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Synthesis of 1,2-Diamines using Nitrogen-Containing Heterocyclic Templates

by

Greg Iacobini

A thesis submitted in partial fulfillment of the requirements
For the degree of Doctor of Philosophy in Chemistry

Department of Chemistry, University of Warwick

July 2012
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Last and by no means least, I want to thank my parents, Pam and Paul, as I never would have made it this far without their encouragement and support.
Declaration

Except where indicated, the work reported in this thesis is an account of my own independent research at the University of Warwick and at Novartis, Horsham, carried out between October 2007 and October 2010. I certify that no material within this thesis has been submitted for a prior degree or a degree at another university.

Signed:

Date:
Abstract

This thesis describes the development of new methods for the synthesis of 1,2-diamines. Chapter one reviews current methods for the synthesis of 1,2-diamines, and their importance in chemistry. Chapter two highlights attempts to synthesise 1,2-diamines using two nitrogen-containing heterocycles, namely 3-phenyl-1,3,5-triazabicyclo[3.2.0]hept-6-ene-2,4-dione and imidazolin-2-one, which both contain an endocyclic double bond. It includes the synthesis of a novel 1,2-diazetine as well as the functionalisation of imidazolin-2-one via a palladium-catalysed cross-coupling reaction with phenyl iodide. Subsequent hydrogenation and hydrolysis was then utilised to afford 1-phenylethane-1,2-diamine dihydrochloride. Chapter three describes the synthesis and functionalisation of a range of 3-methylene-1,2-diazetidines that were subsequently hydrogenated in an asymmetric fashion, with [Rh(NBD)$_2$]BF$_4$ and ligand Mandyphos M004-1, to yield 1,2-diazetidines with up to 89% ee. Reduction with LiDBB allowed for the synthesis of two carbamate-protected 1,2-diamines in three steps. The first examples of epoxidation, reaction with tetracyanoethylene and 1,3-dipolar cycloadditions of 3-methylene-1,2-diazetidines are reported. Chapter four details the experimental procedures and characterisation data for the novel compounds produced.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td><em>azo-bis</em>-Isobutyronitrile</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1′-Bi-2-naphthol</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>cat.</td>
<td>Catalytic</td>
</tr>
<tr>
<td>Cbz</td>
<td>Carbobenzyloxy</td>
</tr>
<tr>
<td>CPME</td>
<td>Cyclopentyl methyl ether</td>
</tr>
<tr>
<td>COD</td>
<td>Cyclooctadiene</td>
</tr>
<tr>
<td>conc.</td>
<td>Concentrated</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation Spectroscopy</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-Diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylidine acetone</td>
</tr>
<tr>
<td>DBB</td>
<td>4,4′-Di-tert-butylbiphenyl</td>
</tr>
<tr>
<td>DBU</td>
<td>1,3-Diazabicyclo[5.4.0]undecane</td>
</tr>
<tr>
<td>de</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Di-iso-butylaluminium hydride</td>
</tr>
<tr>
<td>DMAc</td>
<td>Dimethylacetamide</td>
</tr>
<tr>
<td>DMAP</td>
<td>Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMDO</td>
<td>Dimethylidioxirane</td>
</tr>
<tr>
<td>DMEDA</td>
<td><em>N,N</em>-Dimethylethlenediamine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier Transform</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond Coherence</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear Multiple Quantum Coherence</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectroscopy</td>
</tr>
<tr>
<td>IPA</td>
<td>Isopropyl alcohol</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>lit.</td>
<td>Literature value</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>mol.</td>
<td>Molar</td>
</tr>
<tr>
<td>M.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>Mesyl</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>PMP</td>
<td>para-Methoxyphenyl</td>
</tr>
<tr>
<td>rt</td>
<td>Retention time</td>
</tr>
<tr>
<td>TCNE</td>
<td>Tetracyanoethylene</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Temp.</td>
<td>Temperature</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>tlc</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Tetramethysilane</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>TMEDA</td>
<td>Tetramethylethylenediamine</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra violet</td>
</tr>
</tbody>
</table>
Chapter 1:

Introduction to 1,2-Diamines
1.1 Introduction

This thesis describes the development of new synthetic routes to 1,2-diamines. The 1,2-diamine moiety 1 consists of 2 vicinal amino groups on a carbon backbone (Figure 1.1). It is therefore appropriate to discuss the importance of this class of compounds in various areas of science, as well as discussing current methods for their synthesis. A number of excellent reviews describing this topic have been published.\textsuperscript{1-5} We highlight work of most relevance to our studies in this chapter.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{1,2-diamine}
\end{figure}

1.2 1,2-Diamines in Natural Products

1,2-Diamines are found in a wide range of natural products, many of which have important biological functions.\textsuperscript{2} For example, Biotin (vitamin H) 2 is an essential cofactor to carboxylase-catalysed reactions; it contains the 1,2-diamino moiety within an imidazolidinone ring (Figure 1.2).\textsuperscript{6}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure2.png}
\caption{Biotin}
\end{figure}
Penicillin 3, the well-known family of antibiotics, contains a 2,3-diamino carboxylic acid unit within the penam skeleton (Figure 1.3).

![Penicillin 3](image)

**Figure 1.3**

A similar motif is found in other β-lactam antibiotics such as Cephalosporin A 4 and the monobactam Aztreonam 5 (Figure 1.4).

![Cephalosporin A 4](image)

![Aztreonam 5](image)

**Figure 1.4**

Many natural products, in particular non-ribosomal peptides, possess a diamino carboxylate substructure. These can be found within several families of antibiotics including edeines and tuberactomycin derivatives. Vicinal diamines
are also found within a number of alkaloids, known for their toxic properties, such as mimosine 6 and slaframine 7 (Figure 1.5).9,10

![Mimosine and Slaframine](image)

**Figure 1.5**

### 1.3 1,2-Diamines in Medicinal Chemistry

In addition to natural products, many synthetic compounds containing the 1,2-diamine functionality have been used for medicinal purposes including antiarrhythmics and anticancer drugs.11-13 This section will highlight some important examples.

Cisplatin 8 was found to have anticancer properties by Rosenberg in the 1960s.14 Since this discovery there has been a great deal of interest in developing diamine-platinum complexes that possess greater activity and fewer side effects than Cisplatin, as well as overcome drug resistance that can develop in certain tumours. There are currently several diamine-platinum medicines on the market, including heptaplatin 9 and oxaliplatin 10 (Figure 1.6).15,16
Ethlenediaminetetraacetic acid (EDTA) 11 is a synthetic 1,2-diamine that has found use both within industry and medicine due to its ability to bind to metal ions. It is commonly used in chelation therapy for the removal of excess iron in the body as well as for conditions such as mercury and lead poisoning (Figure 1.7).\textsuperscript{17}

The quinolones are a family of synthetic broad-spectrum antibiotics, a number of which contain vicinal diamines within heterocyclic substituents.\textsuperscript{18} Examples include Lomefloxacin 12, used for the treatment of bronchitis and urinary tract infections, and Moxifloxacin 13, which can be used to treat a number of infections such as bacterial pneumonia and meningitis (Figure 1.8).\textsuperscript{19,20}

\begin{figure}[h]
\centering
\includegraphics[width=0.7\textwidth]{chemical_structures.png}
\caption{Chemical structures of Cisplatin, Heptaplatin, and Oxaliplatin.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{edta.png}
\caption{Structure of Ethlenediaminetetraacetic acid (EDTA).}
\end{figure}
Cyclic 1,2-diamines form key parts of the antiviral drugs Oseltamivir (Tamiflu™) 14 and Zanamivir (Relenza™) 15. Both have been used extensively against influenza A and B viruses (Figure 1.9). 21,22

In 2009 Yao et al. identified a number of 1,2-diamines, such as 16, that possess potent antituberculosis activity (Figure 1.10). 23 Tuberculosis remains one of the worlds most deadly infectious diseases and with the development of antibiotic-resistant strains, new medicines for its treatment are highly sought-after. 24
More recently Daelemans et al. have reported the inhibition of HIV-1 replication by bis-thiadiazolbenzene-1,2-diamine 17 (Figure 1.11). These results may aid the development of next generation treatments for HIV.  

1,2-Diamines are an important class of compounds within organic synthesis, not only as intermediates towards other compounds but also as ligands, chiral auxiliaries and catalysts.  

1,4-Diazabicyclo[2.2.2]octane (DABCO, 18) has been used extensively as a base, as well as a catalyst for the Baylis-Hillman reaction and polyurethane production. In addition, compounds such as tetramethylethylenediamine (TMEDA, 19) are frequently used as additives in reactions to stabilise inorganic salts and organometallic reagents (Figure 1.12).
This section will highlight some of the various different applications that 1,2-diamines have been used for within synthetic chemistry.

### 1.4.1 1,2-Diamines as chiral auxiliaries and resolving agents

Chiral auxiliaries are used for incorporating temporary chirality into an otherwise achiral molecule, thus allowing asymmetric reactions to be carried out.\(^\text{29}\) Since the introduction of chiral auxiliaries there has been much development in the area and in a number of cases, the 1,2-diamine moiety is present within the auxiliary.\(^\text{1}\) For example, Hanessian et al. have demonstrated the use of chiral phosphonamide \(21\), derived from 1,2-diamine \(20\), as a chiral auxiliary for the synthesis of \(22\) in excellent yield and enantioselectivity (Scheme 1.1).\(^\text{30}\)

\[
\text{NHMe} \quad \text{Cl}_2\text{P(O)CH}_2\text{Ph} \quad \text{NHMe} \\
\begin{array}{c}
20 \\
\end{array} \quad \begin{array}{c}
21 \\
\end{array} \quad \begin{array}{c}
22 \\
\end{array}
\]

91%, >98% ee

Scheme 1.1

Mangeney et al. have shown that symmetrical 1,2-diamines such as \(23\) can act as simple but effective resolving agents for chiral aldehydes \(24\).\(^{31-33}\) Aminal
intermediates 25 offer a number of advantages over acetal analogues; no catalyst is required for their formation and they show excellent selectivity for aldehydes over ketones (Scheme 1.2).

![Scheme 1.2](image)

An alternative approach to resolve racemic compounds has been developed via the protonation of prochiral lithium enolates. For example, Vedejs and Lee have reported the use of chiral 1,2-diamines 26 for the enantioselective protonation of the amide enolate derived from amide 27 (Scheme 1.3).34

![Scheme 1.3](image)

**1.4.2 1,2-Diamines as chiral ligands**

There has been an extensive amount of research into the use of chiral 1,2-diamine ligands for the stereoselective addition of organometallic reagents to aldehydes and ketones.35-38 Knochel et al. have demonstrated this with the
addition of dialkylzinc reagents to aldehydes 28 in the presence of Ti(O\textsuperscript{i}Pr\textsubscript{4}} and disulfonamide 29 to give excellent enantioselectivities of the resulting secondary alcohols 30 (Scheme 1.4).\textsuperscript{39}

![Reaction Scheme 1.4]

**Scheme 1.4**

In 1986, Koga and Simpkins first described independently the use of chiral lithium amide bases to stereoselectively deprotonate ketones.\textsuperscript{40,41} Many of the best chiral bases are derived from 1,2-diamines, including several of those first reported by Koga. For example, achiral cyclohexanone 31 can be preferentially deprotonated with 32 to form enolate 33, from one side over the other due to the asymmetry imparted by the base. In this way, silyl enol ether 34 can be formed in moderate to good enantioselectivity (Scheme 1.5).\textsuperscript{42}

![Reaction Scheme 1.5]

**Scheme 1.5**
The stereoselective addition of organolithium compounds to imines 35 in the presence of chiral 1,2-diamine 36 to yield enantiomerically enriched amines 37 has been reported by Cabello et al. (Scheme 1.6).  

\[
\begin{array}{c}
\text{35} \\
\text{36 (20 mol%), } 2\text{RLi, PhH} \\
\text{-78 °C, 2-72 h} \\
\text{yield = 70-99%} \\
\text{ee = 90-94%}
\end{array}
\]

\[
\begin{array}{c}
\text{36} \\
\text{Me}_2\text{N} \\
\text{Ph} \\
\text{NMe}_2
\end{array}
\]

Scheme 1.6

Corey and co-workers described the use of aluminium Lewis acid catalyst 38, based upon a chiral 1,2-diamine scaffold, for stereoselective Diels-Alder reactions.  

\[
\begin{array}{c}
\text{42 (10 mol%), CH}_2\text{Cl}_2 \\
\text{-78-25 °C, 16-84 h} \\
\text{yield = 83-99%} \\
\text{endo:exo = 55:45-95:5} \\
\text{endo ee = 0-94%}
\end{array}
\]

Scheme 1.7
More recently, Evans et al. have demonstrated the use of a [Cu^{II}(salen)] complex as stereoselective catalyst 42 for Diels-Alder reactions. The cycloaddition of 43 and cyclopentadiene in the presence of 42 affords 44 in excellent yields and varying enantioselectivity (Scheme 1.8).\textsuperscript{47}

\begin{equation*}
\begin{array}{c}
\text{43} \\
R = \text{H, Me, Ph, CO}_2\text{Et} \\
X = \text{O, S}
\end{array}
\end{equation*}

\begin{equation*}
\begin{array}{c}
\text{42 (10 mol%), CH}_2\text{Cl}_2 \\
\text{―78-25 °C, 16-84 h} \\
\text{yield = 83-99%} \\
\text{endo:exo = 55:45-95:5} \\
\text{endo ee = 0-94%}
\end{array}
\end{equation*}

\begin{equation*}
\begin{array}{c}
\text{44}
\end{array}
\end{equation*}

\textbf{Scheme 1.8}

Jacobsen et al. have reported the use of similar types of salen ligands, such as 45, for the enantioselective copper-catalysed aziridination of unfunctionalised alkenes 46 to yield a variety of enatiomerically enriched aziridines 47-49 (Scheme 1.9).\textsuperscript{48}
Asymmetric hydrogenation is arguably one of the most important and widely used enantioselective reactions.\textsuperscript{49,50} In particular, asymmetric transfer hydrogenation reactions have received much attention in recent years.\textsuperscript{51} Transfer hydrogenations rely on a source of hydrogen such as formic acid or IPA, which in the presence of a transition metal catalyst can hydrogenate unsaturated functional groups such as imines and ketones. Noyori has demonstrated how ruthenium catalysts with chiral 1,2-diamine ligands, such as \textbf{50}, can reduce a wide range of ketones \textbf{51} to the corresponding alcohols \textbf{52} with excellent enantioselectivities (Scheme 1.10).\textsuperscript{52}
Scheme 1.10

In 2010 Du et al. were successful in coupling cyclic enones 53 with aryl boronic acids to furnish 54 in moderate to excellent enantioselectivity using a rhodium-based catalyst and chiral diamine 55 as a ligand (Scheme 1.11).53

Scheme 1.11

More recently, Wan et al. have utilised 1,2-diamine 56 as a ligand for a copper-catalysed asymmetric Friedel-Crafts alkylation of indoles 57 with nitroalkenes 58 to give substituted indoles 59 with excellent yields and enantioselectivities (Scheme 1.12).54
**Scheme 1.12**

1.4.3 1,2-Diamines as organocatalysts

In recent years there have been many reports of reactions that utilise 1,2-diamines as catalysts themselves. For example, Pansare and Pandya have demonstrated that proline-derived 1,2-diamine 60 is capable of catalysing the asymmetric Michael addition of cyclic ketones 61 to nitroalkenes 62 to yield 63 with excellent enantioselectivities (Scheme 1.13).

**Scheme 1.13**

The asymmetric catalysis of cycloadditions with 1,2-diamines have also been developed. For example Chen and co-workers have reported organocatalyst 64,
derived from 1,2-diamino cyclohexane, that catalyses the 1,3-dipolar cycloaddition of nitrones 65 and nitroalkenes 66 to form isoxazolidines 67, with good enantioselectivity and excellent diastereoselectivity (Scheme 1.14).  

![Scheme 1.14](image)

In 2010, Lei and co-workers described the use of N,N'-dimethylethlenediamine (DMEDA 68) as a catalyst to promote C-H arylation of unactivated benzene with aryl iodides 69. The mechanism is believed to involve an aryl radical anion intermediate and offers considerable scope for coupling reactions of substrates that are sensitive to transition metal-based catalysts (Scheme 1.15).

![Scheme 1.15](image)
1.5 Current Routes to 1,2-Diamines

Since 1,2-diamines have important applications in many areas of chemistry, there is considerable interest in developing new, efficient methods for their synthesis. In particular, pathways that will yield enantiomerically pure 1,2-diamines are much sought after. Currently, there are a variety of different methods available for the synthesis of 1,2-diamines described in the literature; however, each approach usually has some limitations. A number of different synthetic routes have been employed such as the diamination of alkenes, the ring opening of aziridines and imine coupling (Scheme 1.16). This section will outline some of the most important methods that have been applied in the synthesis of 1,2 diamines in recent years.

Scheme 1.16
1.5.1 Diamination of alkenes

The direct addition of two nitrogen atoms across an olefin can be considered to be one of the most attractive routes for the synthesis of 1,2-diamines. However, unlike the analogous dihydroxylation reaction, which has enjoyed much success, the diamination of alkenes has received relatively little attention.59

In 1974, Barluenga and co-workers reported the diamination of olefins 71 to 1,2-diamines 72 using thallium (III) acetate. This process is limited to aryl amines and possesses no enantioselectivity or diastereoselectivity. In addition, thallium salts are known to be highly toxic and their use in large quantities is undesirable (Scheme 1.17).60

Scheme 1.17

A few years later Sharpless and co-workers developed a synthetic route to 1,2-diamines 75 via reaction of triimidoosmium 73 with monosubstituted and disubstituted E-olefins 74.61 The reagent undergoes a stereospecific addition to the alkenes to give cis 1,2-diamines as the major products. This synthesis requires a stoichiometric equivalent of 73, which must be prepared from the costly and highly toxic OsO₄. In addition, this synthesis is only compatible with E-alkenes and no absolute stereochemical control is possible (Scheme 1.18).
In 2001, Li and co-workers reported the catalysed diamination of enones 76. This was achieved in the presence of a rhodium catalyst and offers good diastereomeric control. The resulting heterocycles 77 have been shown to undergo hydrolysis (R = OMe) with hydrochloric acid to yield protected 1,2-diamine 78 (Scheme 1.19).\(^{62}\)

\[
\begin{align*}
\text{Scheme 1.18} \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 1.19} \\
\end{align*}
\]
Since Li’s findings there has been increased interest in the area and several groups have reported the enantioselective dination of olefins.\textsuperscript{63-66} For example, in 2007 Shi \textit{et al.} demonstrated the asymmetric dination of dienes 79 with di-\textit{tert}-butylaziridinone (80) using Pd$_2$(dba)$_3$ as a catalyst and BINOL-based ligand 81.\textsuperscript{67} This reaction affords a range of disubstituted imidazolidinones 82 which can be hydrolysed to 83 and finally to the corresponding 1,2-diamine 84 with excellent enantioselectivities (Scheme 1.20).

![Scheme 1.20](image)

\( R = \text{Alky, aryl, benzyl.} \)
More recently Muniz and co-workers have reported the use of chiral hypervalent iodine complex 85 for the diamination of styrene derivatives 86. This synthesis offers an efficient route to chiral mesyl 1,2-diamines 87 with perhaps the only drawbacks being stoichiometric quantities of 85 needed as well as the forcing conditions required for the removal of the mesyl protecting groups to afford 88 (Scheme 1.21).

\[
\begin{align*}
(R,R)-85 & \quad (S)-87 \\
\text{CH}_2\text{Cl}_2, \text{0 °C} & \\
\text{yield} = 44-75\% \quad \text{ee} = 55-99\%
\end{align*}
\]

\[
\begin{align*}
\text{R} = \text{H, alkyl, Cl, Br, F, CF}_3, \text{OAc, CO}_2\text{Me} & \\
\text{MeO}_2\text{C} & \quad \text{I(OAc)}_2 \\
\text{O} & \quad \text{CO}_2\text{Me} \\
(R,R)-85 & \\
\text{1. Red-Al, THF} & \\
\text{2. BzCl, NaH, THF} & \\
\text{3. Bu}_3\text{SnH, AIBN, PhH} & \\
\text{4. 6M HCl, dioxane} & \\
\text{110 °C, 77\% (R=H)} & \\
\text{(S)-88} & \quad \text{NH}_2 \quad \text{NH}_2 \quad \text{• 2HCl}
\end{align*}
\]

Scheme 1.21

1.5.2 1,2-Diamines from β-amino alcohols and 1,2-diols

The enantioselective syntheses of 1,2-diols and β-amino alcohols have received much attention and there are now a variety of effective methods available for their preparation. In addition, there are a number of optically active β-amino acids available from the chiral pool. As such, their use as intermediates for the synthesis of chiral 1,2-diamines offers an attractive, if sometimes lengthy, route.
Sharpless demonstrated the conversion of homochiral 1,2-diol 89 to the corresponding 1,2-diamine 92 by utilising azide substitution followed by catalytic hydrogenation. This method proceeds in overall modest yield, but with excellent enantioselectivity from an olefin, with the inclusion of a dihydroxylation reaction, this represents a four-step sequence. This synthesis is widely applicable, although clearly not very direct (Scheme 1.22).

