺, 50); HRMS (ES⁺) *m/z* calcd for C₁₅H₁₉⁷⁹BrN₂O₄Na (M+Na)⁺: 393.0420, found: 393.0423.



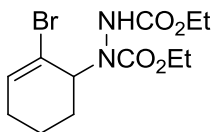
ⁱ Contaminated with ca. 10% *tetrakis*(ethoxycarbonyl)hydrazine: ¹H NMR (300 MHz, CDCl₃) 4.31 (q, *J* = 7.1 Hz), 1.31 (t, *J* = 7.1 Hz); ¹³C NMR (100 MHz, CDCl₃) 150.6 (C), 64.3 (CH₂), 14.1 (CH₃); MS (ES⁺) *m/z* = 343 ([M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₂H₂₁N₂O₈ (M+H)⁺: 321.1292, found: 321.1294. 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-ol²⁰⁰ (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 *in vacuo*. Column chromatography (petroleum ether:ethyl acetate, 12:1) afforded **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⁻¹; ¹H NMR (323K, 400 MHz, CDCl₃) 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); ¹³C NMRⁱ (323K, 150 MHz, CDCl₃) 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 (CH₂), 28.2 (6CH₃), 25.5 (CH₃), 20.5 (CH₃); MS (ES⁺) *m/z* = 403 ([M(⁸¹Br)+Na]⁺, 50), 401 ([M(⁷⁹Br)+Na]⁺, 50); HRMS (ES⁺) *m/z* calcd for C₁₅H₂₇⁷⁹BrN₂O₄Na (M+Na)⁺: 401.1046; found: 401.1053.

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

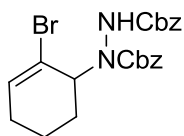


To a solution of 2-bromocyclohex-2-enol^{148,149} (1.46 g, 8.27 mmol) and triphenylphosphine (4.34 g, 16.5 mmol) in THF (25 mL) at 0 °C was added dropwise diethylazodicarboxylate (2.60 mL, 16.5 mmol). The reaction was allowed to warm to room temperature and stirred for 24 h after which time the reaction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

ⁱ Additional data: ¹³C NMR (298K, 150 MHz, CDCl₃) 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 (CH₂), 28.2 (6CH₃), 25.5 (CH₃), 20.5 (CH₃).

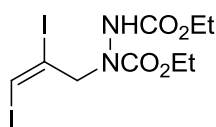
ether:ethyl acetate, 7:1) afforded **101** (2.13 g, 77%) as a white solid. M.p. 71.5-73.5 °C; IR (film) 3661, 3290, 2981, 1751, 1705, 1303, 1221, 1061, 729 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 6.45-6.05 (2H, m), 4.91 (1H, m), 4.37-4.09 (4H, m), 2.23-1.85 (4H, m), 1.85-1.58 (2H, m), 1.39-1.12 (6H, m); ¹³C NMR (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-enyl)hydrazine-1,2-dicarboxylate (**102**)



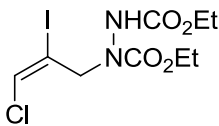
To a solution of 2-bromocyclohex-2-enyl^{148,149} (1.30 g, 7.35 mmol) and triphenylphosphine (3.85 g, 14.7 mmol) in THF (20 mL) at 0 °C was added portionwise dibenzylazodicarboxylate (4.38 g, 14.7 mmol). The reaction was allowed to warm to room temperature and stirred for 20 h after which time the reaction 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, *d*₆-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, *d*₆-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-ol¹⁴³ (233 mg, 0.75 mmol) and triphenylphosphine (394 mg, 1.50 mmol) in THF (6 mL) at 0 °C was added dropwise diethylazodicarboxylate (237 μ 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 *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} ; ^1H 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 (2 CH_3); MS (ES^+) $m/z = 491$ ($[\text{M}+\text{Na}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_9\text{H}_{14}\text{I}_2\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 490.8935; found: 490.8941.

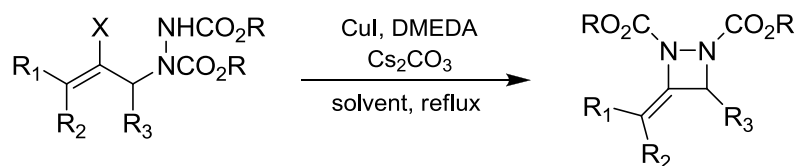
(E)-Diethyl 1-(3-chloro-2-iodoallyl)hydrazine-1,2-dicarboxylate {(E)-104}



To a solution of (*E*)-3-chloro-2-iodoprop-2-en-1-ol¹⁴⁷ (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 *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} ; ^1H 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).

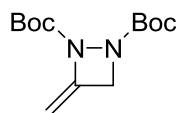
Diethyl 3-methylene-1,2-diazetidene-1,2-dicarboxylate (**89**)

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^+) $m/z = 237$ ($[\text{M}+\text{Na}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_9\text{H}_{15}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 215.1026; found: 215.1027.

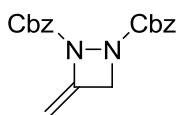
Diethyl 3-methylene-1,2-diazetidene-1,2-dicarboxylate (89) from 96 (2.01 g, 5.87 mmol) was cyclised according to the general procedure with CuI (224 mg, 1.17 mmol), Cs_2CO_3 (3.82 g, 11.7 mmol) and DMEDA (253 μL , 2.35 mmol) in THF (35 mL). After 24h, workup afforded **89** (1.24 g, 99%) as a colourless oil.

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



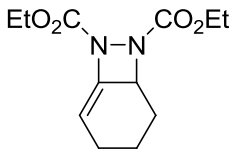
Hydrazodicarboxylate **97** (2.67 g, 6.70 mmol) was cyclised according to the general procedure with CuI (255 mg, 1.34 mmol), Cs_2CO_3 (4.37 g, 13.4 mmol) and DMEDA (288 μL , 2.68 mmol) in THF (35 mL). After 6h, workup afforded **77** (1.79 g, 99%) as a colourless oil. IR (film) 2979, 1715, 1367, 1151, 1117, 842 cm^{-1} ; ^1H 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 (3 CH_3), 27.4 (3 CH_3); MS (ES^+) $m/z = 293$ ($[\text{M}+\text{Na}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 293.1472; found: 293.1475.

Dibenzyl 3-methylene-1,2-diazetidene-1,2-dicarboxylate (**78**)



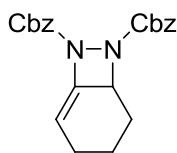
Hydrazodicarboxylate **98** (2.21 g, 4.73 mmol) was cyclised according to the general procedure with CuI (180 mg, 0.95 mmol), Cs₂CO₃ (3.08 g, 9.47 mmol) and DMEDA (204 μ L, 1.89 mmol) in THF (35 mL). After 12h, workup afforded **78** (1.54 g, 96%) as a colourless oil. IR (film) 2964, 1721, 1385, 1310, 1264, 1219, 1095, 736 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 68.6 (CH₂), 68.5 (CH₂), 57.9 (CH₂); MS (ES⁺) *m/z* = 361 ([M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₉H₁₈N₂O₄Na (M+Na)⁺: 361.1159; found: 361.1155.

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



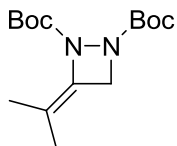
Hydrazodicarboxylate **101** (100 mg, 0.30 mmol) was cyclised according to the general procedure with CuI (11 mg, 0.06 mmol), Cs₂CO₃ (195 mg, 0.60 mmol) and DMEDA (13 μ L, 0.12 mmol) in THF (2 mL). After 16h, workup afforded **105** (72 mg, 95%) as a colourless solid. M.p. 66.5-67.0 °C; IR (film) 2972, 2909, 1766, 1729, 1372, 1243, 1064, 1095, 776 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 160.8 (C), 156.6 (C), 139.5 (C), 98.5 (CH), 67.1 (CH), 62.9 (2CH₂), 27.7 (CH₂), 22.6 (CH₂), 18.3 (CH₂), 14.4 (2CH₃); MS (ES⁺) *m/z* = 531 ([2M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₂H₁₈N₂O₄Na (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), Cs₂CO₃ (1.42 g, 4.36 mmol) and DMEDA (94 μ L, 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.

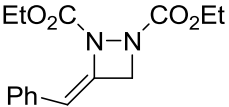
Di-*tert*-butyl 3-(propan-2-ylidene)-1,2-diazetidine-1,2-dicarboxylate (**107**)

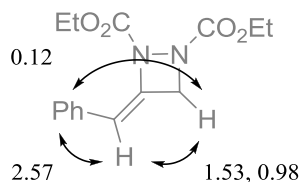


Hydrazodicarboxylate **100** (293 mg, 0.77 mmol) was cyclised according to the general procedure with CuI (29 mg, 0.16 mmol), Cs₂CO₃ (504 mg, 1.55 mmol) and DMEDA (33 μ L, 0.31 mmol) in THF (7 mL). After 24h, usual workup and column chromatography (petroleum ether:ethyl acetate, 14:1) afforded **107** (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 $C_{15}H_{26}N_2O_4Na$ ($M+Na$)⁺: 321.1785, found: 321.1781. Crystals suitable for X-ray diffraction were grown from ethanol by slow evaporation.

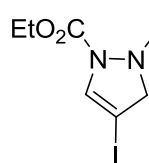
(Z)-Diethyl 3-benzylidene-1,2-diazetidine-1,2-dicarboxylate {(Z)-108}


 Hydrazodicarboxylate (Z)-**99** (74 mg, 0.20 mmol) was cyclised according to the general procedure with CuI (8 mg, 0.04 mmol), Cs₂CO₃ (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; ¹H NMR (600 MHz, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) 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 (2CH₂), 59.3 (CH₂), 14.4 (CH₃), 13.6 (CH₃); MS (ES⁺) *m/z* = 313 ([$M+Na$]⁺, 100); HRMS (ES⁺) *m/z* calcd for $C_{15}H_{18}N_2O_4Na$ ($M+Na$)⁺: 313.1159; found: 313.1155.



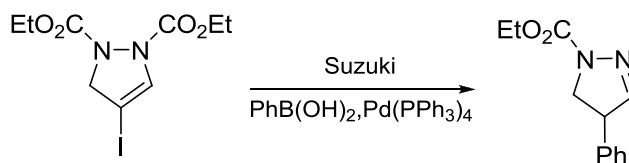
(Z)-108

Diethyl 4-iodo-1*H*-pyrazole-1,2(3*H*)-dicarboxylate (**109**)



To a mixture of (*E*)-**103** (412 mg, 0.88 mmol), CuI (51 mg, 0.26 mmol) and Cs₂CO₃ (574 mg, 1.76 mmol) in THF (8 mL) was added dropwise DMEDA (57 μ 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, 1609, 1371, 1320, 1304, 1156, 1048, 752 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 6.88 (1H, t, *J* = 2.1 Hz), 4.48 (2H, br s), 4.25 (4H, q, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.29 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) 157.1 (C), 152.2 (C), 132.7 (CH), 84.7 (C), 62.6 (CH₂), 62.5 (CH₂), 60.2 (CH₂), 13.8 (2CH₃); MS (ES⁺) *m/z* = 363 ([M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₉H₁₃IN₂O₄Na (M+Na)⁺: 362.9812; found: 362.9802.

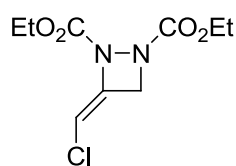
Ethyl 4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate (**111**)



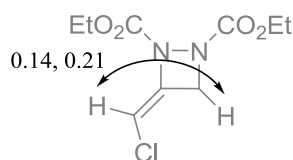
To a stirred solution of diethyl 4-iodo-1*H*-pyrazole-1,2(3*H*)-dicarboxylate (**109**) (75 mg, 0.22 mmol), Pd(PPh₃)₄ (13 mg, 0.01 mmol) and Cs₂CO₃ (144 mg, 0.44 mmol) in toluene (1 mL) and ethanol (1 mL) was added PhB(OH)₂ (54 mg, 0.44 mmol) in one portion and the resultant mixture heated to 100 °C 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 \times 5 mL). The combined organic extracts were washed with brine, dried (MgSO₄), filtered, and concentrated *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, 1348, 1134, 700 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 153.1 (C), 148.5 (CH), 138.7 (C), 129.2 (2CH), 127.9 (CH), 127.5 (2CH), 62.4 (CH_2), 52.6 (CH_2), 51.9 (CH), 14.7 (CH_3); MS (ES^+) $m/z = 459$ ($2\text{M}+\text{Na}^+$), 100); HRMS (ES^+) m/z calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 241.0947; found: 241.0947.

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



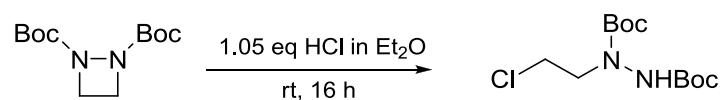
To a mixture of hydrazodicarboxylate (*E*)-**104** (300 mg, 0.80 mmol), CuI (46 mg, 0.24 mmol) and Cs_2CO_3 (520 mg, 1.60 mmol) in toluene (15 mL) was added dropwise DMEDA (52 μL , 0.48 mmol) and the mixture heated at reflux for 26 h. After usual workup, column chromatography (petroleum ether:ethyl acetate, 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, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 160.2 (C), 155.0 (C), 137.7 (C), 98.8 (CH), 63.5 (CH_2), 63.4 (CH_2), 56.5 (CH_2), 14.3 (CH_3), 14.3 (CH_3); MS (ES^+) $m/z = 271$ ($[\text{M}(^{35}\text{Cl})+\text{Na}]^+$, 75), 273 ($[\text{M}(^{37}\text{Cl})+\text{Na}]^+$, 25); HRMS (ES^+) m/z calcd for $\text{C}_9\text{H}_{13}^{35}\text{ClN}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 271.0456; found: 271.0455. Further elution gave **110** (41 mg, 15%) as a white solid.



(E)-110

IV.VII Functionalisation of 1,2-Diazetidines

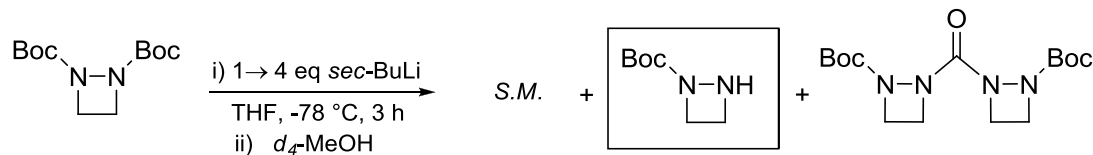
Di-*tert*-butyl 1-(2-chloroethyl)-hydrazine-1,2-dicarboxylate (**30**) from **21**



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 μ L, 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.

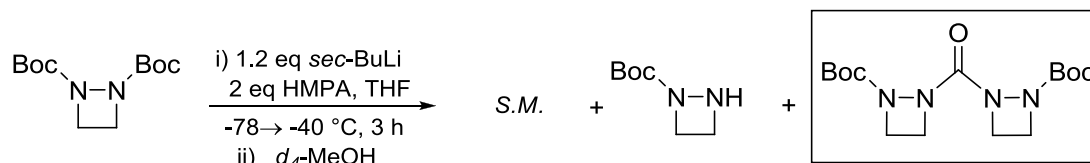
IV.VIII Lithiation Chemistry

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 μ L, 0.27 mmol). After 30 min, the reaction was sampled for LCMS as follows. A 75 μ L aliquot was withdrawn *via* syringe and injected into a 0.1 M NH_4Cl solution (1 mL). The sample was run directly. The presence of starting diazetidine was noted and a further equivalent of *sec*-butyllithium (209 μ L, 0.27 mmol) was added. This sequence was repeated every 30 mins until a total of 835 μ L, 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 d_4 -MeOH (50 μ L) and allowed to warm to room temperature. Water (5 mL) and Et_2O (5 mL) were added and the organic phase separated. The aqueous phase was extracted with Et_2O (3×5 mL) and the combined organic phases were washed with water (5×5 mL), brine, dried (MgSO_4), filtered, and concentrated *in vacuo*. Column chromatography (petroleum ether:ethyl acetate, 2:1 \rightarrow 1:4) ($R_f = 0.07$ 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, CDCl_3) 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^+) $t_r = 0.35$ min, $m/z = 159$ ($\text{M}+\text{H}$) $^+$; HRMS (ES^+) m/z calcd for $\text{C}_7\text{H}_{14}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 181.0947; found: 181.0955.

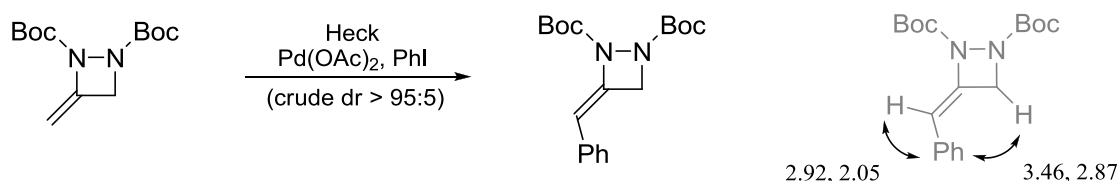
***tert*-Butyl 2,2'-carbonyl-*bis*(1,2-diazetidine-1-carboxylate) (**122**)**



To a stirred solution of di-*tert*-butyl 1,2-diazetidine-1,2-dicarboxylate (70 mg, 0.27 mmol) and hexamethylphosphoramide (94 μ L, 0.54 mmol) in THF (2 mL) at -78 $^{\circ}$ C was added dropwise *sec*-butyllithium (1.4M in cyclohexane) (233 μ L, 0.33 mmol). The mixture was allowed to warm to -40 $^{\circ}$ C over 30 mins and held at this temperature for 2.5 h. The reaction was quenched by the addition of d_4 -MeOH (50 μ L) 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 \times 5 mL) and the combined organic phases were washed with water (5 \times 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⁺) *t*_r = 0.88 min, *m/z* = 343 (M+H)⁺; HRMS (ES⁺) *m/z* calcd for C₁₅H₂₇N₄O₅ (M+H)⁺: 343.1981; found: 343.1985.