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{OH} & \quad \text{OH} \\
89 & \quad \text{MsCl, pyridine} \\
& \quad 0^\circ\text{C, 23 h} \\
\text{Ph} & \quad \text{Ph} \\
\text{OMs} & \quad \text{OMs} \\
90 & \quad \text{NaN}_3, \text{DMF} \\
& \quad 90^\circ\text{C, 24 h} \\
\text{Ph} & \quad \text{Ph} \\
\text{NH}_2 & \quad \text{NH}_2 \\
92 & \quad \text{H}_2, \text{Pd/C, HCl} \\
& \quad \text{MeOH} \\
& \quad 58\% \text{ (3 steps)} \\
\text{Ph} & \quad \text{Ph} \\
\text{N}_3 & \quad \text{N}_3 \\
91 & \quad >99\% \text{ ee} \\
& \quad >99\% \text{ ee}
\end{align*}
\]

Scheme 1.22

The reduction of amino acids offers a straightforward route to enantiomerically pure β-amino alcohols, which can be converted into 1,2-diamines, as demonstrated by Kokotos et al. with the synthesis of 96.\(^{77}\) Again, this is a rather lengthy process, and its reliance on the chiral pool generally limits its applicability to one enantiomeric series, and only a few substitution patterns (Scheme 1.23).
In 2004, Maruoka et al. reported a highly enantioselective synthesis of 1,2-diamines 99 from protected α-amino acid amides 97 using a phase-transfer-catalysed alkylation. This method utilises chiral ammonium salt 100 as the catalyst and leads to 99 in 2 steps (Scheme 1.24).
1.5.3 1,2-Diamines from bis-imines

The electrophilicity and prochirality of bis-imines make them attractive templates onto which functional groups can be added for the synthesis of 1,2-diamines. The example in Scheme 1.25 demonstrates the addition of two equivalents of a Grignard reagent to chiral bis-imine 102 template bearing two $\alpha$-methyl-benzylamino groups to induce stereochemistry.\(^{79}\) Subsequent hydrogenation affords 1,2-diamine 104 in good yield and excellent diastereoselectivity.

\[ \text{Scheme 1.25} \]

Kim and co-workers have adopted a different method using a diaza-Cope rearrangement. This approach allows an efficient synthesis of 1,2-diamines from two equivalents of aldehyde and enantiomerically enriched diamine 105, which acts as a sacrificial source of nitrogen. Formation of bis-imine 106 via diaza-Cope rearrangement, followed by hydrolysis furnishes 107 (Scheme 1.26).\(^{80}\)
1.5.4 Miscellaneous 1,2-diamine syntheses

There is a wide range of other approaches for the synthesis of 1,2-diamines. This final section highlights some of the best of these.

There are numerous well-established methods for the enantioselective synthesis of aziridines.\textsuperscript{81-84} As such, it comes as no surprise that the ring opening of aziridines with nitrogen-based nucleophiles has been employed for the synthesis of 1,2-diamines. The example in Scheme 1.27 demonstrates the ring opening of tri-substituted aziridine 108 with primary and secondary amines to afford 109 under mild conditions and without the use of a Lewis acid catalyst (Scheme 1.26).
Interestingly, $S_n2$ attack occurs at the more substituted end of the aziridine; this is reported to be due to electronic activation from the alkyne.

Scheme 1.27

In 2004, Xu and co-workers reported the asymmetric synthesis of 1,2-diamines 112 via a reductive homocoupling of aromatic N-\textit{tert}-butanesulfanyl imines 110 in the presence of SmI$_2$ and HMPA, followed by deprotection with HCl in methanol.$^{85}$ This process offers a straightforward route to a range of 1,2-diamines with excellent enantioselectivity but is unfortunately hindered by the requirement for two equivalents of SmI$_2$ and HMPA (Scheme 1.28).

Scheme 1.28

Anderson \textit{et al.} have recently utilised an asymmetric nitro-Mannich reaction for the synthesis of $\beta$-nitroamines 115 using copper catalyst 117 with trimethylsilylnitropropanate (113) and a variety of imines 114.$^{86}$ These products
can then undergo reduction with SmI$_2$ to yield a variety of enantiomerically enriched 1,2-diamines 116 (Scheme 1.29).$^{87}$

\[
\begin{array}{c}
\text{O}^+\text{N}^+\text{OTMS} + \text{N}^+\text{PMP} \\
\text{Et} + \text{H} \\
113 \\
\text{R} \\
\text{114} \\
\end{array}
\xrightarrow{117 \text{ (10 mol %)}}
\begin{array}{c}
\text{HN}^-\text{PMP} \\
\text{Et} \\
\text{R} \\
\text{115} \\
\text{NO}_2 \\
\text{yield} = 79-91\% \\
\text{ee} = 70-94\% \\
\end{array}
\xrightarrow{\text{Sml}_2 \text{ MeOH, THF}}
\begin{array}{c}
\text{HN}^-\text{PMP} \\
\text{Et} \\
\text{R} \\
\text{116} \\
\text{NH}_2 \\
\text{yield} = 45-77\% \\
\end{array}
\]

$\text{R} = \text{alkyl, aryl, heteroaryl}$

**Scheme 1.29.**

Maruoka co-workers have also explored the use of asymmetric Mannich reactions for the enantioselective synthesis of 1,2-diamines. It has been shown that $\alpha$-aminoaldehyde 118 reacts with imines 119 in the presence of an appropriate asymmetric catalyst to yield 1,2-diamines 120 or 121 with excellent enantioselectivities.$^{88}$ Furthermore, the diastereoselectivity of the reaction can be controlled by altering reaction conditions and the choice of catalyst, with L-proline (122) showing *syn* selectivity and sulfonamide 123 showing *anti*-selectivity (Scheme 1.30).
1.5.5 Summary

A wide variety of methods for the synthesis of 1,2-diamines have emerged. However relatively few of these examples achieve high levels of enantiomeric control and those that do are often limited in their versatility, allowing for only a narrow range of functionality to be introduced. In some cases the substituents are often incorporated into the product early in the synthesis, which can lead to a lengthy process when libraries of 1,2-diamines are required. Considering their abundance in biologically active compounds and their extensive utility in asymmetric synthesis, we believe there is still much scope for the development of further efficient synthetic routes to a wide range of enantiomerically enriched 1,2-diamines. In the following chapters, we describe new approaches based upon the utilisation of heterocyclic templates for the enantioselective synthesis of 1,2-diamines.
Chapter 2:

Nitrogen-Containing Heterocycles with an

Endocyclic Double Bond
2.1 Introduction

In this thesis, we explore an alternative approach to the synthesis of 1,2-diamines based upon the use of a variety of heterocyclic templates containing two vicinal nitrogen atoms. In this chapter, we describe efforts to use 1,2-diazetine 124 and imidazolin-2-one 125 systems for this purpose (Figure 2.1).

![Diagram of 1,2-diazetine and imidazolin-2-one](image)

**Figure 2.1**

124 and 125 were selected as candidates for this investigation as we believed their respective endocyclic double bonds could provide us with an appropriate method for functionalisation. We envisaged achieving this with a metal-catalysed cross-coupling reaction followed by asymmetric hydrogenation. Subsequent cleavage of the heterocycle was then expected to be realised using literature methods, yielding the desired 1,2-diamine 129 (Scheme 2.1)

![Diagram of synthesis](image)

**Scheme 2.1**
We also wished to investigate an alternative approach utilising cycloadditions, such as the Diels-Alder reaction, for the synthesis of cyclic 1,2-diamines 131 (Scheme 2.2).

Scheme 2.2

Each heterocycle, 124 and 125, will be discussed separately, beginning with background information from the literature regarding their synthesis and known reactions, including potential cleavage techniques. Our efforts to use them as templates for the synthesis of 1,2-diamines will then be presented.

2.2 1,2-Diazetines

2.2.1 Introduction

There are very few reports of 1,2-diazetines in the literature, as their synthesis poses a significant challenge.\textsuperscript{89} By comparison, 1,2-diazetidines (the saturated analogues of 1,2-diazetines) have received more attention and there are a number of known routes for their synthesis.\textsuperscript{90,92} Furthermore, many of the known examples of 1,2-diazetines are as part of larger, more complex molecules and as such are not suitable for our purposes. We will therefore only be concerned with such examples that are relevant to this study.
This section will review the known methods for the synthesis of 1,2-diazetines and their reported reactions. In addition, methods for the cleavage of N–N bonds, which will be required for the synthesis of the desired 1,2-diamines, will be discussed.

2.2.2 Background

To our knowledge, Warrener and Nunn reported the first known synthesis of a 1,2-diazetine in 1972.\textsuperscript{93} Synthesis of \textbf{138} was achieved beginning with a cycloaddition between dimethylazodicarboxylate (\textbf{133}) and \textit{in situ} generated cyclobutadiene via oxidation of the corresponding Fe(CO)\textsubscript{3} complex \textbf{132}, to yield diazabicyclohexane \textbf{134}, which undergoes a second cycloaddition with 2,5-dimethyl-3,4-diphenylcyclpentadiene-2,4-dienone (\textbf{135}) to furnish tricycle \textbf{136}. Irradiation of \textbf{136} with ultraviolet light led to rearrangement with loss of carbon monoxide followed by 1,2-photoaromatisation, via [2+2] electrocyclic ring-opening of the central ring, to give 1,4-dimethyl-2,3-diphenylbenzene (\textbf{137}) and 1,2-diazetine \textbf{138}. In this instance, \textbf{138} was converted to the corresponding 1,2-diazetidine \textbf{139} by catalytic hydrogenation using palladium on carbon (Scheme 2.3).
Diazetine 138 is thermally unstable and is reported to undergo electrocyclic ring-opening to give 140 with a half life of 6.9 h at 25 ℃ (Scheme 2.4).

Scheme 2.3

Scheme 2.4
More recently, Breton et al. have reported the thermally stable, bicyclic diazetine 144. Its synthesis is achieved by oxidation of N-methyl urazole with trichloroethylene to give N-methyltriazolinedione (141), which was then reacted with phenyl vinyl sulfide. Oxidation of the resulting 142 with m-CPBA and subsequent elimination afforded 144 (Scheme 2.5).

Scheme 2.5

Bicyclic diazetine 144 is reported to be a thermally stable crystalline solid that can be sublimed. Breton argues that electrocyclic ring opening of 144 would be unfavourable as product 145 would be a highly strained seven-membered ring. Furthermore, ring opening would likely be reversible as the back reaction is still intramolecular (Scheme 2.6).
Breton has also demonstrated that 144 can act as a suitable dienophile for Diels-Alder reactions with a variety of dienes. Yields range from modest to excellent, with high selectivity for endo products. In addition, it was shown that the products could be converted to \( \Delta^1 \)-1,2-diazetines 148 via deprotection and oxidation. No attempts to reduce diazetidine 147 to the corresponding cyclic 1,2-diamines by cleavage of the N–N bond were reported (Scheme 2.7).

Based on Breton’s pioneering work, it was felt that 1,2-diazetines such as 144, could serve as excellent building blocks for the synthesis of 1,2-diamines. However, its synthesis suffers from poor overall yields, limiting its utility.
(Scheme 2.5). The low yielding step involves cycloaddition of phenyl vinyl sulfide with triazolinedione 141, as copolymer formation is competitive. Breton reported that attempts to improve the yield of 144 with variation in reaction conditions or solvent were unsuccessful. These findings are consistent with those of several other groups who have investigated the cycloaddition of olefins with azo-compounds.\textsuperscript{94-96} For example, Hall and Jones have reported that the cycloaddition of ethyl and phenyl vinyl ethers, 150 and 151, with N-phenyl triazolinedione (149) results in the formation of copolymer 152 (Scheme 2.8).\textsuperscript{97}

![Scheme 2.8](image)

In contrast, the reaction of 2-chloroethyl vinyl ether (153) with 149 is reported to furnish diazetidine 154 in quantitative yield (Scheme 2.9).

![Scheme 2.9](image)

Hall’s characterisation of copolymer 152 is limited to the observation of very broad peaks in the \textsuperscript{1}H NMR spectrum, and so may not be conclusive. However,
a number of other groups have made similar observations on related systems and have also suggested copolymer formation. The analytical data provided for 1,2-diazetidine 154 consists of a melting point, CHN analysis and $^1$H NMR spectrum displaying an ABX pattern that Hall rationalises as evidence for a diazetidine structure. In addition, reaction of 153 with 149 in acetone is reported to give tetrahydrooxadiazine 156. This suggests that the reaction is not concerted and involves zwitterionic intermediate 155, which can be trapped with an appropriate reagent such as acetone (Scheme 2.10).

**Scheme 2.10**

Clearly the reaction is sensitive to the electronic nature of the olefin. One might expect an electron-withdrawing group present in the vinyl ether (e.g. ClCH$_2$CH$_2$O-) may destabilise the zwitterionic intermediate 155, promoting a fast intramolecular ring closing reaction as opposed to intermolecular polymerisation. Manipulation of the substituent on the olefin may therefore allow for improvements in the yield of compounds such as 1,2-diazetine 144.

There are a number of known methods for the cleavage of N–N bonds, many of which utilise reductive conditions such as lithium and liquid ammonia. Moody and co-workers have reported the conversion of aza-β-lactam 157 to 1,2-
diamine 158 using diborane for both carbonyl reduction and N–N bond cleavage (Scheme 2.11).^{99}

![Scheme 2.11](image)

More recently, Shipman and co-workers have demonstrated N–N bond cleavage of 1,2-diazetidine 159 with LiDBB in good yield (Scheme 2.12).^{100}

![Scheme 2.12](image)

The examples of 1,2-diazetines within the literature gave us optimism that such compounds could be used as useful templates for 1,2-diamine synthesis. However, it seemed unlikely that thermally unstable diazetines such as 138 reported by Warrener and Nunn would be suitable for our purposes. Even if 138 could be synthesised and used directly, reactions for further functionalisation (e.g. cycloadditions) are likely to require heating. Bicyclic diazetine 144 is a more attractive substrate, providing its synthesis can be improved. Based on the investigations of Hall and Jones this is expected to be possible by variation of the vinyl sulfide substrate, as the reaction appears to be quite sensitive to the electronic nature of the olefin. Breton has already demonstrated a number of cycloadditions with 144. We expected that with access to large quantities of 144, a number of other interesting reactions could be investigated. For example,
other cycloadditions, such as a 1,3-dipolar cycloaddition, or Heck reactions followed by asymmetric hydrogenation would be of interest. Subsequent deprotection and cleavage of the N–N bond using known literature procedures should then allow us to obtain a variety of 1,2-diamines, such as 161 and 164, through a potentially divergent process (Scheme 2.13).

Scheme 2.13

2.2.3 Synthesis of 1,2-diazetines

We wished to begin by repeating the synthesis of the 1,2-diazetine 144 using the procedure described by Breton. However N-methyl urazole, the precursor to N-methyl-1,2,4-triazolinedione (141), was found to be highly costly, and so N-phenyl urazole was used as an alternative. This was oxidised with trichloromelamine to the corresponding triazolinedione 149 and used directly. [2+2] Cycloaddition with one equivalent of phenyl vinyl sulfide and subsequent oxidation with m-CPBA yielded sulfoxide 166 (Scheme 2.14). Very broad peaks present in the crude ¹H NMR spectrum as well a substantial loss in mass
following column chromatography of 166 suggested polymer formation, however this was not characterised further. The overall yield for this sequence was very low, although not dissimilar to that reported by Breton for the N-methyl series (Scheme 2.5).

![Scheme 2.14](image)

Next, novel 1,2-diazetine 167 was obtained by heating 166 in a sealed tube in chlorobenzene (Scheme 2.15). $^1$H NMR spectroscopy was diagnostic for the characterisation of 167, as the ABX pattern of 166 was no longer present and a new singlet at 6.74 ppm, corresponding to the two diazetine hydrogens, was observed. This value was in accordance with Breton’s characterisation of 144, which is reported to have a singlet at 6.76 ppm. The expected mass for 167 ($m/z = 224 [M+Na]^+$) was also observed by mass spectrometry.
This work indicated that the less expensive $N$-phenyl derivative 149 could be used in place of the $N$-methyl compound. However, with an overall yield of less than 10%, it was clear that this chemistry was far from practical. We therefore considered what alternatives to phenyl vinyl sulfide would be expected to favour formation of diazetidine 165 over polymer. Based on Hall’s observations (Schemes 2.8 and 2.9), some form of electron-withdrawing group on the vinyl sulfide might assist formation of the four-membered ring.  

By analogy with the earlier study, the obvious choice would be 2-chloroethyl vinyl sulfide 169, however this is expected to be extremely toxic, and potentially carcinogenic, based on its structural similarities to bis(2-chloroethyl) sulfide (mustard gas, 168). Indeed, to our knowledge all the known procedures for the synthesis of 169 require bis(2-chloroethyl) sulfide as a precursor (Scheme 2.16).  

![Scheme 2.15](image)

![Scheme 2.16](image)
As such, it was concluded that this would not be a suitable substrate to investigate. Compounds with electron-withdrawing groups present on the phenyl ring of phenyl vinyl sulfide, such as 170-172, were considered as alternatives (Figure 2.2).

![Figure 2.2](image)

Due to the availability of 2,4-dinitrobenzenesulfenyl chloride, 172 was selected for investigation. It was synthesised via the known reaction of 2,4-dinitrobenzenesulfenyl chloride with vinyl trimethylsilane, followed by elimination by heating in ethanol (Scheme 2.17). The distinctive olefinic pattern in the \(^1\)H NMR spectrum of 172 was consistent with the literature, indicating the synthesis was successful. Reaction with 149 was then attempted. Unfortunately, this led to a complex mixture of products from which nothing could be isolated that resembled the desired 1,2-diazetidine 174 after further oxidation with \(m\)-CPBA (Scheme 2.17).
It is possible that a less electron-withdrawing alternative such as \( \text{170} \) or \( \text{171} \) would prove to be a more suitable substrate, however more steps are required for the synthesis of such compounds, leading to an increasingly lengthy synthesis that would not be considered practical. As an alternative, the cycloaddition was attempted with phenyl vinyl sulfoxide, as this would yield \( \text{166} \) directly if successful. Unfortunately no reaction was observed at room temperature, or when heated to 100 °C in a sealed tube (Scheme 2.18).

\[
\text{Ph} \quad \text{N} \equiv \text{N} + \text{Ph-S} \equiv \quad \text{CH}_2\text{Cl}_2, 25 ^\circ \text{C}, 2 \text{ h} \quad \text{no reaction}
\]

Scheme 2.18
Olefins 175-177 with heteroatoms of a different electronic nature to sulfur were then considered. It was believed that if such compounds could be successfully reacted with 149 to furnish the corresponding diazetidines in good yield, then alternative methods for their further functionalisation could be investigated. Therefore reaction of 149 with these commercial olefins was attempted. However, in each case, complex mixtures were obtained with no sign of bicycles 178-180 being observed (Scheme 2.19).

![Scheme 2.19](image)

2.2.4 Conclusions

It has been shown that N-phenyl urazole can be used in place of N-methyl urazole in Breton’s route to bicyclic 1,2-diazetines. However, the approach suffers from similar problems to the literature method, namely very low yields for the “cycloaddition” step. Efforts to circumvent these problems by tuning the nature of the sulfide substituent, or by using alternative heteroatoms were uniformly unsuccessful. As such, progress to developing a practical route to 1,2-diamines based upon the 1,2-diazetine scaffold was thwarted.
2.3 Imidazolin-2-ones

2.3.1 Introduction

In contrast to 1,2-diazetines, imidazolin-2-ones (and their saturated analogues imidazolidin-2-ones) have enjoyed much attention in the literature. Reports for the synthesis of such compounds, both functionalised and unfunctionalised, go back over a century. We imagined that such systems might serve as alternatives to 1,2-diazetines in 1,2-diamine synthesis, as they are not only expected to be more stable than 1,2-diazetines but there are also more established methods for their synthesis. However, the less strained double bond of imidazolin-2-ones compared to 1,2-diazetines, as well as the potential aromatic character of the ring may result in lower reactivity. We wanted to investigate similar methods for their functionalisation as previously discussed for 1,2-diazetines, namely cycloadditions and Heck reactions, followed by cleavage to yield the desired 1,2-diamines (Scheme 2.20).

Scheme 2.20
The following section will briefly highlight literature methods for their synthesis, suitable reactions for their functionalisation as well as methods for their hydrolysis to the corresponding diamines.