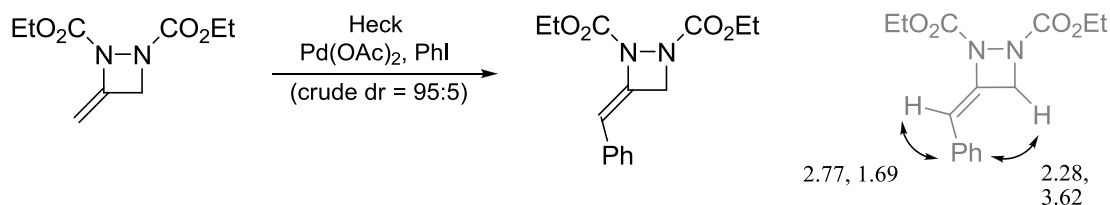
IV.IX Functionalisation of 3-Alkylidene-1,2-Diazetidines

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



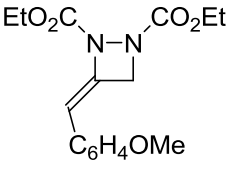
To a stirred mixture of di-*tert*-butyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (**77**) (109 mg, 0.40 mmol), phenyl iodide (68 μ L, 0.61 mmol), Bu₄NCl (112 mg, 0.40 mmol) and palladium(II) acetate (5 mg, 0.02 mmol) in dimethylacetamide (2 mL) was added Cy₂NMe (128 μ L, 0.61 mmol). The reaction was heated at 80 °C for 48 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 \times 10 mL). The combined extracts were washed with water (5 \times 10 mL), dried (MgSO₄), filtered, and concentrated *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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 28.1 (3CH₃), 28.0 (3CH₃); MS (ES⁺) *m/z* = 369 ([M+Na]⁺, 100); HRMS (ES⁺) *m/z* calcd for C₁₉H₂₆N₂O₄Na (M+Na)⁺: 369.1785; found: 369.1789.

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

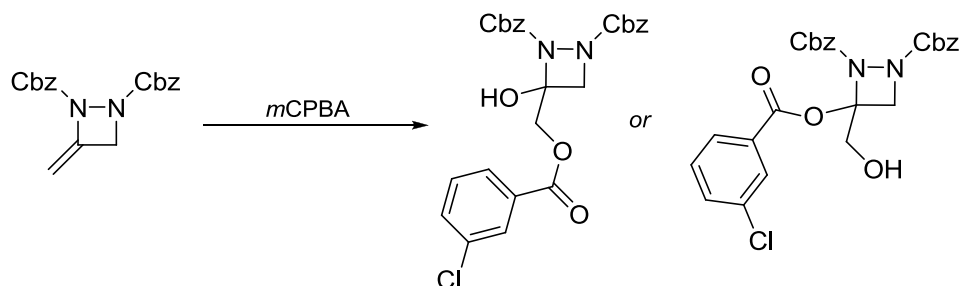


To a stirred mixture of diethyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (**89**) (50 mg, 0.23 mmol), phenyl iodide (39 μ L, 0.35 mmol), Bu₄NCl (65 mg, 0.23 mmol) and palladium(II) acetate (3 mg, 0.01 mmol) in dimethylacetamide (1 mL) was added Cy₂NMe (74 μ L, 0.35 mmol). The reaction was heated 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 \times 10 mL). The combined extracts were washed with water (5 \times 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 (*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}

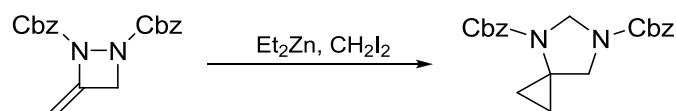
 Prepared from diethyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (**89**) (50 mg, 0.23 mmol), 1-iodo-4-methoxybenzene (82 mg, 0.35 mmol), Bu₄NCl (65 mg, 0.23 mmol), palladium(II)acetate (3 mg, 0.01 mmol) and Cy₂NMe (74 μL, 0.35 mmol) in dimethylacetamide (1 mL) using the procedure as described for (*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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 62.5 (CH₂), 57.8 (CH₂), 54.7 (CH₃), 13.8 (2CH₃); MS (ES⁺) *m/z* = 343 (M+Na)⁺, 100; HRMS (ES⁺) *m/z* calcd for C₁₆H₂₁N₂O₅Na (M+Na)⁺: 321.1445; found: 321.1448.

Dibenzyl 3-((3-chlorobenzoyloxy)methyl)-3-hydroxy-1,2-diazetidine-1,2-dicarboxylate (134 β)/regioisomer (134 α)



To a stirred mixture of dibenzyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (**78**) (100 mg, 0.30 mmol) and K_2CO_3 (53 mg, 0.38 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added portionwise *m*CPBA (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 $Na_2S_2O_3$ (2 mL) and saturated aqueous $NaHCO_3$ (2 mL) were added and the mixture extracted with CH_2Cl_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} ; 1H 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 $C_{26}H_{23}^{35}ClN_2O_7Na$ ($M+Na$) $^+$: 533.1086; found: 533.1087.

Dibenzyl 4,6-diazaspiro[2.4]heptane-4,6-dicarboxylate (**136**)

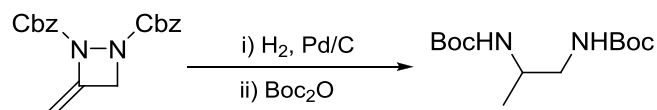


To a stirred solution of dibenzyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (**78**) (150 mg, 0.44 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added diethyl zinc (1.0M in hexanes, 2.22 mL, 2.22 mmol). Diiodomethane (179 μL , 2.22 mmol) was added immediately afterwards and the mixture stirred at 0 °C for 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_4Cl (2 mL) then diluted with Et_2O (10 mL) and water (10 mL). The phases were separated and the aqueous layer extracted with Et_2O (3 \times 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} ; ^1H 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 NMRⁱ (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 (2 CH_2); MS (ES^+) m/z = 389 ($\text{M}+\text{Na}^+$), 100; HRMS (ES^+) m/z calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 389.1472; found: 389.1472.

ⁱ Quaternary carbon not observed.

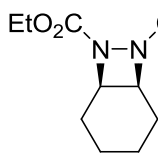
IV.X Reduction Chemistry

tert-Butyl propane-1,2-diyl dicarbamate (**141**)¹⁹³



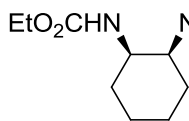
To a stirred solution of dibenzyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (**78**) (300 mg, 0.89 mmol) in MeOH (5 mL) was added 10% palladium on carbon (30 mg, 10% w/w) and the suspension stirred under a hydrogen atmosphere (1 atm) for 4 h. The reaction was filtered through celite (CH₂Cl₂) and 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.¹⁹³

(1*R, 6*S**)-Diethyl 7,8-diazabicyclo[4.2.0]octane-7,8-dicarboxylate {(1*R**, 6*S**)-142}**



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 (1*R**, 6*S**)-**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 C₁₂H₂₀N₂O₄Na (M+Na)⁺: 279.1315; found: 279.1320.

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

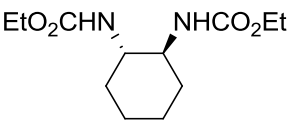


Firstly, a stock solution of LiDBB was prepared as follows. Small pellets of lithium (11 mg, 1.59 mmol) were placed in a Schlenk tube containing 4,4'-di-*tert*-butylbiphenyl (404 mg, 1.52 mmol) and some glass 'anti-bumping' granules. The tube was evacuated and purged with argon several times. The contents 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. (1*R**, 6*S**)-**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 NH_4Cl (1 mL). After warming to room temperature, Et_2O (2 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (3×10 mL). The combined extracts were dried (MgSO_4), filtered, and concentrated *in vacuo*. Column chromatography (petroleum ether:ethyl acetate, 3.5:1) followed by crystallisation (Et_2O /petroleum ether) afforded (1*R**, 2*S**)-**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, CDCl_3) 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); ^{13}C NMR (125 MHz, CDCl_3) 156.5 (2C), 60.9 (2 CH_2), 50.9 (2CH), 29.1 (2 CH_2), 22.0 (2 CH_2), 14.6 (2 CH_3); MS (ES^+) $m/z = 281$ ($[\text{M}+\text{Na}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 281.1472, found: 281.1474.

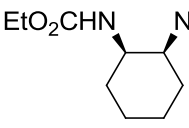
Preparation of authentic samples of (1*R, 2*S**)-144 and (1*S*, 2*S*)-144 for stereochemical assignment:**

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

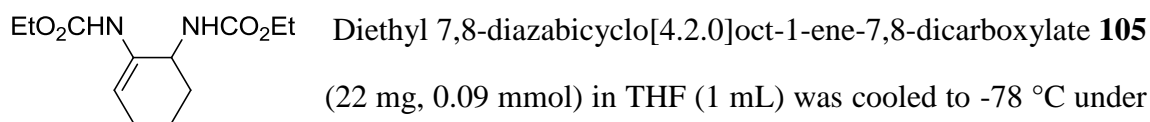

 Ethyl chloroformate (176 μL , 1.84 mmol) in toluene (3 mL) was added to a stirred solution of (1*S*, 2*S*)-1,2-diaminocyclohexane (100 mg, 0.88 mmol) and NaOH (175 mg, 4.38 mmol) in water (3 mL) and the mixture stirred rapidly for 2 h. The resultant white precipitate was filtered, washed with toluene and dried under vacuum for 16 h. Recrystallization from ethanol gave (1*S*, 2*S*)-**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, CDCl_3) 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 (2 CH_2), 55.4 (2CH), 32.9 (2 CH_2), 24.8 (2 CH_2), 14.6 (2 CH_3); MS (ES^+) $m/z = 281$ ($[\text{M}+\text{Na}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 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_2O (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 $^\circ\text{C}$; IR (neat) 3273, 2951, 1684, 1530, 1241, 1104, 1051, 779 cm^{-1} ; ^1H 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 (2 CH_2), 50.8 (2CH), 29.1 (2 CH_2), 22.1 (2 CH_2), 14.6 (2 CH_3); MS (ES^+) $m/z = 281$ ($[\text{M}+\text{Na}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 281.1472, found: 281.1471.

1,2-Diaminocyclohex-2-ene-*N,N'*-diethyl dicarbamate (**143**)



argon. LiDBB, prepared according to method used above, in THF (685 μ L, 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_4Cl (1 mL). After warming to room temperature, Et_2O (2 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (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} ; ^1H 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 (2 CH_3); MS (ES^+) $m/z = 279$ ($[\text{M}+\text{Na}]^+$, 100); HRMS (ES^+) m/z calcd for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 279.1315; found: 279.1317.

IV.XI LC conditions

IV.XI.I 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:

Time (min)	Flow Rate (ml/min)	% A	% B
0	1	97	3
1.5	1	0	100
1.9	1	0	100
2.0	1	97	3

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:

Time (min)	Flow Rate (ml/min)	% A	% B
0	1	97	3
0.1	1	97	3
9.3	1	0	100
9.9	1	0	100
10	1	97	3

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:

Time (min)	Flow Rate (ml/min)	% A	% B
0	20	45	55
1	20	45	55
25	20	20	80
25.2	20	1	99
28.2	20	1	99
28.5	20	45	55
30	20	45	55

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

REFERENCES

- (1) Brown, H. C.; Gerstein, M. *J. Am. Chem. Soc.* **1950**, 72, 2926.
- (2) Deady, L. W.; Leary, G. J.; Topsom, R. D.; Vaughan, J. *J. Org. Chem.* **1963**, 28, 511.
- (3) McCullough, J. P.; Pennington, R. E.; Smith, J. C.; Hossenlopp, I. A.; Waddington, G. *J. Am. Chem. Soc.* **1959**, 81, 5880.
- (4) Cook, E. S.; Rider, T. H. *J. Am. Chem. Soc.* **2002**, 59, 1739.
- (5) Buhle, E. L.; Moore, A. M.; Wiselogle, F. Y. *J. Am. Chem. Soc.* **1943**, 65, 29.
- (6) Lüttringhaus, A.; Jander, J.; Schneider, R. *Chem. Ber.* **1959**, 92, 1756.
- (7) Schmitz, E. *Tetrahedron Lett.* **1961**, 2, 612.
- (8) Makhova, N. N.; Petukhova, V. Y.; Kuznetsov, V. V. *ARKIVOC* **2008**, i, 128.
- (9) Cremer, D.; Gauss, J. *J. Am. Chem. Soc.* **1986**, 108, 7467.
- (10) Gessner, K.; Ball, D. *Theochem.* **2005**, 730, 95.
- (11) Freundlich, H.; Salomon, G. *Chem. Ber.* **1933**, 66, 355.
- (12) Vaughan, W. R.; Klonowski, R. S.; McElhinney, R. S.; Millward, B. B. *J. Org. Chem.* **1961**, 26, 138.
- (13) Richter, R.; Ulrich, H. In *The Chemistry of Heterocyclic Compounds: Small Ring Heterocycles - Part 2*; Wiley: New York, 1983; Vol. 42, pp. 443-545.
- (14) Lohray, B. B.; Bhushan, V. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon: New York, 1996; Vol. 1B, pp. 911-968.

- (15) Cramer, R. D. U.S. Patent 2,456,176, Dec. 14, 1948.
- (16) Miao, W.; Xu, W.; Zhang, Z.; Ma, R.; Chen, S.-H.; Li, G. *Tetrahedron Lett.* **2006**, 47, 6835.
- (17) Cheng, X.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, 47, 4581.
- (18) Hoffmann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, 87, 2046.
- (19) Hoffmann, R.; Woodward, R. B. *Acc. Chem. Res.* **1968**, 1, 17.
- (20) Kauer, J. C.; Schneider, A. K. *J. Am. Chem. Soc.* **1960**, 82, 12.
- (21) Hoffmann, R. W.; Häuser, H. *Angew. Chem.* **1964**, 76, 346.
- (22) Hoffmann, R. W.; Bressel, U.; Gehlhaus, J.; Häuser, H. *Chem. Ber.* **1971**, 104, 873.
- (23) Koerner von Gustorf, E.; White, D. V.; Leitich, J. *Tetrahedron Lett.* **1969**, 10, 3109.
- (24) Firl, J.; Sommer, S. *Tetrahedron Lett.* **1969**, 10, 1133.
- (25) Meyers, A. I. *J. Org. Chem.* **1961**, 26, 218.
- (26) Koerner von Gustorf, E.; White, D. V.; Kim, B.; Hess, D.; Leitich, J. *J. Org. Chem.* **1970**, 35, 1155.
- (27) Koerner von Gustorf, E.; White, D. V.; Leitich, J.; Henneberg, D. *Tetrahedron Lett.* **1969**, 10, 3113.
- (28) Hall, J. H.; Jones, M. L. *J. Org. Chem.* **1983**, 48, 822.
- (29) Firl, J.; Sommer, S. *Tetrahedron Lett.* **1972**, 13, 4713.
- (30) Jensen, F.; Foote, C. S. *J. Am. Chem. Soc.* **1987**, 109, 6376.

- (31) Fischer, G.; Fritz, H.; Rihs, G.; Hunkler, D.; Exner, K.; Knothe, L.; Prinzbach, H. *Eur. J. Org. Chem.* **2000**, 743.
- (32) Kim, D. K.; O'Shea, K. E. *J. Am. Chem. Soc.* **2004**, 126, 700.
- (33) Nunn, E. E.; Warrenner, R. N. *J. Chem. Soc., Chem. Commun.* **1972**, 818.
- (34) Englin, M. A.; Filatov, A. S.; Sirotenkova, N. F. *J. Org. Chem., USSR* **1969**, 5, 1555.
- (35) Horvitz, D. U.S. Patent 3,129,215, Apr. 14, 1964.
- (36) Hall, J. H.; Bigard, W. S. *J. Org. Chem.* **1978**, 43, 2785.
- (37) List, B. *J. Am. Chem. Soc.* **2002**, 124, 5656.
- (38) Xu, W. Chinese patent CN 101092398, Dec. 26, 2007.
- (39) Cheng, X.; Ma, S. *Chem. Comm.* **2009**, 4263.
- (40) Raschig, F. *Ber.* **1907**, 40, 4580.
- (41) Nielsen, A. T.; Moore, D. W.; Atkins, R. L.; Mallory, D.; DiPol, J.; LaBerge, J. *M. J. Org. Chem.* **1976**, 41, 3221.
- (42) Mazhukin, D. G.; Volodarskii, L. B. Tikhonova, L. A.; Tikhonov, L. Y. *Mendeleev Commun.* **1992**, 2, 29.
- (43) Breton, G. W.; Oliver, L. H.; Nickerson, J. E. *J. Org. Chem.* **2007**, 72, 1412.
- (44) Rademacher, P. *Tetrahedron Lett.* **1974**, 15, 83.
- (45) Gebhardt, K. F.; Oberhammer, H.; Zeil, W. *J. Chem. Soc., Faraday Trans. 2* **1980**, 76, 1293.
- (46) Carlson, E. H.; Schaap, A. P.; Raban, M. *J. Org. Chem.* **1973**, 38, 1605.

- (47) Phillips, W. D. In *Determination of organic structures by physical methods*; Phillips, W. D.; Nachod, F. C., Eds.; Academic Press: New York, 1962; p. 452.
- (48) Anderson, J. E.; Lehn, J. M. *J. Am. Chem. Soc.* **1967**, *89*, 81.
- (49) Nelsen, S. F.; Peacock, V. E.; Weisman, G. R.; Landis, M. E.; Spencer, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 2806.
- (50) Landis, M. E.; Mitchell, J. C.; Offen, D. L. *J. Org. Chem.* **1981**, *46*, 501.
- (51) Warrener, R. N.; Nunn, E. E.; Paddon-Row, M. N. *Aust. J. Chem.* **1979**, *32*, 2659.
- (52) Feula, A.; Male, L.; Fossey, J. S. *Org. Lett.* **2010**, *12*, 5044.
- (53) Ye, Y.; Wang, H.; Fan, R. *Org. Lett.* **2010**, *12*, 2802.
- (54) Burkett, B. A.; Ting, S. Z.; Gan, G. C. S.; Chai, C. L. L. *Tetrahedron Lett.* **2009**, *50*, 6590.
- (55) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988.
- (56) Hansen, C. P.; Jensen, A. A.; Christensen, J. K.; Balle, T.; Liljefors, T.; Frølund, B. *J. Med. Chem.* **2008**, *51*, 7380.
- (57) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052.
- (58) Che, Y.; Marshall, G. R. *J. Org. Chem.* **2004**, *69*, 9030.
- (59) Davies, M. W.; Shipman, M.; Tucker, J. H. R.; Walsh, T. R. *J. Am. Chem. Soc.* **2006**, *128*, 14260.
- (60) Shipman, M. *Synlett* **2006**, 3205.
- (61) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069.