2.3.2 Background

The synthesis of unsubstituted imidazolin-2-one 185 is easily achieved via the reduction of hydantoin 184 and subsequent elimination of the resulting hydroxyl group, as described by Whitney (Scheme 2.21).\textsuperscript{108}

![Scheme 2.21]

A similar approach reported by Liao and Kohn allows for the synthesis and functionalisation of imidazolinones 187 from N-benzyl hydantoin 186 in a single step (Scheme 2.22).\textsuperscript{110}

![Scheme 2.22]
Recently Chen and co-workers have described a palladium-catalysed cross-coupling reaction of 185 with a variety aryl halides to give aryl-substituted derivatives 188 in moderate to good yields (Scheme 2.23).\textsuperscript{111}

\[
\begin{array}{c}
\text{HN} \ \text{NH} \\
185 \\
\end{array}
\xrightarrow{\text{ArI, Pd(OAc)}_2, \text{NaOAc} \cdot 3\text{H}_2\text{O, DMSO} \ \text{80} \ ^\circ\text{C}, 6-36 \text{h} }
\begin{array}{c}
\text{HN} \ \text{NH} \\
\text{Ar} \ \text{188} \\
\end{array}
\]

Scheme 2.23

Several groups have shown that diacetylated imidazolinone 189 will participate in Diels-Alder reactions. However, only a very limited number of dienes, such as very reactive cyclopentadiene have been used to date (Scheme 2.24).\textsuperscript{108, 112-114}

\[
\begin{array}{c}
\text{Ac} \ \text{N} \ \text{N} \ \text{Ac} \ \text{189} \\
+ \ \text{xylene, 180} \ ^\circ\text{C} \\
\end{array}
\xrightarrow{69\%}
\begin{array}{c}
\text{Ac} \ \text{N} \ \text{N} \ \text{Ac} \ \text{190} \\
\end{array}
\]

Scheme 2.24

Duschinsky and Kohn have both reported the hydrogenation of imidazolinone 191 (Scheme 2.25).\textsuperscript{115,116} These reactions used palladium on carbon as the catalyst, and as far as we are aware, the influence of chiral catalysts on these transformations has not been explored.

\[
\begin{array}{c}
\text{HN} \ \text{N} \ \text{Me} \\
\text{Ph} \ \text{191} \\
\end{array}
\xrightarrow{\text{H}_2, \text{Pd/C, AcOH} \ \text{25} \ ^\circ\text{C}, 3 \text{ bar}, 40 \text{ h} }
\begin{array}{c}
\text{HN} \ \text{N} \ \text{Me} \\
\text{Ph} \ \text{192} \\
\end{array}
\]

Scheme 2.25
Examples of stereoselective hydrogenations of imidazolinones are less common. To our knowledge, the most relevant example is a procedure patented by Lonza for the diastereoselective hydrogenation of bicyclic imidazolinone 193 as part of a synthetic route towards biotin. In this case, the electronics of the double bond are likely influenced by the adjacent carbonyl group (Scheme 2.26).

![Scheme 2.26](image)

There are many of examples in the literature for the hydrolysis of imidazolidinones to the corresponding 1,2-diamines. This process is usually carried out under rather forcing conditions with either aqueous hydrochloric acid (Scheme 2.27), or a strong base such as barium hydroxide (Scheme 2.28).

![Scheme 2.27](image)
Based on the literature precedent for the synthesis and reactions of imidazolinones, it was thought that such compounds would make appropriate templates for the synthesis of 1,2-diamines. We intended to utilise the routes described by Chen (Scheme 2.23) for the synthesis of a number of substituted imidazolinones. We would then explore asymmetric hydrogenations of these substrates and finally investigate their hydrolysis to the corresponding 1,2-diamines, as described in Scheme 2.20.

### 2.3.3 Synthesis and reactions of imidazolin-2-ones

Imidazolinone 185 was synthesised according to Whitney’s procedure (Scheme 2.21) and subsequently functionalised with phenyl iodide using Chen’s method (Scheme 2.23) to yield phenyl derivative 199 (Scheme 2.29).
Liao and Kohn’s route (Scheme 2.22) was utilised for the synthesis of 200, which had not been reported in their paper. This offered us an alternative substrate, with potentially enhanced solubility in organic solvents, for us to explore reductions (Scheme 2.30).

\[
\text{Scheme 2.30}
\]

Our attention then turned to the hydrogenation reactions of these substrates. We began with conventional heterogeneous catalysts, namely palladium on carbon, to gain some knowledge regarding the reactivity of the double bond. Reactions were carried out using an H-cube® continuous-flow hydrogenation reactor, as this allowed us to reach pressures that were otherwise unobtainable in the laboratory at the time. To our surprise, hydrogenation of 199 to corresponding imidazolidinone 201 proved to be extremely difficult and was only achieved under very forcing conditions. Furthermore, the more hindered \(N\)-benzylated derivative 200 could not be hydrogenated to 202 at all (Table 2.1).
Based on literature examples of similar substrates, which have been reported to be successfully hydrogenated at 3 bar at room temperature, these results were quite unexpected (Scheme 2.25). Possible causes for the lack of reactivity might be steric hindrance, solubility, as well as partial aromatic character of these substrates. Both 199 and 200 were insoluble in most solvents and only sparingly soluble in acetic acid, DMF and DMSO. Next, efforts focused on trying to improve the reactivity of these substrates. The hydrogenation of unsubstituted imidazolinone 185 was investigated, as this compound is both less hindered and more soluble in organic solvents than 199. Hydrogenation was achieved with slightly less forcing conditions, but still required high temperatures and pressures (Scheme 2.31).
These results indicated that there was more to the lack of reactivity than simple steric hindrance or solubility issues. The double bond of such imidazolinones may be rather aromatic in character, with involvement from the nitrogen lone pairs (Scheme 2.32).

By removing the lone pairs from the ring, by introduction of electron-withdrawing substituents on N, the aromatic character of the heterocycle should be reduced. In this way, the reactivity towards hydrogenation might be significantly increased. To explore this idea, the hydrogenation of the diacetylated imidazolidinone 189 was attempted. We were pleased to observe that hydrogenation occurs readily at room temperature and pressure. Interestingly, the isolated product 205 had evidently had an acetyl group removed during the process (based on $^1$H NMR and mass spectroscopic data), presumably by attack from methanol. It is uncertain at which point in the reaction acetyl deprotection occurs. However, considering 189 was purified by recrystallisation from ethanol, it would be expected to be stable to methanol at
ambient temperature, suggesting deprotection occurs on 204 following the hydrogenation of 189 (Scheme 2.33).

\[
\begin{align*}
\text{Ac} - \overset{\text{O}}{\text{N}} - \overset{\text{N}}{\text{NH}} & \overset{\text{Ac}_2\text{O}}{\xrightarrow{150^\circ\text{C}, 1\text{ h}}} \overset{\text{O}}{\text{N}} - \overset{\text{N}}{\text{Ac}} \\
\text{Ac} - \overset{\text{N}}{\text{N}} - \overset{\text{Ac}}{\text{H}} & \xleftarrow{95\%} \overset{\text{O}}{\text{N}} - \overset{\text{N}}{\text{Ac}}
\end{align*}
\]

Scheme 2.33

In light of these results, we began to investigate the synthesis of other \(N\)-substituted imidazolinones. It was hoped that diacetylated imidazolinone 189 could be functionalised directly by Heck-type processes, as depicted in Scheme 2.34, but unfortunately no reaction occurred under the conditions successfully used for the synthesis of 199 (Scheme 2.29).

\[
\begin{align*}
\text{Ac} - \overset{\text{N}}{\text{N}} - \overset{\text{Ac}}{\text{Ac}} & \overset{\text{Phl, Pd(OAc)}_2, \text{NaOAc-3H}_2\text{O}, \text{DMSO}}{\xrightarrow{80^\circ\text{C}, 6\text{ h}}} \text{no reaction}
\end{align*}
\]

Scheme 2.34

To circumvent this problem, the acetylation of 199 was attempted. This proved to be more difficult than expected, with only mono-acetylated 206 being obtained in moderate yield and only traces of 207 being observed. The best
conditions found involved the use of acetyl chloride in DMF with triethylamine as base at 80 °C (Table 2.2).

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>X</th>
<th>additives</th>
<th>solvent</th>
<th>time (h)</th>
<th>temp. (°C)</th>
<th>206 (%)</th>
<th>207 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OAc</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>150</td>
<td>5</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>OAc</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N, DMAP</td>
<td>DMSO</td>
<td>48</td>
<td>80</td>
<td>25</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N, DMAP</td>
<td>DMSO</td>
<td>16</td>
<td>80</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N, DMAP</td>
<td>DMF</td>
<td>3</td>
<td>80</td>
<td>42</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>DMF</td>
<td>3</td>
<td>80</td>
<td>43</td>
<td>trace</td>
</tr>
</tbody>
</table>

Table 2.2

Only one regioisomer of 206 was observed in the crude reaction mixture. The regioselectivity was initially unclear, with nOe studies being inconclusive. Gratifyingly, we were able to obtain suitable crystals for single crystal X-ray diffraction by crystallisation from ethyl acetate by slow evaporation. This X-ray structure confirmed that acylation occurred at the nitrogen atom furthest from the phenyl ring, presumably because it is the most sterically accessible (Figure 2.3).

![Crystal Structure](image)

Figure 2.3
Two related substrates, namely 208 and 209, were then synthesised using 2-methylpropanoyl chloride and 2,2-dimethylpropanoyl chloride respectively. These substrates were expected to have improved organic solubility compared with 206, and perhaps be less susceptible to attack by methanol under the hydrogenation conditions (Scheme 2.35).

![Scheme 2.35](image)

Hydrogenation of 206 proceeds readily under mild conditions, using just a balloon of hydrogen to give the reduced product 210 in excellent yield. Hence it appears that removal of just one lone pair from the heterocycle is sufficient to markedly reduce its aromatic character (Scheme 2.36).

![Scheme 2.36](image)

Phenyl substituted derivative 201 was readily hydrolysed to corresponding diamine 211 under acidic conditions in accordance with literature precedent. The yield for this reaction was not optimised at this time (Scheme 2.37).
Scheme 2.37

With a good understanding of the relative reactivities of these imidazolin-2-ones in hand, our attention now turned to the identification of chiral catalysts to effect asymmetric hydrogenations of these systems. Based on the reports by Lonza (Scheme 2.26), the use of rhodium catalysts with chiral Josiphos ligands appeared an appropriate place to begin.117

Treatment of 206 with [Rh(NBD)$_2$]BF$_4$ and 1 atmosphere of hydrogen in the presence of (R)-1-[(S$_p$)-2-(Diphenylphosphino)ferrocenyl]ethylidicyclohexylphosphine (Josiphos J001-1) for 16 h at room temperature resulted in no reaction (Table 2.3, entry 1). This bulky homogeneous catalyst was clearly insufficiently active to reduce the trisubstituted alkene under these very mild conditions. Higher pressures did not increase the reactivity (entry 2). It was discovered that heating in methanol at 50 °C led to removal of the N-acetyl group (entry 3). Even the more hindered derivative 208 underwent cleavage under these conditions (entry 4). To circumvent this problem the solvent was switched to ethyl acetate. Again no reaction was observed under mild conditions (entries 6-8), and no improvements with made with THF as the solvent (entry 9). Upon increasing the pressure and temperature however, complex mixtures were obtained (entries 10-11). We were unable to isolate any compounds from the crude mixture, but based on mass spectrometry evidence ($m/z$ =207, [M+H]$^+$)
+ 2) it appeared that the substrate had been over-reduced, possibly by cleavage of the ring and hydrogenation of the double bond to give 213 (Figure 2.4).

![Chemical Structure](image)

Table 2.3

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>solvent</th>
<th>pressure (bar)</th>
<th>temp. (°C)</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>206</td>
<td>MeOH</td>
<td>1</td>
<td>25</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>206</td>
<td>MeOH</td>
<td>10</td>
<td>25</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>206</td>
<td>MeOH</td>
<td>10</td>
<td>50</td>
<td>199</td>
</tr>
<tr>
<td>4</td>
<td>208</td>
<td>MeOH</td>
<td>100</td>
<td>100</td>
<td>199</td>
</tr>
<tr>
<td>5</td>
<td>199</td>
<td>MeOH</td>
<td>100</td>
<td>100</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>206</td>
<td>EtOAc</td>
<td>10</td>
<td>50</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>206</td>
<td>EtOAc</td>
<td>20</td>
<td>50</td>
<td>no reaction</td>
</tr>
<tr>
<td>8</td>
<td>206</td>
<td>EtOAc</td>
<td>50</td>
<td>25</td>
<td>no reaction</td>
</tr>
<tr>
<td>9</td>
<td>206</td>
<td>THF</td>
<td>50</td>
<td>50</td>
<td>no reaction</td>
</tr>
<tr>
<td>10</td>
<td>206</td>
<td>EtOAc</td>
<td>50</td>
<td>100</td>
<td>over reduction</td>
</tr>
<tr>
<td>11</td>
<td>206</td>
<td>EtOAc</td>
<td>50</td>
<td>50</td>
<td>over reduction</td>
</tr>
<tr>
<td>12</td>
<td>206</td>
<td>EtOAc</td>
<td>30</td>
<td>50</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

![Chemical Structure](image)

Figure 2.4
If 213 is the product, then cleavage of the ring must occur prior to hydrogenation of the double bond, as no reaction is observed when 210 is subjected to the same conditions (Scheme 2.38).

Scheme 2.38

In light of these results it appeared that the catalyst and ligand choice were not suitable and so alternatives were considered. Rather than screen numerous combinations of catalysts and chiral ligands, it was decided that it would be appropriate to determine first that the required selective reduction could be achieved with an achiral homogeneous catalyst. Wilkinson’s catalyst [Rh(PPh₃)₃Cl] and Crabtree’s catalyst ([Ir(COD)(PCy₃)(Py)]PF₆) were selected for this investigation. No reaction was observed when 208 was treated with [Rh(PPh₃)₃Cl] at 1 bar of hydrogen at room temperature, or when the pressure was increased to 50 bar (Table 2.4, entries 1 and 2). Upon heating to 50 °C, a complex mixture was obtained which contained no evidence for the presence of 212 by either ¹H NMR or mass spectroscopy (entry 3). Once again the mass spectrum contained evidence for a potential over-reduced product 214 (m/z = 235, [M+H]+ + 2) but unfortunately we were unable to isolate this compound. Treatment of 208 with [Ir(COD)(PCy₃)(Py)]PF₆ gave similar complex mixtures, again displaying mass spectrometry evidence for over-reduction, even under 1 bar of hydrogen (entries 4 and 5).
Based upon these results, it appeared that standard homogeneous hydrogenation catalysts were unsuitable for these substrates and so alternative asymmetric reduction methods were considered. Transfer hydrogenation reactions have found widespread use in the reduction of heterocycles, and so these conditions were investigated. Noyori-type reduction of 208 was attempted with a ruthenium/(R,R)-TsDPEN complex and formic acid as the hydride source. Unfortunately, complex mixtures of products were produced when the reaction was performed at 50 °C for 48 h, or at 25 °C for 12 h (Scheme 2.39).

Table 2.4

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>pressure (bar)</th>
<th>time (h)</th>
<th>temp. (°C)</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(PPh$_3$)$_3$Cl]</td>
<td>1</td>
<td>16</td>
<td>25</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(PPh$_3$)$_3$Cl]</td>
<td>50</td>
<td>16</td>
<td>25</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(PPh$_3$)$_3$Cl]</td>
<td>50</td>
<td>16</td>
<td>50</td>
<td>over reduction</td>
</tr>
<tr>
<td>4</td>
<td>[Ir(COD)(PCy$_3$)(Py)]PF$_6$</td>
<td>1</td>
<td>2</td>
<td>25</td>
<td>over reduction</td>
</tr>
<tr>
<td>5</td>
<td>[Ir(COD)(PCy$_3$)(Py)]PF$_6$</td>
<td>1</td>
<td>0.5</td>
<td>25</td>
<td>over reduction</td>
</tr>
</tbody>
</table>

Scheme 2.39
For completeness, the reduction of the non-protected substrate 199 was also attempted. In this instance no reaction occurred and only starting material was observed in the crude $^1$H NMR spectrum (Scheme 2.40).

![Scheme 2.40](image)

**2.4 Conclusions**

During these studies we have successfully synthesised racemic 1,2-diamine 211 via hydrogenation of phenyl-substituted imidazolinone 199 and subsequent hydrolysis with hydrochloric acid (Schemes 2.36 and 2.37). It was discovered that hydrogenation reactions of these compounds are highly sensitive to the nature of the nitrogen substituents, and we were able to demonstrate a dramatic increase in reactivity by regioselectively acetylating imidazolinone 199. Unfortunately, we were unable to extend this procedure to an asymmetric reduction. It is unclear as to why the success of hydrogenation varies greatly between the catalysts and there may be a suitable asymmetric catalyst for such reactions. Nevertheless, considering the large number of catalyst and ligand combinations available as well as the precarious nature of the substrates it was concluded that our efforts should be focused elsewhere. Therefore we decided to investigate the use of related templates with exocyclic double bonds, as it was hoped this would circumvent at least some of the problems associated with the endocyclic analogues, particularly their high levels of aromatic character.
Chapter 3:

Nitrogen-Containing Heterocycles with an

Exocyclic Double Bond
3.1 Introduction

This chapter will discuss the use of nitrogen-containing heterocycles with an exocyclic double bond, such as 215, as templates for the synthesis of 1,2-diamines. We envisioned that the location of the double bond outside of the ring would help circumvent the problems associated with the endocyclic analogues discussed in Chapter 2. In particular, issues arising from low reactivity due to aromatic character (imidazolinones) and difficulties of synthesis and stability (1,2-diazetines). The basic concepts and objectives of this investigation remain the same. Three key processes need to be developed to realise the goal. Firstly, the development of general methods for the functionalisation of the template, secondly, asymmetric reduction to install chirality into the substrate and finally deprotection to reveal the 1,2-diamine 218 (Scheme 3.1).

Scheme 3.1
It has already been suggested that imidazolidin-2-ones and 1,2-diazetidines are suitable candidates, as deprotection to a 1,2-diamine is expected to be straightforward. Therefore, we focused on the use of methyleneimidazolidinones 219 and methylenediazetidines 220 for the synthesis of 1,2-diamines (Figure 3.1).

![Figure 3.1](image)

Each heterocycle will be discussed in turn, beginning with background information from the literature regarding their synthesis and known reactions. Our own findings in relation to the synthesis of 1,2-diamines will then follow.

### 3.2 Methyleneimidazolidinones

#### 3.2.1 Introduction

Reports of both imidazolidinone and imidazolinone based compounds are abundant within the literature.\(^{104-108}\) These structures are found as part of natural products as well as a number medicinal compounds.\(^ {6,124,125}\) However, imidazolidinones with an exocyclic double bond, particularly unsubstituted compounds, are far less common.

#### 3.2.2 Background

In 2000 Lei and Lu reported the synthesis of a variety of imidazolidinones 222, lactams 223 and oxazolidinones 224 using a tandem intramolecular
aminopalladation of alkynes 221 with alkene insertion. The entire process allows the synthesis and functionalisation of the heterocycles in a single step (Scheme 3.2)

Lei and Lu went on to demonstrate that 3-methyleneoxazolidinones 224 (X = O) could be hydrogenated with high enantioselectivities in the presence of a chiral rhodium catalyst (Scheme 3.3). Although hydrogenation of the corresponding 3-methyleneimidazolidinones 222 (X = N) was not reported, the similarity of the compounds suggests such an asymmetric reduction might be feasible.
More recently, Padwa and co-workers have reported the cyclisation of \( N-(p\text{-toluenesulfonyl})-N'-(2\text{-propyn-1-yl})\)urea (226) with \( \text{AuCl}_3 \) to give imidazolidinone 227.\(^{128}\) No reactions of 227 have been reported, other than it slowly isomerises to trisubstituted alkene 228 under acidic conditions (Scheme 3.4).

**Scheme 3.3**

More recently, Padwa and co-workers have reported the cyclisation of \( N-(p\text{-toluenesulfonyl})-N'-(2\text{-propyn-1-yl})\)urea (226) with \( \text{AuCl}_3 \) to give imidazolidinone 227.\(^{128}\) No reactions of 227 have been reported, other than it slowly isomerises to trisubstituted alkene 228 under acidic conditions (Scheme 3.4).

**Scheme 3.4**
Lu and Padwa have separately developed useful synthetic routes to 3-methyleneimidazolidinones, which may be useful for our own studies. Lu’s synthesis allows for the formation and functionalisation of the ring in a single step, however the choice of functionalities introduced is somewhat limited. We therefore proposed utilising Padwa’s synthesis of 227; exploring the reactivity of the double bond and attempt to functionalise it using transition metal catalysed cross-couplings. In addition, Lu’s hydrogenation studies of 3-methyleneoxazolidinones 224 provide us with a good indication of the feasibility of enantioselective reductions to 1,2-diamines, after further hydrolytic opening of the heterocycle.

3.2.3 Reactions of N-tosyl-methyleneimidazolidinone

Synthesis of N-tosyl-methyleneimidazolidinone 227 was carried out according to the procedure outlined in Scheme 3.4. It should be noted that what we assumed was 227 at this point was later determined to be 229. Characterisation of 229/227 shall be discussed later in the chapter, however we shall continue to use the true structure (229) from this point. We initially attempted cross-coupling reactions between 229 and phenyl iodide under Heck conditions.129,130 Even upon further heating to 110 °C, only starting material was recovered. We also examined the conditions used previously for the coupling of phenyl iodide with imidazolinone 185 (Scheme 2.29). Unfortunately, no reaction was observed in this instance (Scheme 3.5).
Scheme 3.5

As initial palladium catalysed cross-couplings were proving unsuccessful, we decided to explore a different approach to functionalisation of the alkene terminus. Cross metathesis reactions with Grubbs I and II catalysts could provide a general route to such compounds.\textsuperscript{131,132} To test this idea, 1-octene was selected as an appropriate substrate due to its good reactivity in cross-metathesis.\textsuperscript{133} However, use of either Grubbs I or II catalysts led only to formation of \(E\)-7-tetradecene (230) and recovery of 229 (Scheme 3.6).

Scheme 3.6

As a result of the apparent lack of reactivity of what was assumed to be 227 towards metathesis, we considered bromination of the double bond and subsequent coupling with a boronic acid by way of Suzuki cross-couplings.
Unfortunately, attempts to brominate the substrate with Br$_2$ led to degradation of the starting material. No reaction was observed using NBS in place of bromine (Scheme 3.7).

**Scheme 3.7**

Whilst attempting to functionalise 229 with substituents on the exocyclic double bond, we also began preliminary hydrogenation studies on the parent substrate. The reaction was found to proceed under mild conditions with palladium on carbon to furnish 231 in a very modest 26% yield. This poor yield is due to two side products that were also isolated. The major side product was identified to be trisubstituted alkene 232, the data for which is consistent with published values for 228 (Scheme 3.4). The structure of the minor product was determined to be the ring-opened compound 233, based on mass spectrometry data as well as characteristic peaks for an $n$-propyl chain present in the $^1$H NMR spectrum (Scheme 3.8).