- (62) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.
- (63) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.
- (64) O'Brien, P.; Wiberg, K. B.; Bailey, W. F.; Hermet, J.-P. R.; McGrath, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15480.
- (65) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708.
- (66) Coldham, I.; Copley, R. C. B.; Haxell, T. F. N.; Howard, S. *Org. Lett.* **2001**, *3*, 3799.
- (67) Coldham, I.; O'Brien, P.; Patel, J. J.; Raimbault, S.; Sanderson, A. J.; Stead, D.; Whittaker, D. T. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2113.
- (68) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2005**, *7*, 1153.
- (69) Montagne, C.; Prevost, N.; Shiers, J. J.; Prie, G.; Rahman, S.; Hayes, J. F.; Shipman, M. *Tetrahedron* **2006**, *62*, 8447.
- (70) Wykypiel, W.; Lohmann, J.; Seebach, D. *Helv. Chim. Acta.* **1981**, *64*, 1337.
- (71) Balle, T.; Begtrup, M.; Jaroszewski, J. W.; Liljefors, T.; Norrby, P.-O. *Org. Biomol. Chem.* **2006**, *4*, 1261.
- (72) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.
- (73) Beyer, U.; Krüger, M.; Schumacher, P.; Unger, C.; Kratz, F. *Monatsh. Chem.* **1997**, *128*, 91.
- (74) Schotten, C. *Ber.* **1884**, *17*, 2544.
- (75) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591.

- (76) Mandolini, L. *J. Am. Chem. Soc.* **1978**, *100*, 550.
- (77) Ahn, J. H.; Huh, S.-C.; Kang, S. K.; Kim, J. A.; Kim, H.-M.; Kim, K. R.; Kwon, H.-M.; Kim, S. Y.; Kim, S. G.; Lee, J. M.; Cheon, H. G.; Kim, S. S.; Yang, S.-D. *Biorg. Med. Chem. Lett.* **2005**, *15*, 1337.
- (78) Ahn, J. H.; Shin, M. S.; Jun, M. A.; Jung, S. H.; Kang, S. K.; Kim, K. R.; Rhee, S. D.; Kang, N. S.; Kim, S. Y.; Sohn, S.-K.; Kim, S. G.; Jin, M. S.; Lee, J. O.; Cheon, H. G.; Kim, S. S. *Biorg. Med. Chem. Lett.* **2007**, *17*, 2622.
- (79) Appel, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 801.
- (80) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
- (81) Kornblum, N.; Pink, P.; Yorka, K. V. *J. Am. Chem. Soc.* **1961**, *83*, 2779.
- (82) Kornblum, N.; Smiley, R. A.; Blackwood, R. K.; Iffland, D. C. *J. Am. Chem. Soc.* **1955**, *77*, 6269.
- (83) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533.
- (84) Pearson, R. G. *Science*. **1966**, *151*, 172.
- (85) Pearson, R. G. *J. Chem. Ed.* **1968**, *45*, 581.
- (86) Pearson, R. G. *J. Chem. Ed.* **1968**, *45*, 643.
- (87) Drago, R. S.; Wayland, B. B. *J. Am. Chem. Soc.* **1965**, *87*, 3571.
- (88) Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223.
- (89) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.
- (90) Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 221.
- (91) Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 209.

- (92) Thompson, M. A.; Schenter, G. K. *J. Phys. Chem.* **1995**, 99, 6374.
- (93) Zhong, M.; Brauman, J. I. *J. Am. Chem. Soc.* **1996**, 118, 636.
- (94) Saragoni, V. G.; Contreras, R. R.; Aizman, A. J. *Int. J. Quantum Chem.* **1993**, 48, 713.
- (95) Nunomoto, S.; Kawakami, Y.; Yamashita, Y.; Takeuchi, H.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 111.
- (96) Kaneti, J.; Kirby, A. J.; Koedjikov, A. H.; Pojarlieff, I. G. *Org. Biomol. Chem.* **2004**, 2, 1098.
- (97) Lee, B. H.; Miller, M. J. *J. Org. Chem.* **1983**, 48, 24.
- (98) Amssoms, K.; Augustyns, K.; Yamani, A.; Zhang, M.; Haemers, A. *Synth. Commun.* **2002**, 32, 319.
- (99) Wescott, L. D.; Mattern, D. L. *J. Org. Chem.* **2003**, 68, 10058.
- (100) Chang, D.; Feiten, H.-J.; Engesser, K.-H.; Beilen, J. B. van; Witholt, B.; Li, Z. *Org. Lett.* **2002**, 4, 1859.
- (101) Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, 89, 4400.
- (102) Cavill, J. L.; Elliott, R. L.; Evans, G.; Jones, I. L.; Platts, J. A.; Ruda, A. M.; Tomkinson, N. C. O. *Tetrahedron* **2006**, 62, 410.
- (103) Yamabe, H.; Kato, H.; Yonezawa, T. *Bull. Chem. Soc. Jpn.* **1971**, 44, 22.
- (104) Godin, G.; Compain, P.; Martin, O. R. *Synlett* **2003**, 2065.
- (105) Bandlish, B.; Garner, A.; Hodges, M.; Timberlake, J. *J. Am. Chem. Soc.* **1975**, 97, 5856.
- (106) Sparrow, D.; Groszos, S.; Cohen, S. *J. Am. Chem. Soc.* **1950**, 72, 3947.

- (107) Ratcliff, M. A.; Kochi, J. K. *J. Org. Chem.* **1972**, *37*, 3268.
- (108) Hodgson, D. M.; Stefane, B.; Miles, T. J.; Witherington, J. *J. Org. Chem.* **2006**, *71*, 8510.
- (109) Bartmann, E. A. *Synthesis* **1993**, 490.
- (110) Shyam, K.; Penketh, P. G.; Divo, A. A.; Loomis, R. H.; Patton, C. L.; Sartorelli, A. C. *J. Med. Chem.* **1990**, *33*, 2259.
- (111) Hrubiec, R. T.; Shyam, K.; Cosby, L. A.; Furubayashi, R.; Sartorelli, A. C. *J. Med. Chem.* **1986**, *29*, 1299.
- (112) Sun, P.; Weinreb, S. M.; Shang, M. *J. Med. Chem.* **1997**, *62*, 8604.
- (113) Dios, A. de; Shih, C.; López De Uralde, B.; Sánchez, C.; Prado, M. del; Martín Cabrejas, L. M.; Pleite, S.; Blanco-Urgoiti, J.; Lorite, M. J.; Nevill, C. R.; Bonjouklian, R.; York, J.; Vieth, M.; Wang, Y.; Magnus, N.; Campbell, R. M.; Anderson, B. D.; McCann, D. J.; Giera, D. D.; Lee, P. A.; Schultz, R. M.; Li, L. C.; Johnson, L. M.; Wolos, J. A. *J. Med. Chem.* **2005**, *48*, 2270.
- (114) Cahn, J. W.; Powell, R. E. *J. Am. Chem. Soc.* **1954**, *76*, 2565.
- (115) Rayson, M. S.; Altarawneh, M.; Mackie, J. C.; Kennedy, E. M.; Dlugogorski, B. *Z. J. Phys. Chem. A* **2010**, *114*, 2597.
- (116) Chattaway, F. D. *J. Chem. Soc.* **1905**, 87, 381.
- (117) Jackson, L. K.; Smart, G. N. R.; Wright, G. F. *J. Am. Chem. Soc.* **1947**, *69*, 1539.
- (118) Shevtsov, A. V.; Kislukhin, A. A.; Kuznetsov, V. V.; Petukhova, V. Y.; Maslennikov, V. A.; Borissova, A. O.; Lyssenko, K. A.; Makhova, N. N. *Mendeleev Commun.* **2007**, *17*, 119.
- (119) Mintz, M. J.; Walling, C. *Org. Synth.* **1969**, *49*, 9.

- (120) Schmitz, E. *Angew. Chem., Int. Ed.* **1964**, 3, 333.
- (121) Shustov, G.; Denisenko, S.; Chervin, I.; Asfandiarov, N.; Kostyanovsky, R. *Tetrahedron*. **1985**, 41, 5719.
- (122) Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, 107, 1862.
- (123) Bull, S. D.; Davies, S. G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D.; Fenton, G. *Chem. Commun.* **2000**, 337.
- (124) Brady, O. L.; Elsmie, G. V. *Analyst* **1926**, 51, 77.
- (125) Roa, G. P.; Murthy, A. R. V. *J. Phys. Chem.* **1964**, 68, 1573.
- (126) Gaunt, M. J.; Boschetti, C. E.; Yu, J.; Spencer, J. B. *Tetrahedron Lett.* **1999**, 40, 1803.
- (127) Xia, J.; Abbas, S. A.; Locke, R. D.; Piskorz, C. F.; Alderfer, J. L.; Matta, K. L. *Tetrahedron Lett.* **2000**, 41, 169.
- (128) Pomerantz, M.; Chou, W.-N.; Witczak, M. K.; Smith, C. G. *J. Org. Chem.* **1987**, 52, 159.
- (129) Chen, L.; Shi, M.; Li, C. *Org. Lett.* **2008**, 10, 5285.
- (130) Fang, Y.; Li, C. *J. Am. Chem. Soc.* **2007**, 129, 8092.
- (131) Zhao, Q.; Li, L.; Fang, Y.; Sun, D.; Li, C. *J. Org. Chem.* **2009**, 74, 459.
- (132) Zhao, Q.; Li, C. *Org. Lett.* **2008**, 10, 4037.
- (133) Lu, H.; Li, C. *Org. Lett.* **2006**, 8, 5365.
- (134) Martín, R.; Rodríguez R. M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, 45, 7079.