**Scheme 3.8**
Since reduced compound 231 was found to be stable to the hydrogenation conditions, it would seem that over-reduced 233 is not derived from this compound. We therefore proposed 233 arises from initial C-N bond cleavage, followed by facile hydrogenation of mono-substituted alkene 234 (Scheme 3.9). No evidence for the presence of 233 could be seen in the crude reaction mixture, which would suggest that this reduction is relatively fast.

Scheme 3.9

We were fortunate enough to grow crystals of 231, from dichloromethane by evaporation, that were of suitable quality for X-ray diffraction. To our considerable surprise, this revealed the structure to be as described, rather than that of 235, which is what we were anticipating at the time (Figure 3.2).
This led us to reevaluate the gold-catalysed cyclisation of 226 reported by Padwa. The most likely explanation for this observation is that ring closure occurs through oxygen rather than nitrogen to afford 229 and not 227 (Scheme 3.10).
As our spectroscopic data for 229/227 was identical to that of Padwa’s, we were quite confident that he had misassigned this cyclisation reaction. However, we could not rule out the possibility that rearrangement occurred during the palladium-catalysed hydrogenation. Therefore we felt it necessary to confirm the structure of 229 through an additional X-ray crystallographic analysis. Suitable crystals were grown from dichloromethane and we were able to confirm that the gold catalysed ring closure reported by Padwa does in fact yield oxazolidinimine 229. We believe that the N-tosyl group is aligned syn to N–H as this will allow for hydrogen bonding with one of the sulfonamide S=O groups (Figure 3.3).

![Figure 3.3](image.png)

Interestingly, Padwa did propose ring closure of urea derivative 226 through oxygen as an alternative mechanism, but concluded that this did not occur (Scheme 3.11). This is presumably because he anticipated the tautomer 236, which did not match the 1H NMR data. One would expect to see an olefinic/aromatic peak for a single hydrogen, as well as a second methyl singlet to correspond to 236, whereas the observed peaks (Appendix 1), could be characterised as either 227 or 229.
Although we were unable to obtain an X-ray structure for the endocyclic isomer 232, our data was consistent with that of Padwa’s for 228. Therefore we believe there is sufficient evidence to show that the compound he proposed is also incorrect and instead has the structure 232 (Figure 3.4).

![Scheme 3.11](image)

**Figure 3.4**

The structure of the over-reduced compound 233 is as we initially proposed, as the product from the over-reduction of 229 will likely tautomerise to the corresponding urea 233 (Scheme 3.12).

![Scheme 3.12](image)
Upon consulting the literature for similar reactions it was discovered that Toste and Campbell have recently reported the synthesis of cyclic carbamimidate $239$ in the presence of a monophosphine gold(I) catalyst.$^{134}$ It is reported that ring-closure occurs through the oxygen atom and is thus fully consistent with our own findings (Scheme 3.13).

![Scheme 3.13](image)

Although Toste and Campbell have also reported an X-ray structure for an analogue of $239$, and thus also confirming ring closure through oxygen, there has not to our knowledge, been any link made between these results and those reported by Padwa. In addition, the variation in substrate, catalyst and reaction conditions show that Toste’s results alone cannot be used as conclusive evidence against the findings of Padwa’s. It is therefore believed that our findings will help remove any ambiguity regarding the gold catalysed ring closure of propargyl urea derivatives.

It is not certain why ring-closure of $226$ occurs preferentially through oxygen. However, based on work by previous group member Mike Brown, it has been shown that ring-closures involving ambident carbamate nucleophiles for the synthesis of 1,2-diazetidines are particularly sensitive to the electronic nature, or the “hardness” of the leaving group, as described by Pearson’s Hard Soft Acids and Bases (HSAB) principle.$^{90,135}$ Dr. Brown demonstrated that altering the
leaving group had a profound effect on the cyclisation of 241, with either 1,2-diazetidine 242 or 243 afforded as the major product, depending on the leaving group R. The structures of both 242 and 243 have been confirmed by X-ray crystallography (Scheme 3.14).\textsuperscript{137}

These observations would suggest that the coordination of AuCl\textsubscript{3} to alkyne 226 creates a “hard” electrophile that favours ring-closure through oxygen, as previously described in Scheme 3.10.

It would be of interest to determine whether or not this preference for closure through oxygen rather than nitrogen is witnessed in other, non-gold catalysed reactions. For instance, one could imagine a similar preference for ring closure through oxygen with the reactions reported by Lu (Scheme 3.15).\textsuperscript{126}
It was hoped that we could compare our $^{13}$C NMR data for 229 with that of Lu’s for methyleneimidazolidinone 222, as it was believed the shift of the peak corresponding to C-2 in 229 and 222 would aid us in determining if Lu’s structure is correct (Figure 3.4).

Unfortunately no $^{13}$C NMR data was published with Lu’s report. However, his more recent paper, which demonstrates the hydrogenation of methyleneoxazolidinones, reports the hydrolysis of 245 to yield N-tosyl amino alcohol 246.$^{127}$ If the palladium-catalysed ring closure occurred through oxygen to afford 247, then subsequent hydrolysis would be expected to give 1,2-diol 248 (Scheme 3.16). Differentiation between 246 and 248 should be trivial by NMR and mass spectroscopy and there should be no ambiguity regarding the
charaterisation of the product. Indeed, Lu’s spectroscopic data is in accordance with other published data for 246.\textsuperscript{136}

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{TsHN} \\
\text{Br} \\
Pd(OAc)\text{}_2 \\
\text{O} \\
\text{N} \\
\text{Ts} \\
247 \\
1. H_2, \text{cat.} \\
2. LiOH, H_2O \\
\text{HO} \\
\text{N} \\
\text{H} \\
\text{Ts} \\
248 \\
\text{not observed} \\
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{TsHN} \\
\text{Br} \\
Pd(OAc)\text{}_2 \\
\text{O} \\
\text{N} \\
\text{Ts} \\
244 \\
1. H_2, \text{cat.} \\
2. LiOH, H_2O \\
\text{HO} \\
\text{N} \\
\text{H} \\
\text{Ts} \\
245 \\
\text{not observed} \\
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{TsHN} \\
\text{Br} \\
Pd(OAc)\text{}_2 \\
\text{O} \\
\text{N} \\
\text{Ts} \\
246 \\
1. H_2, \text{cat.} \\
2. LiOH, H_2O \\
\text{HO} \\
\text{N} \\
\text{H} \\
\text{Ts} \\
246 \\
\end{array}
\end{equation}

\textbf{Scheme 3.16}

\subsection*{3.2.4 Conclusions}

Whilst investigating the use of 227 as a potential template for the synthesis of 1,2-diamines, we determined by X-ray crystallography that the structure for 227 reported in the literature was in fact incorrect, and that the true structure is that of 229. Based on these findings we can now summarise the reactions that have actually been attempted (Scheme 3.17). Whilst we were able to hydrogenate 229 with palladium on carbon, all other attempts to functionalise it were unsuccessful. Although the electronic nature of the double bond in 229 will be different to what was originally anticipated, its lack of reactivity is still surprising.
Once the true structure of 229 had been established, it was evident that this was not a suitable template for the synthesis of 1,2-diamines. The inability to functionalise 229 through palladium or ruthenium catalysed C–C bond forming processes therefore became irrelevant. It is possible that if a synthetic route to methyleneimidazolidinones could be found, it may prove to be a useful template. However, disheartened by the misleading literature in this area we decided to explore an alternative template.
3.3 3-Methylene-1,2-diazetidines

3.3.1 Introduction

Recently Shipman et al. reported the synthesis of 3-methylene-1,2-diazetidines from 2-haloallyl alcohols.\textsuperscript{100} For example, synthesis of 251 is achieved with a reductive coupling of alcohol 249 with diethylazodicarboxylate followed by copper-catalysed ring closure (Scheme 3.18).

\begin{center}
\includegraphics[width=\textwidth]{Scheme_3.18}
\end{center}

Scheme 3.18

This efficient, 2-step synthesis gives excellent yields and the ring closing reaction has been shown to work for a variety of substrates including 252-257 (Figure 3.5).

\begin{center}
\includegraphics[width=\textwidth]{Figure_3.5}
\end{center}

Figure 3.5
Due to the novelty of these compounds, their chemistry is still largely unexplored. Nevertheless Shipman et al. have already demonstrated that unfunctionalised 3-methylenediazetidines 251 and 252 can undergo Heck reactions with aryl iodosides. Although the reported yields are low, the reaction shows excellent diastereoselectivity, with the $E$ isomer being the major product (Scheme 3.19).

![Scheme 3.19]

Mike Brown has also shown that cyclopropanation of 254 produces expanded cyclopropane 261. To account for this finding, it was proposed that a second equivalent of the zinc carbenoid inserts into the N–N bond (Scheme 3.20).

![Scheme 3.20]

Although this reaction was somewhat unexpected, it is consistent with a reaction reported by Taylor and Davis, who observed a similar insertion whilst attempting a rhodium catalysed ring closure to $\beta$-lactam analogues (Scheme 3.21).
Other efforts by Mike Brown to functionalise 251 were less successful. For example, Grubbs metathesis with 1-octene led only to starting material and \( \text{E-7-tetradecene (229)} \) (Scheme 3.22).\(^{137}\)

Reactions with 3-methylene-1,2-diazetidine 255 were also briefly explored, as it was expected to be a potential substrate for Suzuki and Negishi couplings. Unfortunately this was not the case and only starting material was recovered in both instances. Chlorides are generally less reactive in cross-couplings and this presumably accounts for the lack of success in these processes (Scheme 3.23).\(^{139}\)
Preliminary hydrogenation studies of methylenediazetidines were also undertaken. Bicycle 257 was easily hydrogenated to diazetidine 262 under standard palladium on carbon conditions with excellent yield. It was deduced that this reaction proceeded to give exclusively the syn product. Subsequent reduction of 262 with LiDBB provided the protected diamine 263 in good yield (Scheme 3.24).\(^\text{100}\)

![Scheme 3.24](image)

Although the chemistry of 3-methylene-1,2-diazetidines is still largely unexplored, the preliminary results suggest that this class of compounds could prove ideal for the development of a general route to 1,2-diamines. Functionalisation of unsubstituted methylenediazetidines through Heck reactions has been demonstrated. Hydrogenation of bicycle 257 and subsequent cleavage of the N–N bond to yield carbamate-protected 1,2-diamine 263 has also been achieved. We wished to utilise the known Heck chemistry as well as explore other methods of functionalisation to provide a range of substituted 3-
methylene-1,2-diazetidines 265. The asymmetric hydrogenation of these substrates followed by N–N bond cleavage to yield a range of enantiomerically enriched 1,2-diamines 267 could then be investigated (Scheme 3.25).

**Scheme 3.25**

3.3.2 Functionalisation of 3-methylene-1,2-diazetidines

It has already been shown that 3-methylene-1,2-diazetidines are able to undergo Heck-type reactions with aryl iodides, albeit in modest yields (Scheme 3.19).\(^{100}\)

In addition, it is possible to incorporate certain functionalities prior to ring-closure. This however is considered an undesirable method, as the synthesis of the precursor itself then requires several steps, as illustrated for the synthesis of alkene 268 (Scheme 3.26).\(^{137}\)
As a result, we decided to investigate alternative methods for the functionalisation of 3-methylene-1,2-diazetidines. In turn, this would provide us with a variety of suitable substrates for hydrogenation studies.

Following the route outlined in Scheme 3.18, known 3-methylene-1,2-diazetidines 251 and 252 were synthesised. In addition, the novel derivatives 273 and 274 were prepared, as this would provide us a broader range of substrates to investigate (Scheme 3.27).
The Heck reaction reported by Shipman and co-workers (Scheme 3.19) was then used to make 258 and 260, as well as new methylenediazetidines 275 and 276 (Scheme 3.28). Yields were modest in each case, however it was found that lowering the reaction temperature to 70 °C gave the E-isomer of the products exclusively. This was confirmed for 258 by comparing ¹H NMR data with that of Mike Brown’s, who has assigned the structure by X-ray crystallography. It is believed the same stereoselectivity applies to 260, 275 and 276, due to the similarity of the ¹H NMR spectra. The distinct difference (0.42 ppm) in chemical shift for the two terminal ethyl triplets in Z-258 is not witnessed in 260, 275 or 276.
Previous attempts to perform cross coupling reactions with diethyl 3-(chloromethylene)-1,2-diazetidine (255) were unsuccessful (Scheme 3.23). However, we believed that the corresponding bromide would prove more reactive in Suzuki couplings. This approach could nicely complement the existing Heck process and allow for the synthesis of a wider range of substrates, in part, because of the wide range of available boronic acids.

Reaction of 251 with Br$_2$ and DBU was initially unsuccessful, as only degradation of the starting material was observed (Table 3.1, entries 1 and 2). Addition of the reagents at −78 °C yielded a complex mixture, which contained no evidence for 277 (entry 3). Changing the base to triethylamine made no improvement (entry 4). Allowing the mixture to warm to room temperature before the base was added also led to degradation (entry 5). However, 277 was eventually obtained after allowing the reaction mixture to warm to −50 °C before the addition of DBU and then keeping the temperature constant for 4 h. This allowed us to isolate 277 in 42% yield as a single isomer (entry 6). Traces of what is believed to be the other isomer of 277 were observed, however we did not isolate it in a pure state. Attempts to improve upon this yield by adding DBU at different temperatures were unsuccessful (entries 7 and 8). It is also
important to note that this reaction was rather difficult to perform experimentally, and it was highly irreproducible.

![Chemical structure of 251 and 277]

<table>
<thead>
<tr>
<th>entry</th>
<th>time A(^1) (h)</th>
<th>temp. X (^{\circ})C</th>
<th>base</th>
<th>time B(^1) (h)</th>
<th>temp. Y (^{\circ})C</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>DBU</td>
<td>4</td>
<td>25</td>
<td>degradation</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
<td>DBU</td>
<td>1</td>
<td>0</td>
<td>degradation</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>-78</td>
<td>DBU</td>
<td>4</td>
<td>-78-&gt;25</td>
<td>mixture</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>-78</td>
<td>Et(_3)N</td>
<td>4</td>
<td>-78-&gt;25</td>
<td>mixture</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>-78-&gt;25</td>
<td>DBU</td>
<td>4</td>
<td>25</td>
<td>degradation</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>-78-&gt;50</td>
<td>DBU</td>
<td>4</td>
<td>-50</td>
<td>277 (42%)</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>-78-&gt;60</td>
<td>DBU</td>
<td>4</td>
<td>-60</td>
<td>277 (12%)</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>-78-&gt;40</td>
<td>DBU</td>
<td>4</td>
<td>-40</td>
<td>277 (7%)</td>
</tr>
</tbody>
</table>

**Table 3.1.** \(^1\)Time the reaction was maintained at the corresponding temperature.

The geometry of 277 is not certain. However, the difference in shift of the triplets corresponding to the two terminal ethyl hydrogens in the \(^1\)H NMR spectrum of 277 is very small (0.03 ppm). Based on the observed shifts for the analogous hydrogens in *E*-258 (1.38, 1.33 ppm) and *Z*-258 (1.36, 0.94 ppm), one would expect a bromine in the Z position to have a more profound effect on these shifts in 277. Tentatively, this would suggest that in this case it is the *E* isomer of 277 that has been obtained.

The synthesis of 277 was also achieved with N-bromosuccinimide (NBS), however this also led to a complex mixture of products and 277 was only
obtained in very low yield. Lowering the reaction temperature led to only traces of product (Scheme 3.29).

![Scheme 3.29](image)

It had initially been hoped that the bromination and subsequent coupling of 277 with an appropriate boronic acid would allow us to synthesise functionalised methylenediazetidines in good yields. Unfortunately, as the bromination step was proving to be particularly difficult, this route did not appear to be suitable. Nevertheless, the Suzuki coupling of 277 and phenyl boronic acid afforded $E$-258 in 50% yield without optimisation (Scheme 3.30).\(^\text{140}\) \(^\text{1}^\text{H NMR data for this reaction was consistent with that of E-258 obtained from the Heck reaction (Figure 3.6), confirming the geometry is the same. However this does not prove the geometry of 277, as Suzuki has shown that this reaction does not necessarily proceed with retention at the vinyl halide position.}^\text{141}\) Therefore we can only speculate that this reaction proceeded with retention of stereochemistry based on the $^\text{1}^\text{H NMR data, as previously discussed.}

![Scheme 3.30](image)
3.3.3 Hydrogenation Studies of 3-Methylene1,2-diazetidines

Shipman and co-workers have previously reported that hydrogenation of dibenzyl 7,8-diazabicyclo[4.2.0]oct-1-ene-7,8-dicarboxylate (257), proceeds smoothly under heterogenous hydrogenation conditions (Scheme 3.24). We wished to investigate the enantioselective hydrogenation of the functionalised methylenediazetidines 258, 260, 275 and 276. To do this, the use of chiral homogenous catalysts would most likely be required. Although the chemistry of 3-methylene-1,2-diazetidines is still largely unexplored, there are a number of examples in the literature for the asymmetric hydrogenation of related systems that proceed with excellent enantioselectivity. Lu’s work, which has been discussed previously (Scheme 3.3), involves the hydrogenation of structures that share a number of similarities with 3-methylene-1,2-diazetidines, namely nitrogen containing heterocycles with exocyclic double bonds. In addition, there is a lot of research into the enantioselective hydrogenation of enamides. For example, Zhang and co-workers have demonstrated the asymmetric hydrogenation of a variety of enamides 278 with excellent enantioselectivities using a rhodium catalyst and (R,R)-BICP (Scheme 3.31). Although it is still unclear as to how chemically similar the double bond of a 3-methylene-1,2-diazetidine is to that of an enamide, we believe that such examples provide a good indication of the feasibility of the asymmetric hydrogenation of such systems.
As the only previous example for the hydrogenation of a methylenediazetidine involved strained bicycle 257 (Scheme 3.24), we felt it necessary to investigate the hydrogenation of unfunctionalised methylenediazetidine 251 with palladium on carbon as catalyst before exploring the large variety of chiral homogeneous catalysts that are available. The reaction proceeds slowly in ethyl acetate to give a mixture of desired product 280, as well as the over-reduced product 281 (Table 3.2 entry 1). Switching the solvent to methanol increases the rate of reaction but also that of over-reduction (entry 2). Using triethylsilane as a hydrogen source proved to be a convenient alternative to a hydrogen balloon, as it offered faster reactions without compromising yields or selectivity (entries 3 and 4).\textsuperscript{144} Under the most effective conditions (entry 4) the reduced 1,2-diazetidine 280 was isolated in 70\% yield.
Characterisation of the two products was straightforward using NMR and mass spectroscopy techniques. A doublet in the \(^1\)H NMR spectrum of 280, corresponding to the exocyclic methyl group, as well as one new ring hydrogen, were diagnostic in its characterisation. The over-reduced product 281 displayed two extra mass units in the mass spectrum as well as a characteristic \(n\)-propyl pattern in the \(^1\)H NMR spectrum, similar to that of 232 (Scheme 3.8). This was mildly surprising, as we expected any over-reduction that might have occurred would involve cleavage of the N–N bond. However, based on the \(^1\)H NMR data, this was clearly not the case.

Next the hydrogenation of the phenyl-substituted methylenediazetidine 258 was investigated. Under a balloon of hydrogen, the reaction was found to be extremely slow, and even after three days only traces of 282 and 283 were observed. However, the use of triethylsilane again proved effective, enabling the reaction to go to completion within 8 hours. Unfortunately, the presence of

<table>
<thead>
<tr>
<th>H(_2) source</th>
<th>catalyst</th>
<th>solvent</th>
<th>Time (h)</th>
<th>280 (%)</th>
<th>281 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 H(_2) (1Bar)</td>
<td>Pd/C</td>
<td>EtOAc</td>
<td>24</td>
<td>68</td>
<td>5</td>
</tr>
<tr>
<td>2 H(_2) (1Bar)</td>
<td>Pd/C</td>
<td>MeOH</td>
<td>16</td>
<td>54</td>
<td>23</td>
</tr>
<tr>
<td>3 Et(_3)SiH</td>
<td>PdCl(_2)</td>
<td>EtOH</td>
<td>2</td>
<td>62</td>
<td>29</td>
</tr>
<tr>
<td>4 Et(_3)SiH</td>
<td>PdCl(_2)</td>
<td>EtOAc</td>
<td>4</td>
<td>70</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 3.2.
the phenyl substituent lead to increased quantities of over-reduction (Scheme 3.32).

Scheme 3.32

The occurrence of this increased over-reduction may have arisen for either electronic or steric reasons. Clearly the double bond of 258 is more hindered than that of parent 251 and so palladium will not coordinate as easily, whereas C–N bond insertion, leading to over-reduction to 283, would be less affected by the presence of the phenyl substituent. From an electronic viewpoint, the presence of the phenyl substituent on 258 may simply alter the electronics of the system in a way that increases the lability of the C–N bond.

Before turning our attention to chiral catalysts, we wished to attempt a hydrogenation with Wilkinson’s catalyst. As many asymmetric hydrogenation complexes are based on homogeneous rhodium complexes, we believed a hydrogenation with Wilkinson’s catalyst would offer some initial insights into the reactivity of these chiral catalysts. No reaction occurred at 1 bar, although this was not altogether unexpected, and the reaction was found to proceed under higher temperature and pressure. Although the yield for the reaction is modest,
we were pleased to observe that under these conditions, problems of over-reduction were avoided (Scheme 3.33).