- (135) Rivero, M. R.; Buchwald, S. L. *Org. Lett.* **2007**, 9, 973.
- (136) Uemura, T.; Chatani, N. *J. Org. Chem.* **2005**, 70, 8631.
- (137) Yamashita, Y.; Ishitani, H.; Kobayashi, S. *J. Can. Chem.* **2000**, 78, 666.
- (138) Brosse, N.; Pinto, M.-F.; Jamart-Grégoire, B. *J. Org. Chem.* **2000**, 65, 4370.
- (139) Brosse, N.; Pinto, M. F.; Bodiguel, J.; Jamart-Grégoire, B. *J. Org. Chem.* **2001**, 66, 2869.
- (140) Sammes, P. G.; Smith, S. *J. Chem. Soc., Chem. Commun.* **1983**, 682.
- (141) Dow, R. L.; Kelly, R. C.; Schletter, I.; Wierenga, W. *Synth. Commun.* **1981**, 11, 43.
- (142) Irifune, S.; Kibayashi, T.; Ishii, Y.; Ogawa, M. *Synthesis* **1988**, 366.
- (143) Larson, S.; Luidhardt, T.; Kabalka, G.; Pagni, R. *Tetrahedron Lett.* **1988**, 29, 35.
- (144) Myers, A. G.; Alauddin, M. M.; Fuhry, M. A. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett.* **1989**, 4, 6997.
- (145) Bellina, F.; Carpita, A.; Santis, M. D.; Rossi, R. *Tetrahedron Lett.* **1994**, 35, 6913.
- (146) Bowman, W. R.; Bridge, C. F.; Brookes, P.; Cloonan, M. O.; Leach, D. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 58.
- (147) Lemay, A. B.; Vulic, K. S.; Ogilvie, W. W. *J. Org. Chem.* **2006**, 71, 3615.
- (148) Kim, K.-M.; Park, I.-H. *Synthesis* **2004**, 2641.
- (149) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, 103, 5454.
- (150) Nishikawa, T.; Kajii, S.; Isobe, M. *Chem. Lett.* **2004**, 33, 440.

- (151) Cesati, R. R.; Dwyer, G.; Jones, R. C.; Hayes, M. P.; Yalamanchili, P.; Casebier, D. S. *Org. Lett.* **2007**, *9*, 5617.
- (152) Toumi, M.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 572.
- (153) Vintonyak, V. V.; Calà, M.; Lay, F.; Kunze, B.; Sasse, F.; Maier, M. E. *Chem.–Eur. J.* **2008**, *14*, 3709.
- (154) Asakawa, K.; Noguchi, N.; Takashima, S.; Nakada, M. *Tetrahedron: Asymmetry* **2008**, *19*, 2304.
- (155) Lu, H.; Yuan, X.; Zhu, S.; Sun, C.; Li, C. *J. Org. Chem.* **2008**, *73*, 8665.
- (156) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529.
- (157) Qin, H.-L.; Panek, J. S. *Org. Lett.* **2008**, *10*, 2477.
- (158) Brown, M. J.; Clarkson, G. J.; Fox, D. J.; Inglis, G. G.; Shipman, M. *Tetrahedron Lett.* **2010**, *51*, 382-384.
- (159) Ojala, C.; Ojala, W.; Gleason, W. *Acta Crystallogr.* **1998**, *C54*, 60.
- (160) Linke, K.-H.; Kalker, H. G. *Z. Anorg. Allg. Chem.* **1977**, *434*, 165.
- (161) Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169.
- (162) Yamada, S. *Angew. Chem., Int. Ed.* **1993**, *32*, 1083.
- (163) Çavdar, H.; Saraçologlu, N. *Tetrahedron* **2005**, *61*, 2401.
- (164) Szeimies, G. *Tetrahedron Lett.* **1970**, *11*, 1949.
- (165) Jennings, W. B.; Boyd, D. R. In *Cyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takechi, Y., Eds.; VCH: Cambridge, 1992; pp 105-158.

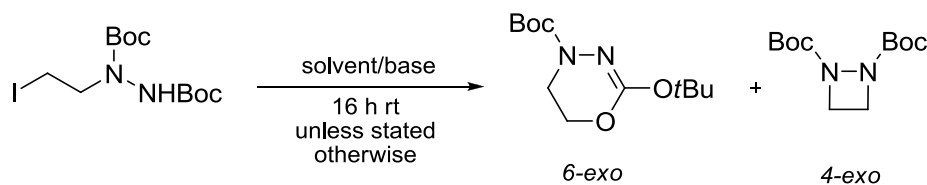
- (166) Lambert, J. B.; Packard, B. S.; Oliver, W. L. *J. Org. Chem.* **1971**, 36, 1309.
- (167) Nielsen, I. M. B. *J. Phys. Chem. A* **1998**, 102, 3193.
- (168) Reich, H. J.; Sanders, A. W.; Fiedler, A. T.; Bevan, M. J. *J. Am. Chem. Soc.* **2002**, 124, 13386.
- (169) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, 65, 385.
- (170) Glaze, W. H.; Adams, G. M. *J. Am. Chem. Soc.* **1966**, 88, 4653.
- (171) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, 110, 8145.
- (172) Quast, H.; Vélez, C. A. W. *Angew. Chem., Int. Ed.* **1974**, 13, 342.
- (173) Hodgson, D. M.; Kloesges, J. *Angew. Chem., Int. Ed.* **2010**, 49, 2900.
- (174) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, 44, 581.
- (175) Heck, R.; Nolley Jr, J. *J. Org. Chem.* **1972**, 37, 2320.
- (176) Jeffery, T. *Tetrahedron*. **1996**, 52, 10113.
- (177) Gürtler, C.; Buchwald, S. L. *Chem.–Eur. J.* **1999**, 5, 3107.
- (178) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, 37, 3387.
- (179) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, 123, 6989.
- (180) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, 123, 2719.
- (181) Fu, G. C. *Acc. Chem. Res.* **2008**, 41, 1555.
- (182) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, 3, 4295.
- (183) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, 52, 4130.

- (184) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
- (185) Belderrain, T. R.; Grubbs, R. H. *Organometallics* **1997**, *16*, 4001.
- (186) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
- (187) Liang, Y.; Raju, R.; Le, T.; Taylor, C.; Howell, A. *Tetrahedron Lett.* **2009**, *50*, 1020.
- (188) Raju, R.; Howell, A. R. *Org. Lett.* **2006**, *8*, 2139.
- (189) Kotha, S. *Tetrahedron* **2002**, *58*, 9633.
- (190) Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91.
- (191) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323.
- (192) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 113.
- (193) Enders, D.; Wiedemann, J. *Synthesis* **1996**, 1443.
- (194) Rajadhyaksha, R. A.; Karwa, S. L. *Chem. Eng. Sci.* **1986**, *41*, 1765.
- (195) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.
- (196) Brown, M. J.; Clarkson, G. J.; Inglis, G. G.; Shipman, M. *Org. Lett.* [Online early access]. DOI: 10.1021/ol200193n. Published Online: Mar 2, 2011.
- (197) Tiers, G. V. D. *J. Chem. Educ.* **1990**, *67*, 258.
- (198) Spivak, D.; Shea, K. J. *J. Org. Chem.* **1999**, *64*, 4627.
- (199) Choppin, A.; Rogers, J. W. *J. Am. Chem. Soc.* **1948**, *70*, 2967.
- (200) Jacobi, P. A.; Li, Y. *Org. Lett.* **2003**, *5*, 701.

(201) Bennani, Y. L.; Hanessian, S. *Tetrahedron* **1996**, 52, 13837.