We began our study into the asymmetric hydrogenation of methylenediazetidines with the \([\text{Rh(NBD)}_2]\text{BF}_4\) catalyst and the Josiphos ligand that we used initially for the attempted hydrogenation of phenylimidazolinone 210 (Scheme 2.38). Under the same conditions used previously, \((R)-280\) was obtained in 89% yield and an encouraging 44% ee. The assignment of the absolute stereochemistry of 280 will be discussed later in this chapter (Scheme 3.34).

Determination of the enantiomeric purity of 280 was achieved with HPLC analysis using a Chiralcel AD column (5% \(i\)PrOH/\(n\)-hexane; 1.0 mL/min; 220
nm) to reveal an ee of 44% [R = 22.19 min (major), 24.74 (minor)]. A racemic sample of 280 obtained from the previous reaction with Wilkinson’s catalyst (Scheme 3.33) was used as a standard in this analysis.

Encouraged by this result, we examined the variation of the metal source and reaction conditions with this Josiphos ligand. Changing the solvent to methanol led to decreased enantioselectivity, as well as preference for the S enantiomer (Table 3.3, entry 1). Lowering the temperature to 30 °C was found to eliminate the formation of 281 as well as increase the enantioselectivity of 280 to 61% (entry 2). However, the rate of reaction was significantly reduced and starting material was mostly recovered. Using dichloromethane as the solvent under the same conditions resulted in both a loss in rate and enantioselectivity (entry 3). Finally switching the metal source to [Rh(COD)Cl]₂ was found to give slightly lower enantioselectivities but also further decreases in the rate of reaction (entries 4 and 5).

![Diagram of the reaction](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>280 (%)</th>
<th>281 (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(NBD)₂]BF₄</td>
<td>MeOH</td>
<td>50</td>
<td>63</td>
<td>10</td>
<td>4 (S)</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(NBD)₂]BF₄</td>
<td>EtOAc</td>
<td>30</td>
<td>28</td>
<td>0</td>
<td>61 (R)</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(NBD)₂]BF₄</td>
<td>CH₂Cl₂</td>
<td>30</td>
<td>8</td>
<td>0</td>
<td>53 (R)</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(COD)Cl]₂</td>
<td>EtOAc</td>
<td>30</td>
<td>2</td>
<td>0</td>
<td>58 (R)</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(COD)Cl]₂</td>
<td>CH₂Cl₂</td>
<td>30</td>
<td>8</td>
<td>0</td>
<td>49 (R)</td>
</tr>
</tbody>
</table>

Table 3.3
Having concluded that our first choice of catalyst and solvent appeared to be the most suitable, we applied these conditions to the hydrogenation of 252, as we wanted to explore what effect (if any) the bulkier butyl groups would have on enantioselectivity. Hydrogenation of 252 proceeded in slightly lower yield than 251, but we were pleased to observe an ee of 60% at 50 °C with no evidence of over-reduction (Scheme 3.35).

![Scheme 3.35](image)

In addition, we also wished to investigate how effective these conditions were for the enantioselective hydrogenation of substituted methylenediazetidines, such as 258. The presence of a phenyl substituent was found to decrease the rate of hydrogenation significantly, as only a trace of product was observed after 5 h. Increasing the reaction time to 72 h allowed us to isolate 282 in 54% with 33% ee (Scheme 3.36).

![Scheme 3.36](image)

Following on from these initial results, we turned our attention to variation of the chiral ligand with a view to improving the enantioselectivities. For the purposes of the study, methylenediazetidine 251 was chosen as the substrate.
Although higher enantioselectivities would likely be obtained at lower temperatures, for convenience, ligand screening was conducted at 50 °C in order to get good conversions (Scheme 3.37).

Scheme 3.37

To begin with, other Josiphos ligands were investigated (Figure 3.6), followed by other ferrocene-based complexes Walphos and Taniaphos (Figure 3.7). Members of the Mandyphos family of ligands were found to be particularly promising (Figure 3.8). These ligands are all produced by Solvias™ and are commercially available. Finally, three ligands based on the more conventional BINAP type structure were investigated (Figure 3.9).

Figure 3.6
Figure 3.7

**Walphos W001-1**
yield = 34%
ee = 70% (S)

**Walphos W002-1**
yield = 54%
ee = 80% (S)

**Taniaphos T001-1**
yield = 52%
ee = 25% (R)

**Taniaphos T002-1**
yield = 85%
ee = 27% (S)

Figure 3.8

**Mandyphos M001-1**
yield = 92%
ee = 80% (S)

**Mandyphos M004-1**
yield = 98%
ee = 89% (S)

where Ar = 

![Chemical structure](image-url)
Following this investigation, it was quite apparent that Mandyphos M004-1 was the best ligand for the hydrogenation of methylenediazetidine 251, offering both excellent yield (98%) and enantioselectivity (89% ee). Of the ligands screened, M004-1 would appear to be the most bulky, this presumably limits the orientation with which 251 can coordinate to the catalyst and so increases the preference for one face over another.

Hydrogenation of other methylenediazetidines was then investigated with these reaction conditions, as it was hoped Mandyphos M004-1 would prove to be a ligand of broad scope for this asymmetric transformation. Unfortunately this was not the case, and the enantioselectivities with substituted methylenediazetidines were considerably lower. It should be noted that we were only able assign absolute stereochemistry of 280 based on the study in the next section (3.3.4), therefore the configurations of the other substrates 282, 284–287 are unknown (Table 3.4).
It is unclear why enantioselectivity decreases for substituted methylenediazetidines with M004-1. The decrease in rate of hydrogenation observed for these sterically hindered substrates (Scheme 3.36) suggests that they are unable to bind as effectively to the catalyst as 251 and this weaker coordination could be less facially selective. M004-1 has been shown to be an excellent ligand for other tri-substituted alkenes, such as 288 (Scheme 3.38).\(^{145}\) Hydrogenation of 288 was successful under far milder conditions than we have been able to achieve with our substrates. This may be due to the carbonyl group adjacent to the double bond in 288, which most likely chelates to the rhodium catalyst and increases the rate. Presumably this coordination also leads to better facial selectivity.
Scheme 3.38

Due to time constraints we were unable to continue to investigate other catalyst and ligand combinations for the substituted derivatives. Nevertheless it is believed that further study could lead to identification of ligands for the enantioselective hydrogenation of a wide range of methylenediazetidines to 1,2-diazetidines.

3.3.4 N–N bond cleavage and assignment of stereochemistry

Diazetidines 280 and 282 were reductively cleaved with LiDBB to yield the corresponding carbamate-protected 1,2-diamines (Scheme 3.39).100

Scheme 3.39

To ascertain the absolute stereochemistry of 280 produced in the asymmetric hydrogenations, we prepared authentic samples of 290 in racemic and enantiomerically enriched forms from commercially available (±) and (R)-1,2-diamino propane (292) and ethyl chloroformate (Scheme 3.40)
Diamine 290 possesses very little UV activity; making chiral HPLC detection difficult. The enantiomers could not be resolved by chiral HPLC on a Chiralcel AD column or by gas chromatography using a Chrompak CP-Chirasil Dex Cβ column. However, $^1$H NMR analysis of (±)-290 in $d_6$-benzene in the presence of William H. Pirkle’s alcohol (S enantiomer) allowed us to resolve the doublet, corresponding to the methyl group at C-3, into two separate peaks. Spiking the $^1$H NMR sample with an equivalent amount of (R)-290 enabled us to determine that by the increased integration of the upfield signal, this peak corresponded to the R enantiomer. $^1$H NMR analysis of 290, obtained by reduction with LiDBB (Scheme 3.39) with Pirkle’s alcohol resulted in resolution with the predominant peak being the downfield signal. Thus, we were able to determine that asymmetric hydrogenation of 251 with Mandyphos M004-1 is selective for the S enantiomer (Figure 3.10). Furthermore, integration of the resolved doublets were found to give 89% ee, this indicates that the LiDBB reduction causes no racemisation, as the ee is equal to that of the starting 1,2-diazetidine 280 (Appendix 2).
In summary we have demonstrated an efficient two-step synthesis of protected 1,2-diamine 290 from methylenediazetidine 251 with good yields and excellent enantioselectivity (Scheme 3.41).
3.3.5 Other reactions of 3-methylene-1,2-diazetidines

In other studies, we have further explored the chemistry of the exocyclic double bond of these substrates. We began our investigations with the Diels-Alder cycloaddition reaction. The electronic nature of the methylenediazetidine is not fully understood, although the $^1$H NMR for the two olefinic hydrogens (4.94 and 4.40 ppm in CDCl$_3$) would indicate a relatively electron neutral double bond. We began using 1,3-cyclopentadiene, which is known to be a highly reactive diene, providing good yields of cycloadducts with a wide range of electron-deficient dienophiles.\textsuperscript{147} Methylene diazetidine \textbf{251} was heated with 5 equivalents of freshly cracked 1,3-cyclopentadiene in a sealed tube at 150 °C. Unfortunately, only starting material and cyclopentadiene dimer were recovered from this reaction (Scheme 3.42).

\begin{equation}
\text{EtO}_2\text{C}_2\text{N} - \text{N} - \text{CO}_2\text{Et} + \text{PhMe} \xrightarrow{150 \degree C, 6 h} \text{no reaction}
\end{equation}

\textbf{Scheme 3.42}

The lack of reactivity with 1,3-cyclopentadiene suggests that the double bond of \textbf{251} is not electron-deficient and that an inverse electron demand Diels-Alder reaction might be more appropriate.\textsuperscript{148} Thus, cycloaddition with the electron-deficient diene, ethyl sorbate was attempted. No reaction was observed at room temperature, or when heated to 100 °C (Scheme 3.43).

\begin{equation}
\text{EtO}_2\text{C}_2\text{N} - \text{N} - \text{CO}_2\text{Et} + \text{CO}_2\text{Et} \xrightarrow{25 \degree C, 48 h \text{ or } 100 \degree C, 24 h} \text{no reaction}
\end{equation}

\textbf{Scheme 3.43}
Next, 1,3-dipolar cycloadditions were explored. The azomethine ylide 293 (generated in situ from sarcosine ethyl ester and paraformaldehyde) was found to react with methylenediazetidine 251 to yield a complex mixture of compounds, alongside large quantities of unreacted starting material. A peak corresponding to either 294 or 295 was present in the crude mass spectrum (m/z = 366, [M+Na]+), however all attempts to isolate 294 by column chromatography were unsuccessful and only more complex mixtures were obtained, with no conclusive peaks identified in the corresponding ¹H NMR spectra (Scheme 3.44).

![Scheme 3.44](image)

Cycloaddition reactions with nitrile oxides were also explored. It was believed that reaction of 251 with phenyl nitrile oxide (296) would furnish one of the two spirocyclic regioisomers 297 or 298 (Scheme 3.45).
was formed \textit{in situ} by the deprotonation of 299, which subsequently reacted with 251 to form unidentified product 300 (Scheme 3.46).

\begin{align*}
\text{EtO}_2\text{C}_2\text{N}_2\text{CO}_2\text{Et} + \text{PhCH}_2\text{Cl} & \xrightarrow{\text{CH}_2\text{Cl}_2, \text{Et}_3\text{N}, 25 \, ^\circ\text{C}, 12 \, \text{h}} ? \\
\text{EtO}_2\text{C}_2\text{N}_2\text{CO}_2\text{Et} & \xrightarrow{\text{CH}_2\text{Cl}_2, \text{Et}_3\text{N}, 25 \, ^\circ\text{C}, 12 \, \text{h}} \text{EtO}_2\text{C}_2\text{N}_2\text{CO}_2\text{Et} \\
\text{EtO}_2\text{C}_2\text{N}_2\text{CO}_2\text{Et} & \xrightarrow{\text{CH}_2\text{Cl}_2, \text{Et}_3\text{N}, 25 \, ^\circ\text{C}, 12 \, \text{h}} \text{EtO}_2\text{C}_2\text{N}_2\text{CO}_2\text{Et}
\end{align*}

Scheme 3.45

Unknown product 300 possessed the correct mass for both 297 and 298 (m/z = 356 [M+Na]), however the $^1$H NMR spectrum was not convincing. Peaks corresponding to the phenyl ring, two ethyl chains, and what was initially thought to be two diazetidine ring hydrogens were present, but the remaining two hydrogens appeared far further downfield than one would expect in either of the expected products (Appendix 3). Based upon this NMR data, we proposed that reaction of 251 with phenyl nitrile oxide initially forms 297, which then undergoes ring-opening followed by aromatisation to afford isoxazole 300 (Scheme 3.47).

\begin{align*}
\text{EtO}_2\text{C}_2\text{N}_2\text{CO}_2\text{Et} + \text{PhCH}_2\text{Cl} & \xrightarrow{\text{CH}_2\text{Cl}_2, \text{Et}_3\text{N}, 25 \, ^\circ\text{C}, 12 \, \text{h}} \text{EtO}_2\text{C}_2\text{N}_2\text{CO}_2\text{Et} \\
\text{EtO}_2\text{C}_2\text{N}_2\text{CO}_2\text{Et} & \xrightarrow{\text{CH}_2\text{Cl}_2, \text{Et}_3\text{N}, 25 \, ^\circ\text{C}, 12 \, \text{h}} \text{EtO}_2\text{C}_2\text{N}_2\text{CO}_2\text{Et}
\end{align*}

Scheme 3.47
As it is unlikely that 298 would be able to undergo this ring-opening process, it is believed that 300 is the correct regioisomer for this reaction.

The same reaction was attempted with methylenediazetidine 274, as the intermediate would be unable to aromatise and so the spirocyclic intermediate may be obtained. However, no reaction was observed with this highly hindered substrate, and the starting material remained unchanged (Scheme 3.48).

Scheme 3.48

In other chemistry, tetracyanoethylene was found to react with a number of methylenediazetidines under mild conditions to yield the novel, spirocyclic diazetidines 301-304. The tetra-substituted alkene 274 proceeded in low yield, although this was not unexpected due to the steric hindrance of the double bond (Scheme 3.49).
These compounds were isolated as stable crystalline solids and we were able to obtain an X-ray structure of 303 that clearly reveals the intriguing spirocyclic structure (Figure 3.11).

Figure 3.11

Mike Brown had previously attempted epoxidation of 254 with m-CPBA. However, this led to ring-opened product, either 306 or 307, which is expected.
to arise from attack of the carboxylate onto the initially formed epoxide 305 (Scheme 3.50).

![Scheme 3.50](image)

**Scheme 3.50**

Although epoxide 305 was not obtained, the presence of the ring-opened compound suggests that its formation does occur. We therefore decided to investigate epoxidation with milder conditions. DMDO was selected as an oxidising agent, as no nucleophilic side-products are produced.\(^{153}\) The reaction was found to proceed easily under mild conditions to give epoxide 308 in excellent yield. Mass spectroscopic analysis of 308 revealed it to have the correct mass \((m/z = 253 \text{ [M+Na]}^+)\) and the \(^1\text{H NMR}\) spectrum displayed four doublets corresponding to the four ring hydrogens (Appendix 4). The spirocyclic compound was found to be quite unstable, rapidly degrading on silica gel, or within several days when stored under nitrogen. Fortunately, the reaction was sufficiently clean that the product could be isolated without the need for purification (Scheme 3.51).
The conditions used for the epoxidation of 251 were also applied to diazetidines 252, 273 and 274. Based on crude ¹H NMR and mass spectroscopy data, the reactions are believed to have been successful. However the desired compounds were not produced cleanly, and we were unable isolate them due to their instability.

Compounds containing cyclopropane rings are prominent in a wide range of natural products and many possess biological activity. Noranthroplone (309) for example, exhibits cytotoxicity against B-16 melanoma cells whereas (+)-E-chrysanthemic acid (310) is a potent insecticide (Figure 3.12).

With this mind, we thought that the cyclopropanation of substituted methylenediazetidines would provide a potentially useful synthetic route to a variety of novel functionalised 1,2-diamino cyclopropane products. The cyclopropanation of methylenediazetidine 254, which also leads to unexpected carbenoid insertion into the N–N bond, has already been reported (Scheme
It was expected however, that compounds such as 261 should be capable of hydrolysis under aqueous acidic conditions. This would provide an alternative route to the corresponding 1,2-diamines compared to direct N–N bond cleavage as previously discussed. Cyclopropanation of 251 led to the expected product 311, although all attempts to purify it led to degradation. Therefore it was hydrolysed directly with hydrochloric acid to 312, tentatively assigned based on the ^1H NMR spectrum, which possesses a broad singlet at 0.83 ppm, integrating to four hydrogens, which is assigned to the cyclopropane ring. In addition, mass spectroscopic data are in accordance with the structure (m/z = 253 [M+Na]^+) (Scheme 3.52).

Scheme 3.52

The low yield for this reaction likely arises from the first step not going to completion, as there is a significant amount of starting material still present in the crude ^1H NMR spectrum. Increasing the reaction time (3 days) and equivalents of diethyl zinc and diiodomethane (10 eq. of each) did not help drive the reaction to completion. The cyclopropanation of 258 was then
attempted, however no product was observed and only starting material was recovered. Increasing the reaction temperature did not yield any of expected product 313 (Scheme 3.53). Unfortunately due to time constraints, we were unable to pursue this chemistry further.

Scheme 3.53

3.4 Conclusions and Future Work

We have identified conditions for the asymmetric synthesis of 1,2-diaminopropane, with high ee, via a two-step process. This method has been extended to other substrates, however the enantioselectivities are lower. For example, with phenyl substituted 258, the ee fell to 33% with Josiphos J001-1 (Scheme 3.36). We have been successful in widening the scope of the Heck coupling reaction (Scheme 3.28) and demonstrating the first Suzuki coupling with bromide 277. The first examples of [2+2] (Scheme 3.49) and [2+3] (Scheme 3.47) cycloadditions of 251 have been realised. Taken together with the lack of reactivity with both electron-rich and electron-poor dienes in Diels-Alder reactions, these suggest that the double bond of these substrates is essentially electronically neutral. In addition, we have achieved the first epoxidation of 3-methylene-1,2-diazetidine (Scheme 3.54).
Although the Heck coupling proceeds with modest yields, it is believed that with optimisation the Suzuki reaction could provide a suitable alternative method. However, in order for this to be a viable option, the synthesis of bromide 277 would need to be further improved. This might be achieved through synthesis of 277 in which the bromine substituent is already in place. For example, bromination of alkene 314 followed by reduction could provide us with a suitable substrate for methylenediazetidine synthesis (Scheme 3.55). This method relies on the copper-catalysed ring closure favouring four over five-membered ring formation. Based on competition studies carried out on similar substrates by Li and co-workers, this might be the case and certainly merits further investigation.162
The hydrogenation of methylenediazetidine 251 has been achieved with excellent yield and enantioselectivity. Unfortunately, the same ligand proved to be unsuitable for functionalised methylenediazetidines 258, 260, 275 and 276. Presumably, high enantioselectivities with these substrates could be achieved, however a more rigorous ligand/catalyst screen would be required. If this were successful, the synthesis of a wide range of functionalised and enantiomerically enriched 1,2-diamines could be achieved, adding a new potentially powerful method to the literature.

Scheme 3.55
Chapter 4:

Experimental
General Information

Anhydrous solvents were purchased in Sure/Seal™ bottles from Sigma-Aldrich. All other solvents and reagents were used as received or purified by standard protocols. Petroleum ether refers to the fraction of petroleum ether having a boiling point between 40-60 °C. All experiments were performed under an inert atmosphere and moisture sensitive reactions were performed in flame-dried or oven-dried glassware.

Column chromatography was carried out using Matrex silica 60 unless otherwise stated. Thin layer chromatography was performed on pre-coated aluminium-backed plates (Merck Kieselgel 60 F_{254}) and were visualised using UV light and stained with potassium permanganate followed by heating.

Melting points were recorded on a Gallenkamp MPD350 apparatus and are reported uncorrected. Single crystal X-ray diffraction data were obtained using a Siemens SMART XRD system or an Oxford Diffraction Gemini XRD system. Optical rotations were measured with a AA1000 polarimeter and are quoted in $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$.

Infrared spectra were recorded on an Avatar 320 FT-IR or PerkinElmer Spectrum One FT-IR spectrometer with internal calibration. $^1$H and $^{13}$C spectra were recorded at 300 MHz and 75 MHz respectively on a Bruker DPX-300; at 400 MHz and 100MHz respectively on a Bruker DPX-400. Signals in the $^1$H NMR are reported as singlets (s), doublets (d), triplets (t), etc, which refer to the observed spin-spin coupling patterns. Chemical shifts are quoted in ppm,
downfield from TMS, with the residual solvent as internal standard. Coupling constants ($J$) are reported in Hertz. Ambiguous signals were assigned using COSY, HMQC, HMBC and nOe correlative spectra.

Low-resolution mass spectra were recorded on an Esquire 2000 platform with electrospray ionisation. High-resolution mass spectra were obtained using a Bruker MicroTOF instrument.