APPENDIX

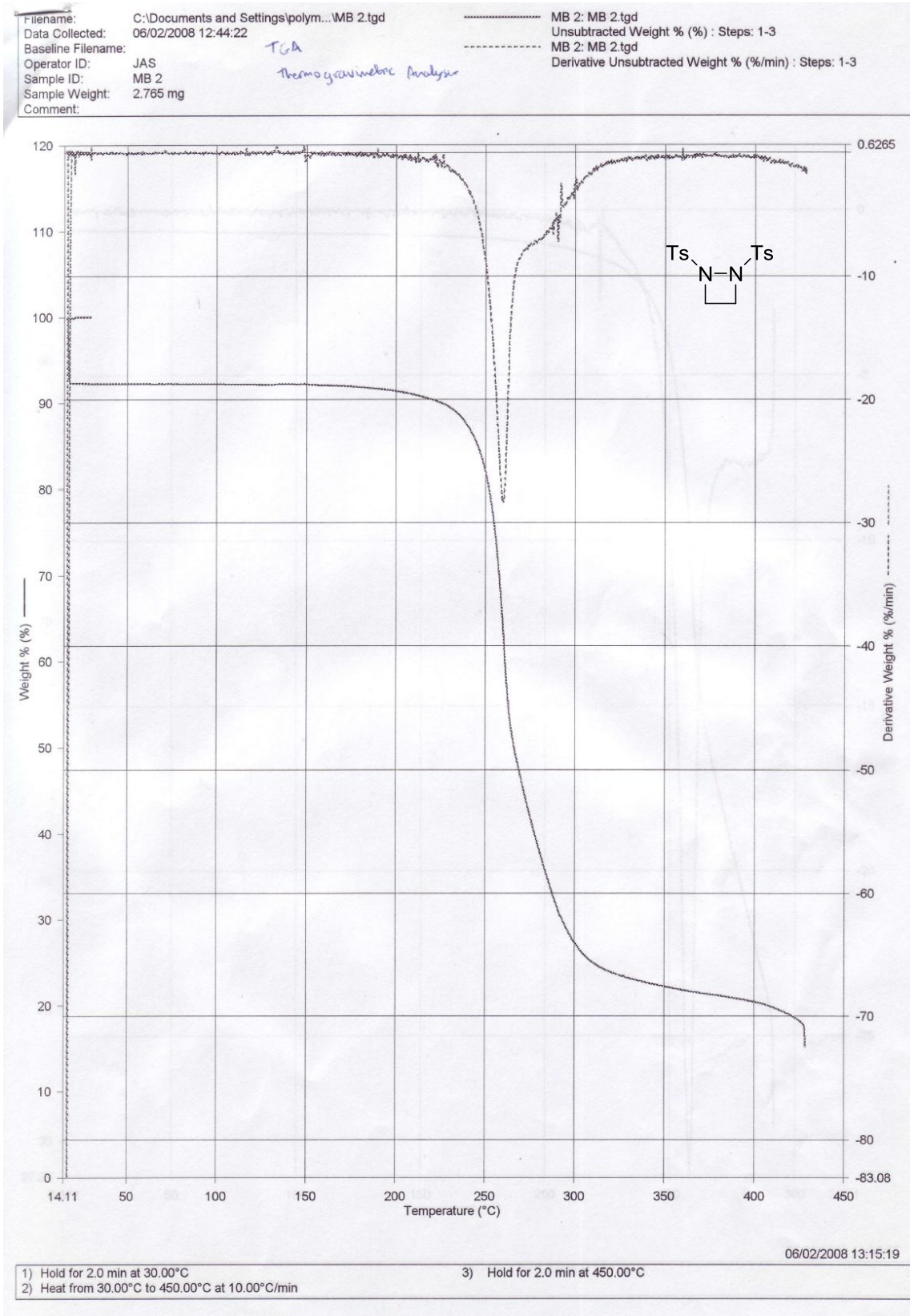
I Solvent/Base Studies



entry		base	solvent	sm : 6- <i>exo</i> : 4- <i>exo</i> : other ^a				6- <i>exo</i> : 4- <i>exo</i> ^a	
1	8 eq	Cs ₂ CO ₃	CH ₃ CN	0	46	54	-	46	: 54
2	3 eq	Cs ₂ CO ₃	CH ₃ CN	0	45	55	-	45	: 55
3	1 eq	Cs ₂ CO ₃	CH ₃ CN	trace	43	57	-	43	: 57
4	1.5 eq	Cs ₂ CO ₃	CH ₃ CN: H ₂ O (7:1)	~100	trace	trace	-	-	: -
5	1.5 eq	Cs ₂ CO ₃	CH ₃ CN: MeOH (7:1)	0	52	47	-	52	: 47
6	8 eq	Cs ₂ CO ₃	MeOH	0	86	0	14	100	: 0
7	8 eq	Cs ₂ CO ₃	acetone	42	32	26	-	55	: 44
8	8 eq	Cs ₂ CO ₃	DCM	36	36	29	-	55	: 44
9	8 eq	Li ₂ CO ₃	CH ₃ CN	~100	trace	trace	-	-	: -
10	1.4 eq	<i>sec</i> -BuLi	THF, -78 °C to rt, 3 h	0	72	0	28	100	: 0
11	1.7 eq	KOtBu	THF, 0 °C to rt, 3 h	trace	72	5	23	93	: 7
12	1.7 eq	KOtBu	CH ₃ CN, 0 °C to rt, 3 h	0	69	9	22	89	: 11
13	1.2 eq	NaOtBu	THF, 0 °C to rt, 3 h	0	94	6	-	94	: 6
14	8 eq	DBU	CH ₃ CN	0	45	55	-	45	: 55
15	8 eq	TBD	CH ₃ CN	22	39	39	-	50	: 50
16	8 eq	TMG	CH ₃ CN	31	21	28	21	43	: 57

Table I.I. ^a Determined by ¹H NMR analysis of the crude reaction mixture; sm = starting material.

II Thermogravimetric Analysis of 53



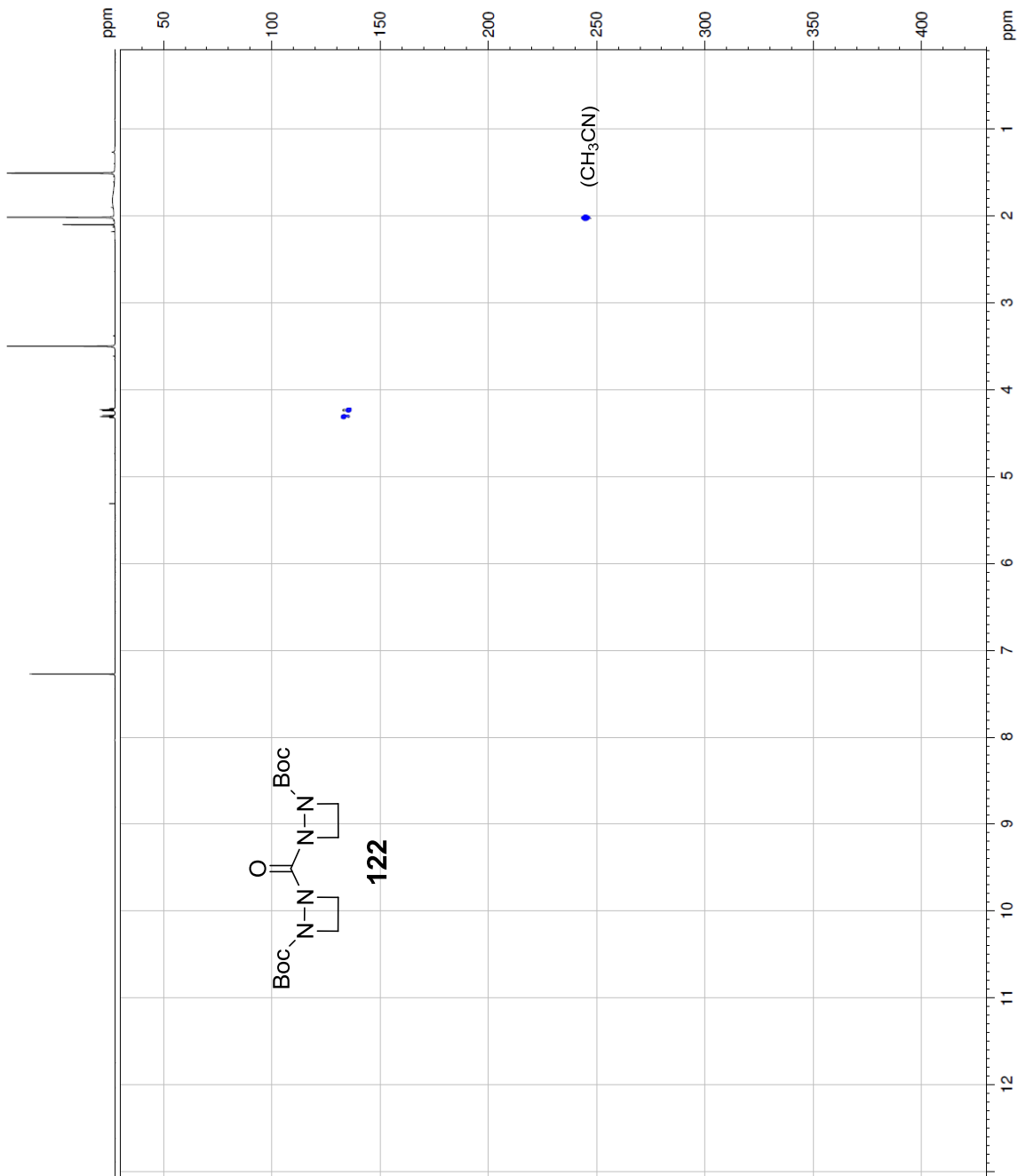
III ^{15}N HMBC of 122

PT3989
R18701-4-3
mb664548
7198
0
15N HMBC
CDCI3
Brown, Mike 2

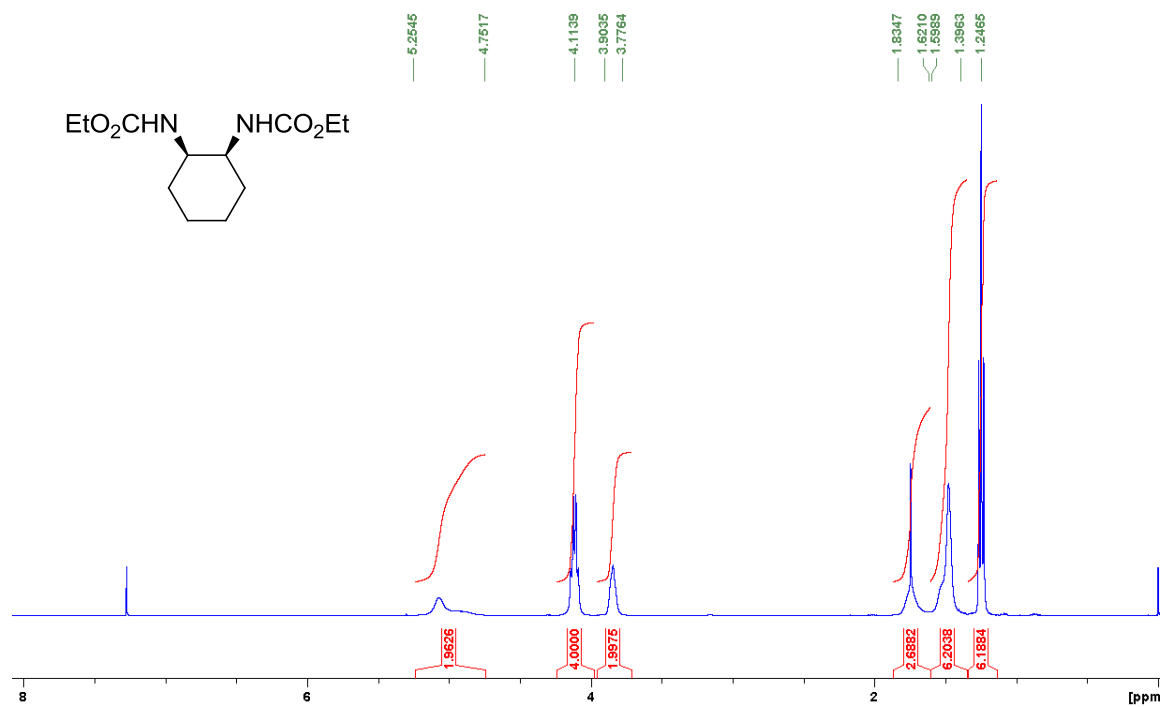
[illegible]