Chiral HPLC was conducted using a Gilson system using a Chiralcel AD column (1-5% iPrOH/n-hexane; 1.0 mL/min). UV absorbance was monitored at 220 nm by a Ranin Dynamax model UV-1. Racemic samples of the hydrogenation products were synthesised with Wilkinson’s catalyst (Appendix 5).
4-Phenyl-1,2,4-triazoline-3,5-dione (149)

To a stirred solution of 4-phenylurazole (200 mg, 1.13 mmol) in CH$_2$Cl$_2$ (20 mL) was added trichloromelamine (778 mg, 3.39 mmol) and the solution was stirred under nitrogen at room temperature for 3 h. The reaction mixture was filtered to separate the white precipitate and the solvent was removed in vacuo to provide 149 (197 mg, 99%) as a red solid that was used without further purification. $^1$H NMR (300 MHz, CDCl$_3$) 7.35 - 7.55 (5H, m, ArH), $^{13}$C NMR (75 MHz, CDCl$_3$) 158.7 (2C, ArC), 130.1 (1C, ArC), 129.5 (2C, ArCH), 129.1 (2C, ArCH), 125.2 (1C, ArC); $m/z$ (ES$^+$) 176 [M+H]$^+$. Data is in accordance with the reported values of Risi et al.$^{157}$

3-Phenyl-6-phenylsulfinyl-1,3,5-triazabicyclo[3.2.0]hepta-2,4-dione (166)

A solution of 149 (167 mg, 0.95 mmol) in CH$_2$Cl$_2$ (10 mL) was added to phenyl vinyl sulfide (0.13 mL, 0.95 mmol) in CH$_2$Cl$_2$ (7 mL) and stirred under nitrogen at room temperature for 0.5 h, by which point the solution had changed from deep red to pale yellow. The mixture was cooled to 0 °C and mCPBA (213 mg, 77 %, 0.95 mmol) was added in portions over 10 minutes, the mixture was allowed to reach room temperature and stirred for a further 1.5 h. The mixture
was then washed with a NaHCO$_3$(aq) solution (2 x 10 mL) and brine (2 x 10 mL), dried over MgSO$_4$ and concentrated in vacuo to afford a pale yellow solid. Column chromatography on silica gel (25% ethyl acetate in petroleum ether) gave 166 (22 mg, 7%) as a pale yellow solid (single diastereomer). M.p. 221.2-221.7 °C; IR (film) 1712 (C=O), 1045 (S=O), 743 (ArH) cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) 7.48 – 7.80 (10H, m, ArH), 5.91 (1H, dd, $J = 6.0, 7.3$ Hz, H-6), 4.55 (1H, dd, $J = 6.0, 10.0$ Hz, H-7), 4.36 (1H dd, $J = 7.3, 10.0$ Hz, H-7); $^{13}$C NMR (100 MHz, CDCl$_3$) 162.0 (1C, C-4) 161.1 (1C, C-2), 131.9 (ArCH), 131.4 (1C, ArC), 129.6 (ArCH), 129.1 (ArCH), 128.8 (ArCH), 126.5 (ArCH), 124.5 (ArCH), 79.5 (1C, C-6), 55.8 (1C, C-7); m/z (ES$^+$) 328 [M+H$^+$], 350 [M+Na$^+$]; HRMS (ES$^+$) $m/z$ calculated for C$_{16}$H$_{13}$N$_3$O$_3$SNa [M+Na$^+$]: 350.0570; found: 350.0578.

3-Phenyl-1,3,5-triazabicyclo[3.2.0]hept-6-ene-2,4-dione (167)

A solution of 166 (18 mg, 0.06 mmol) in chlorobenzene (3 mL) was placed in a high-pressure tube that was degassed and filled with nitrogen. The tube was heated to 150 °C for 3 h, allowed to cool and the mixture was filtered through Celite$. The solvent was removed in vacuo to give a viscous brown oil. Column chromatography (10% ethyl acetate in petroleum ether) gave 167 (5 mg, 48%) as a white solid. M.p. 137.8-138.4 °C; IR (film) 1728 (C=O), 1490 (Ar), 727 (Ar-H) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 7.36 – 7.47 (5H, m, ArH), 6.74 (2H, s, H-

$^1$Aromatic quaternary carbon is not observed
6, H-7); $^{13}$C NMR (100 MHz, CDCl$_3$) 155.0 (2C, C-2, C-4), 130.9 (1C, ArCH), 130.8 (1C, ArC), 129.5 (2C, ArCH), 129.3 (2C, ArCH), 125.4 (2C, C-6, C-7) m/z (ES$^+$) 224 [M+Na]$^+$; HRMS (ES$^+$) m/z calculated for C$_{10}$H$_8$N$_3$O$_2$ [M+H]$^+$: 202.0611; found: 202.0610.

1H-Imidazolin-2-one (185)

To a stirred suspension of hydantoin (4.00 g, 40.0 mmol) in THF (50 mL) at 0 °C was added DIBALH (1.5 M in toluene, 80 mL, 120.0 mmol) dropwise over 30 minutes. The reaction mixture was stirred for 1 h at 0 °C. Aqueous methanol (90%, 200 mL) was carefully added and the mixture was stirred at reflux for 16 h. Upon cooling the mixture was filtered and concentrated in vacuo. The crude product was recrystallised from ethanol to yield 185 (2.15 g, 64%) as a white crystalline solid. M.p. 250 - 251 °C; $^1$H NMR (400MHz, DMSO-$d_6$) 9.70 (2H, br s, NH), 6.24 (2H, s, CH); MS (ES$^+$) m/z 107 [M+Na]$^+$. Data is in accordance with the reported values of Banti et al.$^{112}$

4-Phenyl-1H-imidazolin-2-one (199)

To a solution of 185 (1.00 g, 11.90 mmol), Pd(OAc)$_2$ (133 mg, 0.59 mmol) and NaOAc$\cdot$3H$_2$O (4.85 g, 35.7 mmol) in DMSO (50 mL) was added Iodobenzene (2.01 mL, 17.85 mmol). The reaction mixture was stirred at 80 °C for 6 h. Upon
cooling, the solvent was removed via distillation. The crude product was recrystallised from IPA to yield 199 as a white crystalline solid (1.12 g, 52%). 

$^1$H NMR (400MHz, DMSO-$d_6$) 10.50 (1H, s, NH), 10.04 (1H, s, NH), 7.49 (2H, d, $J = 7.7$ Hz, ArH) 7.31 (2H, t, $J = 7.7$ Hz, ArH), 7.16 (1H, t, $J = 7.4$ Hz, ArH) 6.88 (1H, s, H-5); MS (ES$^+$) $m/z$ 183 [M+Na]$^+$. Data is in accordance with Chen et al.$^{111}$

**3-Benzylimidazolidin-2,4-dione (186)**

![Formula of 3-Benzylimidazolidin-2,4-dione (186)](image)

To a solution of hydantoin (1.00 g, 10 mmol) and potassium carbonate (5.52 g, 40 mmol) in DMF (25 mL) was added benzyl bromide (1.43 mL, 12 mmol) and stirred at 25 °C for 36 h. The reaction mixture was then diluted with water (100 mL) and extracted with CH$_2$Cl$_2$ (3 x 100 mL). The combined organic layers were washed with water (5 x 300 mL), dried over MgSO$_4$ and concentrated in vacuo. The crude product was recrystallised from ethanol to afford 186 (1.39 g, 72%) as a white crystalline solid. $^1$H NMR (400 MHz, CDCl$_3$) 7.23 – 7.48 (5H, m, ArH), 5.51 (1H, br s, H-1), 4.69 (2H, s, NCH$_2$Ph) 3.98 (2H, s, H-5); (ES$^+$) $m/z$ = 213 [M+Na]$^+$. Data is in accordance with Kohn and co-workers.$^{158}$
3-Benzy1-4-phenylimidazolin-2-one (200)

To a solution of 186 (500 mg, 2.6 mmol) in THF (10 mL) at -25 °C was added phenyl magnesium chloride (15.8 mL, 1M in Et₂O, 15.8 mmol). The solution was then allowed to warm to 25 °C. After 16 h the reaction was quenched with methanol (2 mL) and diluted with Et₂O. The mixture was then washed with NH₄Cl(aq) (3 x 50 mL) and concentrated in vacuo. Purification on silica gel (25% ethyl acetate in petroleum ether afforded 200 (188 mg, 29%) as a white solid. 

¹H NMR (400 MHz, CDCl₃) 10.14 (1H, br s, H-1), 7.19 – 7.49 (8H, m, ArH) 7.12 (2H, d, 8.0 Hz, ArH), 6.40 (1H, d, 2.5 Hz, H-5), 4.97 (2H, s, NCH₂Ph); (ES⁺) m/z = 251 [M+H]⁺. Data is in accordance with the values reported by Meanwell et al.¹⁵⁹

4-Phenylimidazolidin-2-one (201)

A solution of 199 (300 mg, 1.88 mmol) in acetic acid (5 mL) was passed through an H-Cube® loaded with a 10% palladium on carbon cartridge at 100 bar, 100 °C until no starting material remained by LCMS. The mixture was then concentrated in vacuo. Purification on silica gel (50% ethyl acetate in petroleum ether) afforded 201 (161 mg, 53%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) 7.34 (5H, m, ArH), 6.80 (1H, s, NH), 6.26 (1H, s, NH), 4.73 (1H, dd, J = 6.8, 9.8 Hz, H-4), 3.69 (1H, dd, J = 9.8, 11.4 Hz, H-5), 3.01 (1H, dd, J = 6.8,
11.4 Hz, H-5); (ES$^+$) $m/z = 162$ [M+H]$^+$. Data is in accordance with the values reported by Kohn et al.$^{158}$

**1-Phenylethane-1,2-diamine dihydrochloride (211)**

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{NH} \\
\text{PH} & \quad \text{2HCl}
\end{align*}
\]

A solution of 201 (120 mg, 0.75 mmol) in THF (3 mL) and 4M HCl (2 mL) was stirred at 80 °C for 6 h. Upon cooling, the reaction mixture was concentrated *in vacuo* and the resulting residue was washed with IPA to afford 211 (84 mg, 54%) as a white solid. M.p. = 300-301 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) 9.01 (6H, br s, NH), 7.60-7.70 (2H, m, ArH), 7.35-7.50 (3H, m, ArH), 4.70 (1H, t, $J = 6.5$ Hz, H-1), 3.55 (1H, dd, $J = 6.5$, 13.4 Hz, H-2), 3.23 (1H, dd, $J = 6.5$, 13.4 Hz, H-2). Data is accordance with the values reported by Muniz and co-workers.$^{68}$

**Imidazolidin-2-one (203)**

\[
\begin{align*}
\text{O} & \quad \text{NH} \\
\text{H} & \quad \text{N}
\end{align*}
\]

A solution of 185 (46 mg, 0.55 mmol) in methanol (5 mL) was passed through an H-Cube® loaded with a 10% palladium on carbon cartridge at 50 bar, 100 °C until no starting material remained by LCMS. The solution was then concentrated *in vacuo*. Purification on silica gel (33% ethyl acetate in petroleum ether) afforded 203 (29 mg, 64%) as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) 6.11 (2H, br s, H-1, H-3) 3.26 (4H, s, H-4, H-5); (ES$^+$) $m/z = 87$ [M+H]$^+$. The Data is in accordance with the values reported by Mizuno et al.$^{160}$
1,3-Diacetylimidazolin-2-one (189)

A solution of 185 (950 mg, 11.3 mmol) in acetic anhydride (10 mL) was stirred under reflux at 150 °C for 1 h. The mixture was concentrated in vacuo. Recrystallisation from ethanol afforded 189 (1.29 g, 68%) as a white crystalline solid. $^1$H NMR (300 MHz, DMSO-d$_6$) 7.15 (2H, s, H-4, H-5), 2.53 (6H, s, CH$_3$); (ES$^+$) m/z = 191 [M+Na]$^+$. Data is in accordance with the values reported by Banti and co-workers.$^{112}$

1-Acetylimidazolidin-2-one (205)

To a solution of 185 (75 mg, 0.45 mmol) in methanol (2 mL) was added 10% palladium on carbon (8 mg) and the suspension was stirred under a hydrogen atmosphere at 25 °C for 18 h. the reaction mixture was filtered over a plug of Celite®, washed through with methanol (20 ml) and concentrated in vacuo. Purification on silica gel (33% ethyl acetate in petroleum ether) afforded 205 (54 mg, 95%) as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) 6.19 (1H, br s, H-3), 3.96 (2H, t, J = 8.0 Hz, H-5) 3.51 (2H, t, J = 8.0 Hz, H-4), 2.50 (3H, s, CH$_3$); (ES$^+$) m/z = 151 [M+Na]$^+$. Data is in accordance with the values reported by Bach and co-workers.$^{161}$

1-Acetyl-4-phenyl-imidazolin-2-one (206)

\[
\text{HN-} \quad \text{N}^1 \quad \text{Ac} \\
\text{Ph}
\]

To a solution of 199 (500 mg, 3.12 mmol) in DMF (10 mL) was added dropwise acetyl chloride (244 µL, 3.44 mmol) and triethylamine (480 µL, 3.44 mmol) and the resulting reaction was stirred at 80 °C for 3 h. Upon cooling, the solution was diluted with water (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were then washed with water (5 x 150 mL), dried over MgSO₄ and concentrated in vacuo. Purification on silica gel (25% ethyl acetate in petroleum ether) afforded 206 (320 mg, 46%) as a white crystalline solid. M.p. 236.5 – 238.1 °C; IR (film) 3151 (N-H), 1698 (C=O), 1357 (C-O), 730 (Ar-H) cm⁻¹; ¹H NMR (400 MHz, DMSO-ｄ₆) 11.24 (1H, s, H-3) 7.46 (2H, d, J = 7.5 Hz, ArH), 7.30-7.46 (4H, m, ArH, H-5), 2.56 (3H, s, COCH₃); ¹³C NMR (100 MHz, DMSO-ｄ₆) 167.8 (1C, C-2), 152.0 (1C, NCOCH₃), 128.8 (2C, ArCH), 128.0 (1C, ArCH), 127.6 (1C, ArC), 124.5 (1C, C-4), 124.0 (2C, ArCH), 102.7 (1C, C-5), 23.6 (1C, COCH₃); (ES⁺) m/z = 225 [M+Na]⁺; HRMS (ES⁺) m/z calculated for C₁₁H₁₀N₂O₂Na [M+Na]⁺: 225.0634; found: 225.0635.

1-(2-Methylpropanoyl)-4-phenyl-imidazolin-2-one (208)

\[
\text{HN-} \quad \text{N}^1 \quad \text{COPr} \\
\text{Ph}
\]

To a solution of 199 (500 mg, 3.12 mmol) in DMF was added 2-methylpropanoyl chloride (360 µL, 3.44 mmol) triethylamine (480 µL, 3.44 mmol) and the resulting reaction was stirred at 80 °C for 3 h. Upon cooling, the
solution was diluted with water (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were then washed with water (5 x 150 mL), dried over MgSO₄ and concentrated in vacuo. Purification on silica gel (20% ethyl acetate in petroleum ether) afforded 208 (388 mg, 54%) as a white crystalline solid. M.p. 198.6 – 199.3 °C; IR (film) 3150 (NH), 2970 (CH), 1694 (C=O), 728 (Ar-H); ¹H NMR (400 MHz, DMSO-d₆) 10.46 (1H, br s, H-3), 7.40 – 7.46 (2H, m, ArH) 7.19 – 7.32 (4H, m, ArH, H-5), 3.91 (1H, sept, J = 6.8 Hz, NCOCH(CH₃)₂), 1.24 (6H, d, J = 6.8 Hz, NCOCH(CH₃)₂); ¹³C NMR (100 MHz, DMSO-d₆) 175.0 (1C, C-2), 151.5 (1C, NCOCH(CH₃)₂), 128.8 (2C, ArCH), 128.1 (1C, ArCH), 128.0 (1C, ArC), 124.6 (1C, C-4), 124.1 (2C, ArCH), 103.2 (1C, C-5), 32.3 (1C, NCOCH(CH₃)₂), 18.5 (2C, NCOCH(CH₃)₂); (ES⁺) m/z = 253 [M+Na]⁺; HRMS (ES⁺) m/z calculated for C₁₃H₁₄N₂O₂Na [M+Na]⁺: 253.0947; found: 253.0947.

1-(2,2-Dimethylpropanoyl)-4-phenyl-imidazol-2-one (209)

\[
\begin{align*}
\text{HN} & \quad \text{COBu} \\
\text{Ph} & \quad \quad \text{HN} \\
\end{align*}
\]

To a solution of 199 (500 mg, 3.12 mmol) in DMF was added 2,2-dimethylpropanoyl chloride (424 µL, 3.44 mmol) triethylamine (480 µL, 3.44 mmol) and the resulting reaction was stirred at 80 °C for 3 h. Upon cooling, the solution was diluted with water (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were then washed with water (5 x 150 mL), dried over MgSO₄ and concentrated in vacuo. Purification on silica gel (20% ethyl acetate in petroleum ether) afforded 209 (388 mg, 51%) as a white crystalline
solid. M.p. 214.2 – 215.3 °C; IR (film) 3167 (NH), 2973 (CH$_3$), 1715 (C=O), 757 (Ar-H); $^1$H NMR (400 MHz, CDCl$_3$) 11.11 (1H, br s, H-3) 7.48 (2H, d, $J$ = 7.4 Hz, ArH), 7.22 – 7.30 (4H, m, ArH, H-5), 1.46 (9H, s, 3 x CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) 176.8 (1C, C-2), 152.3 (1C, NCO(CH$_3$)$_3$), 129.1 (2C, ArCH), 128.5 (1C, ArCH), 128.4 (1C, ArC), 125.2 (1C, C-4), 124.0 (2C, ArCH), 105.5 (1C, C-5), 41.5 (1C, NCO(CH$_3$)$_2$), 25.9 (3C, NCO(CH$_3$)$_3$); (ES$^+$) $m/z$ = 267 [M+Na]$^+$; HRMS (ES$^+$) $m/z$ calculated for C$_{14}$H$_{16}$N$_2$O$_2$Na $[M+Na]^+$: 267.1104; found: 267.1105.

1-Acetyl-4-phenyl-imidazolidin-2-one (210)

\[
\begin{align*}
\text{HN} & \quad \text{N-Ac} \\
\text{Ph} & \quad \text{O}
\end{align*}
\]

To a solution of 206 (200 mg, 1.0 mmol) in methanol (5 mL) was added 10% palladium on carbon (20 mg) and the suspension was stirred under a hydrogen atmosphere at 25 °C for 16 h. The reaction mixture was filtered over a plug of Celite®, washed through with methanol (20 ml) and concentrated in vacuo. Purification on silica gel (25% ethyl acetate in petroleum ether) afforded 210 (185 mg, 92%) as a crystalline white solid. M.p. 164.1 – 166.3 °C; IR (film) 3168 (NH), 1647 (C=O), 734 (ArH); $^1$H NMR (400 MHz, CDCl$_3$) 7.21 – 7.44 (5H, m, ArH), 6.23 (1H, br s, H-3), 4.70 (1H, dd, $J$ = 6.7, 9.8 Hz, H-4), 4.21 (1H, dd, $J$ = 9.7, 11.3 Hz, H-5), 3.61 (1H, dd, $J$ = 6.5, 11.5 Hz, H-5), 2.41 (3H, s, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) 170.7 (1C, C-2), 156.3 (1C, NCOCH$_3$), 140.5 (1C, ArC), 129.2 (2C, ArCH), 128.7 (1C, ArCH), 125.9 (2C, ArCH), 52.0 (1C, C-4), 50.7 (1C, C-5), 23.5 (1C, CH$_3$); (ES$^+$) $m/z$ = 227 [M+Na]$^+$; HRMS
(ES’) m/z calculated for C_{11}H_{13}N_{2}O_{3}S [M+Na]^+: 227.0791; found: 227.0791.