Analytical Chemistry MDR
Stevenage

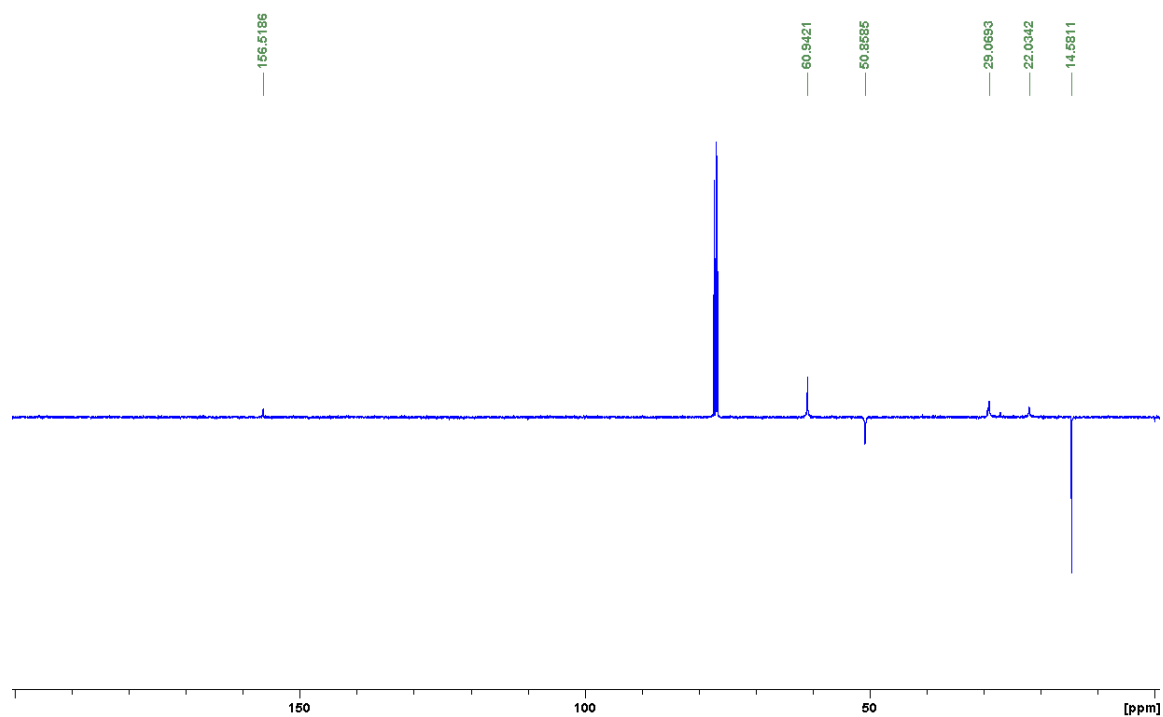
 GlaxoSmithKline



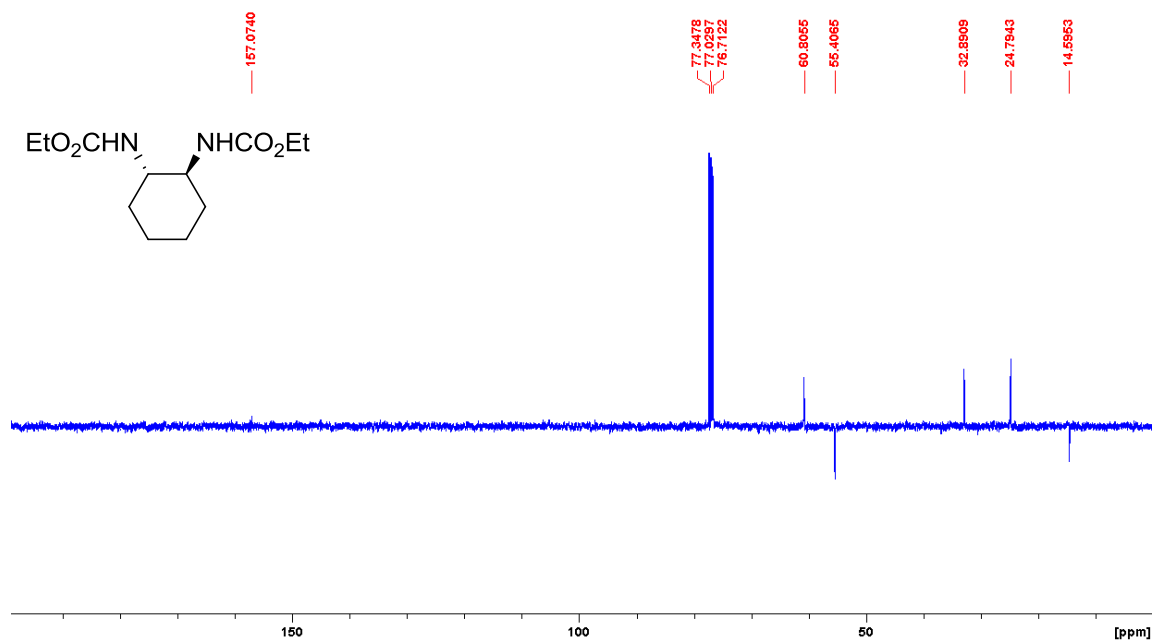
IV Stereochemical Assignment of Diamine 144



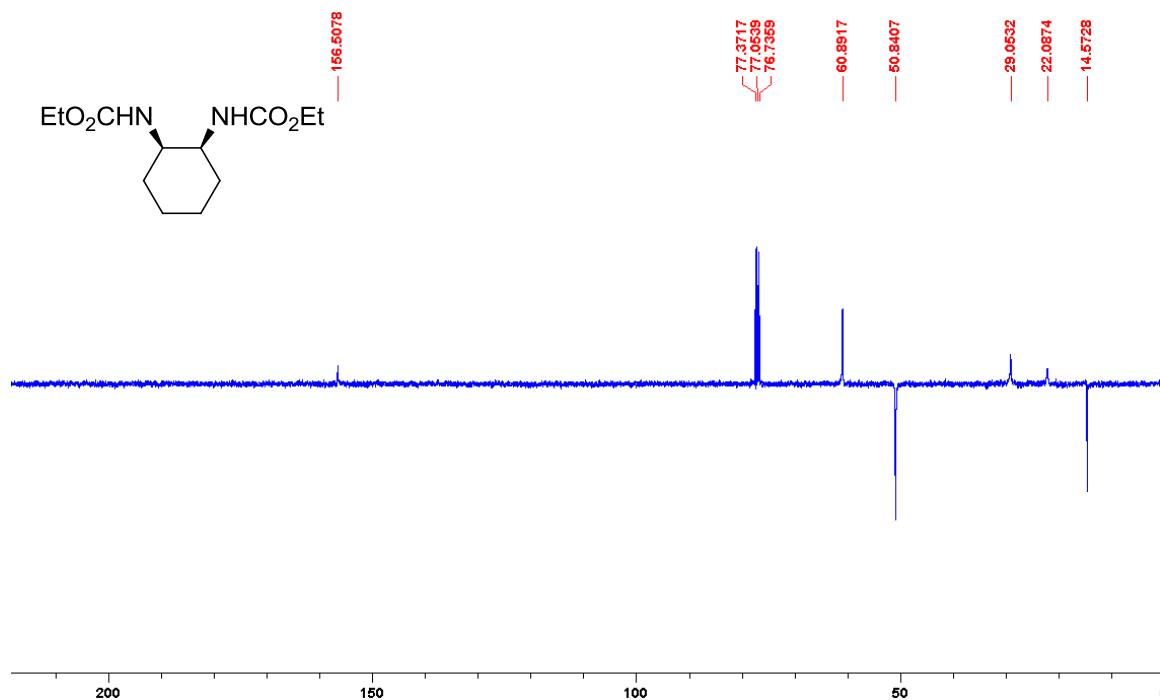
144 ¹H NMR (400 MHz, CDCl₃)



144 ¹³C NMR (125 MHz, CDCl₃)



(1*S*,2*S*)-**144** (from diamine) ¹³C NMR (100 MHz, CDCl₃)



(1*R**,2*S**)-**144** (from diamine) ¹³C NMR (100 MHz, CDCl₃)