**N-Tosyl-5-methylene-1,3-oxazolidin-2-imine (229)**

![Chemical Structure](image)

To a solution of N-tosyl-N’-(2-propyn-1-yl)urea (498 mg, 1.98 mmol) in acetonitrile (10 mL) was added gold (III) chloride (60 mg, 0.20 mmol) and the mixture was heated to reflux for 2 h. Upon cooling to room temperature, triethylamine was added and the reaction mixture was stirred for a further 2 minutes. The solution was then filtered over a plug of silica, washed through with ethyl acetate (20 mL) and concentrated *in vacuo*. Purification on silica gel (25% ethyl acetate in hexane) afforded 235 (338 mg, 68%) as a white crystalline solid. M.p. = 147.3 – 148.5 °C, IR (film) 3318 (N-H), 1635 (C=N), 1163 (SO₂), 851 (ArH) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 8.02 (1H, br s, H-3), 7.84 (2H, d, J = 8.3 Hz, ArH), 7.28 (2H, d, J = 8.3 Hz, ArH), 4.87 (1H, dd, J = 2.5, 6.1 Hz, C=CH), 4.46 (1H, m, C=CH), 4.41 (2H, t, J = 2.5 Hz, H-4), 2.42 (3H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃) 160.0 (1C, C-2), 150.8 (1C, C-5), 143.3 (1C, ArC), 138.9 (1C, ArC), 129.5 (2C, ArCH), 126.4 (2C, ArCH), 88.6 (C=CH₂), 46.0 (1C, C-4), 21.5 (1C, CH₃); (ES’) m/z = 275 [M+Na]^+; HRMS (ES’) m/z calculated for C_{11}H_{13}N_{2}O_{3}S [M+H]^+: 253.0641; found: 253.0639.
To a solution of 235 (200 mg, 1.0 mmol) in methanol (5 mL) was added 10% palladium on carbon (20 mg) and the suspension was stirred under a hydrogen atmosphere at 25 °C for 16 h. The reaction mixture was filtered over a plug of Celite®, washed through with methanol (20 ml) and concentrated in vacuo. Purification on silica gel (25% ethyl acetate in petroleum ether) afforded 233 (94 mg, 19%) as a colourless oil. IR (film) 3340 (N-H), 1667 (C=N), 1156 (SO₂), 872 (ArH) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.85 (2H, d, J = 8.5 Hz, ArH), 7.31 (2H, d, J = 8.5 Hz, ArH), 6.54 (1H, br m, NH), 6.26 (1H, br s, NH), 3.15 (2H, t, J = 7.3 Hz, H-1), 2.45 (3H, s, CH₃), 1.48 (2H, sex, J = 7.3 Hz, H-2), 0.85 (3H, t, J = 7.3 Hz, H-3); ¹³C NMR (100 MHz, CDCl₃) 152.1 (1C, CO), 144.7 (1C, ArC), 136.7 (1C, ArC), 129.9 (1C, ArCH), 129.7 (1C, ArCH), 127.0 (1C, ArCH), 126.4 (1C, ArCH), 42.0 (1C, C-1), 22.8 (1C, C-2), 21.5 (1C, CH₃), 11.2 (1C, CH₃); (ES⁺) m/z = 279 [M+Na]⁺; HRMS (ES⁺) m/z calculated for C₁₁H₁₆N₂O₅SNa [M+Na]⁺: 279.0774; found: 279.0776. Further elucidation afforded 232 (149 mg, 30%) as a white solid. ¹H NMR (400 MHz, CDCl₃) 7.84 (2H, d, J = 8.0 Hz, ArH), 7.25 (2H, d, J = 8.0 Hz, ArH), 6.53 (1H, q, J = 1.4 Hz, H-4), 2.40 (3H, s, CH₃), 2.14 (3H, d, J = 1.4 Hz, CH₃); (ES⁺) m/z = 275 [M+Na]⁺. The data is accordance with the values reported by Padwa for isomer 228. Further elucidation afforded 229 (185 mg, 26%) as a crystalline white solid. M.p. 138.8-139.3 °C; IR (film) 3354 (N-H) 1616 (1=NH) 1153 (SO₂) cm⁻¹;
$^1$H NMR (400 MHz, CDCl$_3$) 7.78 (2H, d, $J = 8.2$ Hz, ArH), 7.73 (1H, s, H-3), 7.23 (2H, d, $J = 8.2$ Hz, ArH), 4.84 (1H, m, H-5), 3.85 (1H, t, $J = 9.0$ Hz, H-4), 3.33 (1H, dd, $J = 7.6$, 9.1 Hz, H-4), 2.37 (3H, s, Ar-CH$_3$), 1.40 (3H, s, -CH$_3$);

$^{13}$C NMR (100 MHz, CDCl$_3$) 161.5 (1C, C-2), 142.8 (1C, ArC), 139.5 (1C, ArC), 129.3 (2C, ArCH), 126.1 (2C, ArCH), 76.3 (1C, C-5), 49.1 (1C, C-4), 21.5 (1C, Ar-CH$_3$), 19.9 (1C, CHCH$_3$); (ES$^+$) $m/z$ = 277 [M+Na]$^+$; HRMS (ES$^+$) $m/z$ calculated for C$_{11}$H$_{15}$N$_2$O$_3$SNa [M+Na]$^+$: 277.0617; found: 277.0617.

**Synthesis of Hydrazodicarboxylates: General Procedure 1**

To a mixture of alcohol (1.0 molar equiv) and triphenylphosphine (2.05 molar equiv) in THF at 0 °C was added drop-wise the azodicarboxylate (2.05 molar equiv). The reaction was allowed to reach room temperature, stirred for 24 h then concentrated *in vacuo*. Purification of the products was achieved by column chromatography (petroleum ether and ethyl acetate).

**Diethyl 1-(2-bromoallyl)hydrazine-1,2-dicarboxylate (250)**

250 was synthesised according to General Procedure 1 with the following: 2-Bromoallyl alcohol (1.00 g, 7.30 mmol), triphenylphosphine (3.94 g, 14.96 mmol), diethylazodicarboxylate (2.35 mL, 14.96 mmol) and THF (100 mL). Purification on silica gel (12.5% ethyl acetate in petroleum ether) afforded 250
(1.93 g, 90%) as a colourless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) 6.72 (1H, m, NH), 5.79 (1H, br s, CBr=CH), 5.57 (1H, d, J = 1.9 Hz, CBr=CH), 4.41-4.23 (2H, m, NCH\(_2\)CBr), 4.15 (4H, br q, \(J = 7.1\) Hz, CO\(_2\)C\(_2\)H\(_5\)CH\(_3\)), 1.23 (6H, t, \(J = 7.1\) Hz, CO\(_2\)C\(_2\)H\(_5\)CH\(_3\)), 1.14 (6H, t, \(J = 7.1\) Hz, CO\(_2\)C\(_2\)H\(_5\)CH\(_3\)); MS (ES+) \(m/z\) = 319 [M\(^{79}\)Br]+Na\(^+\), 317 ([M\(^{79}\)Br]+Na\(^+\)]. Data is in accordance with the values reported by Shipman and co-workers.\(^{100}\)

**Di-isopropyl 1-(2-bromoallyl)hydrazine-1,2-dicarboxylate (271)**

271 was synthesised according to General Procedure 1 with the following: 2-Bromoallyl alcohol (1.56 g, 11.39 mmol), triphenylphosphine (6.16 g, 23.4 mmol), di-isopropylazodicarboxylate (4.60 mL, 23.4 mmol) and THF (120 mL). Purification on silica gel (12.5% ethyl acetate in petroleum ether) afforded 271 (2.75 g, 75%) as a white crystalline solid. M.p. 68.0 – 69.1 °C; IR (film) 3283 (N-H) 1682 (C=O), 1628 (C=C), 761 (C-Br) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 6.50-6.86 (1H, br m, NH) 5.82 (1H, br s, CBr=CH), 5.61 (1H, s, CBr=CH), 4.97 (2H, br m, CO\(_2\)C\(_2\)H\(_5\)CH\(_3\)) 4.35 (2H, br s, NCH\(_2\)CBr), 1.26 (12H, d, \(J = 6.3\) Hz, CH\(_3\)); \(^13\)C NMR (100 MHz, CDCl\(_3\)) 155.8 (1C, CO\(_2\)CH(CH\(_3\))\(_2\)), 155.5 (1C, CO\(_2\)CH(CH\(_3\))\(_2\)), 128.2 (1C, -CBr=CH\(_2\)), 119.9 and 119.4 (1C, -CBr=CH\(_2\)), 70.6 (1C, CO\(_2\)CH(CH\(_3\))\(_2\)), 70.0 (1C, CO\(_2\)CH(CH\(_3\))\(_2\)), 58.0 and 57.3 (1C, NCH\(_2\)CBr), 22.0 (2C, CH\(_3\)), 21.9 (2C, CH\(_3\)); MS (ES\(^+\)) \(m/z\) = 345 [M\(^{79}\)Br]+Na\(^+\), 347 [M\(^{81}\)Br]+Na\(^+\); HRMS (ES\(^+\)) \(m/z\) calculated for C\(_{11}\)H\(_{19}\)\(^{79}\)BrN\(_2\)O\(_4\)Na [M+Na\(^+\)]: 345.0420; found: 345.0416.
Di-tert-butyl 1-(2-bromoallyl)hydrazine-1,2-dicarboxylate (270)

270 was synthesised according to General Procedure 1 with the following: 2-Bromoallyl alcohol (0.4 g, 2.94 mmol), triphenylphosphine (1.50 g, 6.03 mmol), di-tert-butyl azodicarboxylate (1.39 g, 23.4 mmol) and THF (50 mL). Purification on silica gel (12.5% ethyl acetate in petroleum ether) afforded 270 (946 mg, 92%) as a white crystalline solid. M.p. 136.6 – 138.5 °C; IR (film) 3315 (N-H), 1708 (C=O), 1146 (C-O) cm⁻¹; ¹H NMR (400MHz, CDCl₃) 6.10 - 6.39 (1H, br m, H-2), 5.80 (1H, br d, J = 18.2 Hz, CBr=CH), 5.59 (1H, s, CBr=CH), 4.30 (2H, br s, NC₃H₂CBr), 1.47 (18H, s, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) 154.7 (2C, CO₂C(CH₃)₃), 128.8 (1C, -CBr=CH₂), 119.4 (1C, -CBr=CH₂), 81.8 (2C, CO₂C(CH₃)₃), 58.3 (1C, NCH₂CBr), 28.2 (3C, -C(CH₃)₃), 28.1 (3C, -C(CH₃)₃); MS (ES⁺) m/z = 373 [M⁺Br]+Na⁺, 375 [M⁺⁸¹Br]+Na⁺; HRMS (ES⁺) m/z calculated for C₁₃H₂₃⁷⁹BrN₂O₄Na [M+Na]⁺: 373.0733; found: 373.0731.

Di-ethyl 1-(2-bromo-3-methylbut-2-enyl)hydrazine-1,2-dicarboxylate (272)

272 was synthesised according to General Procedure 1 with the following: 2-bromo-3-methylbut-2-en-1-ol (1.00 g, 6.06 mmol), triphenylphosphine (3.24 g, 12.42 mmol), diethylazodicarboxylate (2.65 mL, 12.42 mmol) and THF (100 mL). Purification on silica gel afforded 272 (1.42 g, 75%) as a colourless oil. IR (film) 3300 (N-H), 2985 (C-H), 1704 (C=O), 730 (C-Br); ¹H NMR (400 MHz,
CDCl$_3$) 6.31-6.58 (1H, m, NH), 4.51 (2H, br s, NCH$_2$CBr), 4.23 (4H, q, J = 7.1 Hz, CO$_2$CH$_2$CH$_3$), 1.91 (3H, s, CH$_3$), 1.83 (3H, s, CH$_3$), 1.27, (6H, t, J = 7.1 Hz, CO$_2$CH$_2$CH$_3$); $^1$HNMR (100 MHz, CDCl$_3$) 156.0 (1C, CO$_2$C(CH$_3$)$_3$), 155.4 (1C, CO$_2$C(CH$_3$)$_3$), 137.0 and 136.6 (1C, -CBr=C(CH$_3$)$_2$), 115.3 (1C, -CBr=C(CH$_3$)$_2$), 62.5 (1C, CO$_2$CH$_2$CH$_3$), 61.9 (1C, CO$_2$CH$_2$CH$_3$), 53.9 and 53.3 (1C, NCH$_2$CBr), 25.5 (1C, CH$_3$), 20.4 (1C, CH$_3$), 14.4 (1C, CH$_3$), 14.1 (1C, CH$_3$); MS (ES$^+$) m/z = 345 [M(79Br)+Na]$^+$, 347 [M(81Br)+Na]$^+$; HRMS (ES$^+$) m/z calculated for C$_{11}$H$_{19}$79BrN$_2$O$_4$Na [M+Na]$^+$: 345.0420; found: 345.0225.

**Synthesis of 3-methylene-1,2-diazetidines: General Procedure 2**

![Chemical structure](image)

To a mixture of hydrazodicarboxylate (1.0 molar equiv.), CuI (0.2 molar equiv) and Cs$_2$CO$_3$ (2.0 molar equiv.) in THF was added dropwise $N,N'$-dimethylethlenediamine (DMEDA) (0.4 molar equiv) and the mixture stirred at reflux for 16 h. The reaction was allowed to cool to room temperature, filtered through a plug of silica and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether:ethyl acetate).

**Diethyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (251)**

![Chemical structure](image)

251 was synthesised according to General Procedure 2 with the following: 250 (1.87 g, 6.37 mmol), copper iodide (242 mg, 1.26 mmol), DMEDA (275 µL,
2.55 mmol), Cs$_2$CO$_3$ (4.16 g, 12.75 mmol) and THF (50 mL). Purification on silica gel (20% ethyl acetate in petroleum ether) afforded 251 (1.31 g, 96%) as a colourless oil. $^1$H NMR (400 MHz, CDCl$_3$) 4.94 (1H, dt, $J = 3.3$, 2.3 Hz, C=CH), 4.65 (2H, t, $J = 2.3$ Hz, H-4), 4.40 (1H, dt, $J = 3.3$, 2.3 Hz, C=CH), 4.28 (2H, q, $J = 7.1$ Hz, CO$_2$C$_2$H$_2$CH$_3$), 4.22 (2H, q, $J = 7.1$ Hz, CO$_2$C$_2$H$_2$CH$_3$), 1.31 (3H, t, $J = 7.1$ Hz, CH(C$_3$H$_3$)$_2$), 1.28 (3H, t, $J = 7.1$ Hz, CH(C$_3$H$_3$)$_2$); MS (ES$^+$) m/z = 237 [M+Na]$^+$. Data is in accordance with the values reported by Shipman and co-workers.$^{100}$

Di-iso-propyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (273)

$$\begin{align*}
&\text{PrO}_2\text{C} \quad \text{N-N} \quad \text{Co}_2\text{Pr} \\
&\bigg<\bigg< \quad \text{CH} \bigg(\text{CH}_3\bigg)_2 \bigg> \quad \text{CH} \bigg(\text{CH}_3\bigg)_2 \\
&\text{CO}_2 \quad \text{Pr} \quad \text{CO}_2 \quad \text{Pr}
\end{align*}$$

273 was synthesised according to General Procedure 2 with the following: 271 (821 mg, 2.55 mmol), copper iodide (97 mg, 0.51 mmol), DMEDA (108 µL, 1.02 mmol), Cs$_2$CO$_3$ (1.66 g, 5.10 mmol) and THF (20 mL). Purification on silica gel (20% ethyl acetate in petroleum ether) afforded 273 (567 mg, 92%) as a colourless oil. IR (film) 2982 (>CH$_3$), 1716 (C=O), 1091 (C-O) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 4.96 – 5.10 (3H, m, C=C=H, 2 x COCH(CH$_3$)$_2$), 4.63–4.65 (2H, m, H-4), 4.39–4.41 (1H, m, C=CH), 1.33 (6H, d, $J = 6.2$ Hz, CH(CH$_3$)$_2$), 1.29 (6H, d, $J = 6.2$ Hz, CH(CH$_3$)$_2$); $^{13}$CNMR (100 MHz, CDCl$_3$) 160.1 (1C, CO$_2$CH(CH$_3$)$_2$), 154.9 (1C, CO$_2$CH(CH$_3$)$_2$) 142.4 (1C, C-3), 90.1 (1C, C=CH) 71.0 (1C, COCH(CH$_3$)$_2$) 70.1 (1C, COCH(CH$_3$)$_2$) 56.2 (1C, C-4), 21.9 (1C, CH$_3$), 21.8 (1C, CH$_3$), 21.7 (1C, CH$_3$), 21.5 (1C, CH$_3$); MS (ES$^+$) m/z = 265 [M+Na]$^+$, HRMS (ES$^+$) m/z calculated for C$_{11}$H$_{18}$N$_2$O$_4$Na [M+Na]$^+$: 265.1159; found: 265.1156.
Di-tert-butyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (252)

252 was synthesised according to General Procedure 2 with the following: 270 (534 mg, 1.52 mmol), copper iodide (58 mg, 0.31 mmol), DMEDA (67 µL, 0.62 mmol), Cs₂CO₃ (985 mg, 3.02 mmol) and THF (10 mL). Purification on silica gel (20% ethyl acetate in petroleum ether) afforded 252 (398 mg, 97%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) 4.91-4.87 (1H, m, C=C-H), 4.59 (2H, t, J = 2.3 Hz, H-4), 4.37-4.34 (1H, m, C=C-H), 1.54 (9H, s, C(CH₃)₃), 1.50 (9H, s, C(CH₃)₃); MS (ES⁺) m/z = 293 [M+Na]⁺. Data is in accordance with the values reported by Shipman and co-workers.

Diethyl 3-(propan-2-ylidene)-1,2-diazetidine-1,2-dicarboxylate (274)

274 was synthesised according to General Procedure 2 with the following: 272 (870 mg, 2.70 mmol), copper iodide (118 mg, 0.62 mmol), DMEDA (132 µL, 1.24 mmol), Cs₂CO₃ (2.03 g, 6.22 mmol) and THF (20 mL). Purification on silica gel (20% ethyl acetate in petroleum ether) afforded 274 (610 mg, 93%) as a colourless oil. IR (film) 2985 (-CH₃), 1710 (C=O), 1269 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 4.68 (2H, br s, H-4), 4.23 (2H, 2H, J = 7.1 Hz, CO₂CH₂CH₃), 4.23 (2H, 2H, J = 7.1 Hz, CO₂CH₂CH₃), 1.78 (3H, m, C=CC(CH₃)₂), 1.49 (3H, br s, C=CC(CH₃)₂), 1.29 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃), 1.27 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) 160.5 (1C,
C\textsubscript{11}H\textsubscript{19}N\textsubscript{2}O\textsubscript{4}Na [M+Na]\textsuperscript{+} calculated: 265.1159; found: 265.1155.

**General Procedure 3**

![Chemical structure](image)

To a stirred mixture of diethyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (1 molar equiv.), phenyl iodide (1.5 molar equiv.), Bu\textsubscript{4}NCl (1 molar equiv) and Pd(OAc)\textsubscript{2} (0.04 molar equiv.), in dimethylacetamide was added Cy\textsubscript{2}NMe (1.5 molar equiv.). The reaction was stirred at 70 °C until no starting material remained by tlc, allowed to cool to room temperature and diluted with Et\textsubscript{2}O and water. The phases were separated and the aqueous layer extracted with Et\textsubscript{2}O. The combined extracts were washed with water, dried over MgSO\textsubscript{4}, filtered, and concentrated in vacuo. The crude product was purified on silica gel (ethyl acetate in hexane).

**Diethyl (3E)-3-benzylidene-1,2-diazetidine-1,2-dicarboxylate (258)**

![Chemical structure](image)

258 was synthesised according to General Procedure 3 with the following: 251 (500 mg, 2.34 mmol), phenyl iodide (0.391 mL, 3.51 mmol), Bu\textsubscript{4}NCl (651 mg,
2.34 mmol), palladium (II) acetate (21 mg, 0.09 mmol), Cy₂NMe (0.74 mL, 3.51 mmol) and DMAc (10 mL). Purification on silica gel (12.5% ethyl acetate in hexane) afforded 258 (304 mg, 45%) as a white crystalline solid. ^1H NMR (400 MHz, CDCl₃) 7.31 (2H, t, J = 7.5 Hz, ArH), 7.18 (1H, t, J = 7.5 Hz, ArH), 7.03 (2H, d, J = 7.5 Hz, ArH), 6.49 (1H, d, J = 2.5 Hz C=CHPh), 5.00 (2H, d, J = 2.5 Hz, H-4), 4.35 (2H, q, J = 7.1 Hz, CO₂CH₂CH₃), 4.29 (2H, q, J = 7.2 Hz, CO₂CH₂CH₃), 1.38 (3H, t, J = 7.2 Hz, CO₂CH₂CH₃), 1.33 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃); MS (ES⁺) m/z = 313 [M+Na]⁺. Data is in accordance with that reported by Shipman and co-workers.¹⁰⁰

**Diethyl (3E)-3-benzylidene-1,2-diazetidine-1,2-dicarboxylate (258) with Suzuki coupling**

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\[ \text{EtO}_2\text{C} \quad \text{N} \quad \text{N} \quad \text{CO}_2\text{Et} \quad \text{EtO}_2\text{C} \quad \text{N} \quad \text{N} \quad \text{CO}_2\text{Et} \]
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To a stirred solution of 277 (40 mg, 0.14 mmol) in 1,4-dioxane (1 mL) was added PhB(OH)₂ (50 mg, 0.41 mmol), XPhos (4 mg, 0.008 mmol), Pd₂dba₃ (3 mg, 0.003 mmol) and Cs₂CO₃ (98 mg, 0.30 mmol). The reaction was stirred at 110 °C for 1 h. Upon cooling, the reaction mixture was filtered over Celite®, washed through with CH₂Cl₂ (10 mL) and concentrated in vacuo. Purification on silica gel (12.5% ethyl acetate in hexane) afforded 258 (19 mg, 50%) as a white crystalline solid. Data is as previously described.
Diethyl (3E)-3-(4-tert-butyl-benzylidene)-1,2-diazetidine-1,2-dicarboxylate (276)

was synthesised according to General Procedure 3 with the following: 251 (200 mg, 0.94 mmol), 4-tert-butyliodobenzene (0.198 mL, 1.12 mmol), Bu₄NCl (260 mg, 0.94 mmol), palladium (II) acetate (15 mg, 0.07 mmol), Cy₂NMe (238 mg, 1.12 mmol) and DMAc (6 mL). Purification on silica gel (12.5% ethyl acetate in hexane) afforded 276 (136 mg, 42%) as a colourless oil. IR (neat) 2963 (CH₃), 1720 (C=O), 1316 (C-O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.34 (2H, d, J = 8.4 Hz, ArH), 6.98 (2H, d, J = 8.4 Hz, ArH), 6.44 (1H, t, J = 2.4 Hz, C=CHAr), 5.01 (2H, d, J = 2.4 Hz, H-4), 4.36 (2H, q, J = 7.1 Hz, CO₂C₂H₅), 4.29 (2H, q, J = 7.1 Hz, CO₂C₂H₅), 1.38 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃), 1.34 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃), 1.31 (9H, s, Ar-C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) 160.5 (CO₂C₂H₅), 155.5 (CO₂C₂H₅), 149.6 (1C, ArC), 136.5 (1C, C-3), 131.8 (1C, ArC), 126.4 (2C, ArCH), 125.8 (2C, ArCH), 63.3 (1C, CO₂C₂H₅), 63.1 (1C, CO₂C₂H₅), 58.5 (1C, C-4), 34.5 (1C, Ar-C(CH₃)₃), 31.3 (3C, Ar-C(CH₃)₂), 14.5 (1C, CO₂C₂H₅), 14.4 (1C, CO₂C₂H₅); MS (ES⁺) m/z = 369 [M+Na]⁺, HRMS (ES⁺) m/z calculated for C₁₉H₂₆N₂O₄Na [M+Na]⁺: 369.1785; found: 365.1786.
Diethyl (3E)-3-(4-methoxybenzylidene)-1,2-diazetidine-1,2-dicarboxylate (260)

260 was synthesised according to General Procedure 3 with the following: 251 (200 mg, 0.94 mmol), 4-iodoanisole (528 mg, 1.40 mmol), Bu₄NCl (260 mg, 0.94 mmol), palladium (II) acetate (15 mg, 0.07 mmol), Cy₂NMe (0.30 mL, 1.4 mmol) and DMAC (6 mL). Purification on silica gel (12.5% ethyl acetate in hexane) afforded 260 (101 mg, 34%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) 6.94 (2H, d, J = 8.9 Hz, ArH), 6.83 (2H, d, J = 8.9 Hz, ArH), 6.38 (1H, t, J = 2.5 Hz, C=CHAr), 4.96 (2H, d, J = 2.5 Hz, H-4), 4.32 (2H, q, J = 7.1 Hz, CO₂CH₂CH₃), 4.26 (2H, q, J = 7.1 Hz, CO₂CH₂CH₃), 3.77 (3H, s, OCH₃), 1.34 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃), 1.30 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃); MS (ES⁺) m/z = 343 [M+Na]⁺. The data is in accordance with that reported by Shipman and co-workers.¹⁰⁰

Diethyl (3E)-3-(naphthalene-2-ylidene)-1,2-diazetidine-1,2-dicarboxylate (275)

275 was synthesised according to General Procedure 3 with the following: 251 (200 mg, 0.94 mmol), 2-iodonaphthalene (285 mg, 1.12 mmol), Bu₄NCl (260 mg, 0.94 mmol), palladium (II) acetate (15 mg, 0.07 mmol), Cy₂NMe (238 mg,
1.12 mmol) and DMAc (6 mL). Purification on silica gel (10% ethyl acetate in hexane) afforded 275 (101 mg, 34%) as a white crystalline solid. M.p 113.2 – 113.8 °C; IR (neat) 2981 (-CH₃), 1713 (C=O), 1284 (C–O), 745 (Ar–H) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.74–7.80 (3H, m, ArH), 7.40–7.49 (3H, m, ArH), 7.13 (1H, dd, J = 1.7 and 8.6 Hz, ArH), 6.63 (1H, t, J = 2.4 Hz, C=CHAr), 5.11 (2H, d, J = 2.4 Hz, H-4), 4.38 (2H, q, J = 7.1 Hz, CO₂CH₂CH₃), 4.34 (2H, q, J = 7.1 Hz, CO₂CH₂CH₃), 1.41 (3 H, t, J = 7.1 Hz, CO₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) 160.4 (1C, CO₂CH₂CH₃), 155.4 (1C, CO₂CH₂CH₃), 137.5 (1C, C-3), 133.7 (1C, ArC) 132.2 (1C, ArC), 132.0 (1C, ArC), 128.5 (1C, ArCH), 127.7 (1C, ArCH), 127.6 (1C, ArCH), 126.5 (1C, ArCH), 125.9 (1C, ArCH), 125.7 (1C, ArCH), 124.4 (1C, ArCH), 108.2 (1C, C=CHAr) 63.3 (1C, CO₂CH₂CH₃), 63.2 (1C, CO₂CH₂CH₃), 58.6 (1C, C-4), 14.5 (1C, CO₂CH₂CH₃), 14.4 (1C, CO₂CH₂CH₃); MS (ES⁺) m/z = 363 [M+Na]⁺, HRMS (ES⁺) m/z calculated for C₁₉H₂₁N₂O₄ [M+H]⁺: 341.1496; found: 341.1497.

Diethyl (3E)-3-(bromomethylene)-1,2-diazetidine-1,2-dicarboxylate (277)

To a stirred solution of 251 (200 mg, 0.94 mmol) in CH₂Cl₂ (4 mL) at -78 °C was added bromine (0.046 mL) dropwise. After 1 h the solution was allowed to reach -60 °C, DBU was added dropwise and the reaction mixture was stirred for a further 4 h whilst being allowed to slowly warm to 25 °C. The reaction
mixture was poured into brine (20 mL) and extracted with CH$_2$Cl$_2$ (3 x 20 ml). The combined organic layers were dried over MgSO$_4$, filtered and concentrated under vacuum. Purification on silica gel (10% ethyl acetate in petroleum ether) afforded 277 (115 mg, 42%) as a colourless oil. IR (film) 2983 (CH$_3$), 1731 (C=O), 694 (C-Br) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 6.05 (1H, t, $J = 2.6$ Hz, C=C=CHBr), 4.62 (2H, d, $J = 2.6$ Hz, H-4), 4.32 (2H, q, $J = 7.1$ Hz, CO$_2$CH$_2$CH$_3$), 4.27 (2H, q, $J = 7.1$ Hz, CO$_2$CH$_2$CH$_3$), 1.35 (3H, t, $J = 7.1$ Hz, CO$_2$CH$_2$CH$_3$); $^{13}$C NMR (150 MHz, CDCl$_3$) 159.2 (1C, C=O), 153.7 (1C, CO$_2$CH$_2$CH$_3$), 137.8 (1C, C-3), 84.1 (1C, C=CHBr), 62.5 (1C, CO$_2$CH$_2$CH$_3$), 62.4 (1C, CO$_2$CH$_2$CH$_3$), 57.0 (1C, C-4), 13.3 (1C, CO$_2$CH$_2$CH$_3$), 13.3 (1C, CO$_2$CH$_2$CH$_3$); MS (ES$^+$) $m/z$ = 315 [M($^{79}$Br)+Na]$^+$, 317 [M($^{81}$Br)+Na]$^+$; HRMS (ES$^+$) $m/z$ calculated for C$_9$H$_{13}$$^{79}$BrN$_2$O$_4$Na [M($^{79}$Br)+Na]$^+$: 314.9951; found: 314.9952.

Diethyl 3-methyl-1,2-diazetidine-1,2-dicarboxylate (280) and diethyl 1-(propyl)hydrazine-1,2-dicarboxylate (281)

To a solution of 251 (200 mg, 0.93 mmol) in methanol (5 mL) was added 10% palladium on carbon (20 mg) and the suspension was stirred under a hydrogen atmosphere at 25 °C for 16 h. The reaction mixture was filtered over a plug of Celite®, washed through with methanol (20 ml) and concentrated in vacuo. Purification on silica gel (12.5% ethyl acetate in petroleum ether) afforded 281 (47 mg, 23%) as a colourless oil. IR (film) 3295 (N-H), 2983 (C-H), 1694 (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 6.31-6.64 (1H, m, H-2), 4.14-4.22
(4H, m, CO₂CH₂CH₃), 3.46 (2H, m, NCH₂CH₂CH₃), 1.59 (2H, quin, J = 7.3 Hz, NCH₂CH₂CH₃), 1.24-1.28 (6H, m, CO₂CH₂CH₃), 0.90 (3H, t, J = 7.3 Hz, NCH₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) 156.3 (2C, CO₂CH₂CH₃), 62.4 (1C, CO₂CH₂CH₃), 62.0 (1C, CO₂CH₂CH₃), 42.7 (1C, NCH₂CH₂CH₃) 20.7 (1C, NCH₂CH₂CH₃), 14.6 (1C, CO₂CH₂CH₃), 14.5 (1C, CO₂CH₂CH₃), 11.1 (1C, NCH₂CH₂CH₃); MS (ES⁺) m/z = 241 [M+Na]+, HRMS (ES⁺) m/z calculated for C₉H₁₈N₂O₄Na [M+Na]+: 241.1159; found: 241.1160. Further elucidation afforded 280 (108 mg, 54%) as a colourless oil. IR (film) 2977 (CH₃), 1702 (C=O), 1273 (C-O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 4.39-4.47 (1H, m, H-3), 4.32 (1H, t, J = 8.0 Hz, H-4), 4.15-4.27 (4H, m, CO₂CH₂CH₃), 3.74 (1H, dd, J = 6.2, 8.0 Hz, H-4), 1.48 (3H, d, J = 6.3 Hz, >CHCH₂), 1.28 (6H, t, J = 7.2 Hz, CO₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) 161.1 (1C, CO₂CH₂CH₃), 160.9 (1C, CO₂CH₂CH₃), 62.6 (1C, CO₂CH₂CH₃), 62.4 (1C, CO₂CH₂CH₃), 58.1 (1C, C-3), 56.1 (1C, C-4), 20.7 (1C, >CHCH₂), 14.4 (2C, CO₂CH₂CH₃); MS (ES⁺) m/z = 239 [M+Na]+, HRMS (ES⁺) m/z calculated for C₉H₁₆N₂O₄Na [M+Na]+: 239.1002; found: 239.1004.

**General Procedure 4**

To a test tube containing a solution of 3-methylene-1,2-diazetidine-1,2-dicarboxylate (1 molar equiv.) in ethyl acetate was added the rhodium catalyst (0.011 molar equiv.) followed by the ferrocene-based ligand (0.014 molar equiv). The test tube was placed within a high pressure Parr hydrogenator,
purged with hydrogen three times and then charged with hydrogen to 50 Bar. The reaction was stirred at 50 °C for the required amount of time, allowed to cool and concentrated in vacuo. Purification on silica gel (ethyl acetate in hexane) afforded the desired compound.

(S)-Diethyl 3-methyl-1,2-diazetidine-1,2-dicarboxylate ((S)-280)

![Chemical Structure]

280 was synthesised according to General Procedure 4 with the following: 251 (250 mg, 1.17 mmol), [Rh(NBD)_2]BF_4 (5 mg, 0.01 mmol), (S_p,S'_p)-1,1'-Bis[bis(4-methoxy-3,5-dimethylphenyl) phosphino]- 2,2'- bis [ (R) - α- (dimethylamino)benzyl]ferrocene (17 mg, 0.02 mmol) and ethyl acetate (2 mL). Purification on silica gel (15 % ethyl acetate in hexane) afforded 280 (244 mg, 98%, 89% ee) as a colourless oil. Spectroscopic data as previously described.

Diethyl 3-methyl-1,2-diazetidine-1,2-dicarboxylate (284)

![Chemical Structure]

284 was synthesised according to General Procedure 4 with the following: 252 (50 mg, 0.19 mmol), [Rh(NBD)_2]BF_4 (1 mg, 0.01 mmol), (S_p,S'_p)-1,1'-Bis[bis(4-methoxy-3,5-dimethylphenyl) phosphino]- 2,2'- bis [ (R) - α- (dimethylamino)benzyl]ferrocene (3 mg, 0.001 mmol) and ethyl acetate (2 ml). Purification on silica gel (12.5% ethyl acetate in hexane) afforded 284 (26 mg, 52%, 52% ee) as a colourless oil. [α]_D^{20} = +24.5 (EtOAc); IR (neat) 2979 (CH_3), 1700 (C=O), 1158 (C-O) cm⁻¹; ^1H NMR (400 MHz, CDCl₃) 4.29-4.36
(1H, m, H-3), 4.21 (1H, t, J = 7.9 Hz, H-4), 3.65 (1H, dd, J = 6.4, 7.9 Hz), 1.49 (9H, s, CO₂C(CH₃)₃), 1.48 (9H, s, CO₂C(CH₃)₃), 1.45 (3H, d, J = 6.4 Hz, >C-CH₃); ¹³C NMR (100 MHz, CDCl₃) 160.1 (1C, CO₂C(CH₃)₂), 160.0 (1C, CO₂C(CH₃)₃), 81.8 (1C, CO₂C(CH₃)₂), 81.7 (1C, CO₂C(CH₃)₃), 57.4 (1C, C-3), 55.6 (1C, C-4), 28.1 (6C, CO₂C(CH₃)₂), 20.7 (1C, >C-CH₃); MS (ES⁺) m/z = 295 [M+Na]⁺, HRMS (ES⁺) m/z calculated for C₁₃H₂₄N₂O₄Na [M+Na]⁺: 295.1652; found: 295.1652.

**Diethyl 3-benzyl-1,2-diazetidine-1,2-dicarboxylate (282)**

![Chemical Structure](image)

282 was synthesised according to General Procedure 4 with the following: 258 (50 mg, 0.17 mmol), [Rh(NBD)₂]BF₄ (1 mg, 0.01 mmol), (R)-1-[(S₉)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (2 mg, 0.01 mmol), and ethyl acetate (2 mL). Purification of silica gel (20% ethyl acetate in hexane) afforded 282 (27 mg, 54% 33% ee) as a colourless oil. [α]D³₀ = +36.0 (EtOAc); IR (film) 2984 (CH₃), 1705 (C=O), 1270 (C-O), 702 (Ar-H) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.18-7.30 (5H, m, ArH), 4.52-4.59 (1H, m, H-3), 4.06-4.26 (5H, m, H-4, 2 x CO₂C₂H₂CH₃), 3.82 (1H, dd, J = 6.0, 8.4 Hz, H-4), 3.11 (1H, dd, J = 5.0, 14.0 Hz, -CHPh), 3.04 (1H, dd, J = 7.7, 14.0 Hz, -CHPh), 1.25 (3H, t, J = 7.1 Hz, CO₂C₂H₂CH₃), 1.22 (3H, t, J = 7.1 Hz, CO₂C₂H₂CH₃); ¹³C NMR (100 MHz, CDCl₃) 160.8 (2C, CO₂C₂H₂CH₃), 135.4 (1C, ArC), 129.5 (2C, ArCH), 128.4 (2C, ArCH), 126.4 (1C, ArCH), 62.5 (2C, CO₂C₂H₂CH₃), 62.1 (1C, C-3), 53.8 (1C, C-4), 40.2 (1C, -CH₂Ph), 14.4 (2C, CO₂C₂H₂CH₃); MS (ES⁺) m/z =...

Diethyl 3-(4-methoxybenzyl)-1,2-diazetidine-1,2-dicarboxylate (287)

287 was synthesised according to General Procedure 4 with the following: 260 (50 mg, 0.16 mmol), [Rh(NBD)₂]BF₄ (1 mg, 0.01 mmol), (R)-1-[(S₆)-2-(diphenylphosphino)ferrocenyl]ethylidicyclohexylphosphine (2 mg, 0.01 mmol), and ethyl acetate (2 mL). Purification on silica gel (20% ethyl acetate in hexane) afforded 287 (17 mg, 34%, 18% ee) as a colourless oil. [α]30⁰ = +12.3 (EtOAc); IR (neat) 2980 (CH₃), 1705 (C=O), 1244 (C-O), 769 (ArH) cm⁻¹; ¹H NMR (400 MHz, CDCl₃), 7.13 (2H, d, J = 8.6 Hz, ArH), 6.84 (2H, d, J = 8.6 Hz, ArH), 4.50-4.57 (1H, m, H-3), 4.07-4.30 (5H, m, H-4, 2 x CO₂CH₂CH₃), 3.83 (1H, dd, J = 6.1, 8.4 Hz, H-4), 3.79 (3H, s, -OCH₃), 3.00 (1H, dd, J = 7.6, 14.1 Hz, -CHAr), 1.28 (3H, t, J = 7.2 Hz, CO₂CH₂CH₃), 1.24 (3H, t, J = 7.2 Hz, CO₂CH₂CH₃); ¹³C NMR (150 MHz, CDCl₃) 160.8 (2C, CO₂CH₂CH₃), 158.7 (1C, ArC-OCH₃), 130.5 (2C, ArCH), 127.3 (1C, ArC), 114.0 (2C, ArCH), 62.5 (2C, CO₂CH₂CH₃), 55.2 (Ar-OCH₃), 53.7 (1C, C-4), 39.2 (1C, -CH₂Ar), 14.4 (2C, CO₂CH₂CH₃); MS (ES⁺) m/z = 345 [M+Na]+, HRMS (ES⁺) m/z calculated for C₁₆H₂₂N₂O₅Na [M+Na]+: 345.1421; found: 345.1419.
Diethyl 3-(4-tert-butylbenzyl)-1,2-diazetidine-1,2-dicarboxylate (285)

285 was synthesised according to General Procedure 4 with the following: 276 (80 mg, 0.23 mmol), [Rh(NBD)]_2BF_4 (1 mg, 0.01 mmol), (R)-1-[(S)_2]-2-(diphenylphosphino)ferrocenyl]ethylidicyclohexylphosphine (3 mg, 0.01 mmol), and ethyl acetate (2 mL). Purification on silica gel (10% ethyl acetate in hexane) afforded 285 (46 mg, 58%, 19% ee) as a colourless oil. \([\alpha]^{30}_{D} = +14.6 \text{ (EtOAc); IR (film) 2959 (CH}_3\text{), 1707 (C=O), 1270 (C-O) cm}^{-1}; \text{ }^1\text{H NMR (400 MHz, CDCl}_3\text{) 7.32 (2H, d, } J = 8.5 \text{ Hz, ArH), 7.14 (2H, d, } J = 8.5 \text{ Hz, ArH), 4.53-4.59 (1H, m, H}_3\text{), 4.07-4.29 (5H, H}_4\text{, 2 x CO}_2\text{CH}_2\text{CH}_3\text{), 3.85 (1H, dd, } J = 6.0, 8.3 \text{ Hz, H}_4\text{), 3.11 (1H, dd, } J = 4.8, 14.1 \text{ Hz, -CHAr), 3.03 (1H, dd, } J = 8.0, 14.1 \text{ Hz, -CHAr), 1.30 (9H, s, -C(CH}_3\text{)_3\text{), 1.27 (3H, t, } J = 7.1 \text{ Hz, CO}_2\text{CH}_2\text{CH}_3\text{), 1.24 (3H, t, } J = 7.1 \text{ Hz, CO}_2\text{CH}_2\text{CH}_3\text{); }^{13}\text{C NMR (100 MHz, CDCl}_3\text{) 160.9 (2C, CO}_2\text{CH}_2\text{CH}_3\text{), 149.9 (1C, ArC-C(CH}_3\text{)_3\text{), 132.3 (1C, ArC), 129.2 (2C, ArCH), 125.5 (2C, ArCH), 62.5 (2C, CO}_2\text{CH}_2\text{CH}_3\text{), 62.2 (1C, C-3), 53.9 (1C, C-4), 39.7 1C, -CH}_2\text{Ar), 34.5 (1C, Ar-C(CH}_3\text{)_3\text{), 31.4 (3C, Ar-C(CH}_3\text{)_3\text{), 14.4 (2C, CO}_2\text{CH}_2\text{CH}_3\text{); MS (ES') } m/z = 371 \text{ [M+Na]+, HRMS (ES') } m/z \text{ calculated for C}_{19}\text{H}_{26}\text{N}_2\text{O}_4\text{Na [M+Na]+: 371.1941; found: 371.1933.} \)
Diethyl 3-(naphthalene-2-ylmethyl)-1,2-diazetidine-1,2-dicarboxylate (286)

286 was synthesised according to General Procedure 4 with the following: 275 (40 mg, 0.118 mmol), [Rh(NBD)]_2BF_4 (1 mg, 0.003 mmol), (R)-1-[(S_p)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (3 mg, 0.003 mmol), and ethyl acetate (2 mL). Purification on silica gel (12.5% ethyl acetate in hexane) afforded 286 (22 mg, 55%, <30% ee) as a colourless oil. [α]_D^30 = +22.1 (EtOAc); IR (film) 2981 (CH_3), 1749 (C=O), 1296 (C-O), 750 (ArH) cm^{-1}; ^1H NMR (400 MHz, CDCl_3), 7.78-7.82 (3H, m, ArH), 7.67 (1H, s, ArH), 7.43-7.49 (2H, m, ArH), 7.35 (1H, dd, J = 1.7, 8.4 Hz, ArH), 4.64-4.70 (1H, m, H-3), 3.96-4.30 (5H, m, H-4, 2 x CO_2C_6H_5), 3.90 (1H, dd, J = 6.0, 8.4 Hz, H-4), 3.30 (1H, dd, J = 4.9, 14.0 Hz, -CHAr), 3.23 (1H, dd, J = 7.6, 14.0 Hz, CHAr), 1.24 (3H, t, J = 7.1 Hz, CO_2C_6H_5), 1.15 (3H, t, J = 7.1 Hz, CO_2C_6H_5); ^13C NMR (100 MHz,CDCl_3) 160.9 (1C, CO_2C_6H_5), 160.8 (1C, CO_2C_6H_5), 133.5 (1C, ArC), 132.9 (1C, ArC), 132.5 (1C, ArC), 128.2 (1C, ArCH), 128.1 (1C, ArCH), 127.7 (1C, ArCH), 127.6 (1C, ArC), 127.5 (1C, ArCH), 126.2 (1C, ArCH), 125.8 (1C, ArCH), 62.6 (1C, CO_2C_6H_5), 62.5 (1C, CO_2C_6H_5), 62.2 (1C, C-3), 53.9 (1C, C-4), 40.4 (1C, -CH_2Ar), 14.4 (1C, CO_2C_6H_5), 14.3 (1C, CO_2C_6H_5); MS (ES') m/z = 365 [M+Na]^+, HRMS (ES') m/z calculated for C_{19}H_{22}N_2O_4Na [M+Na]^+: 365.1472; found: 365.1472.
**General Procedure 5**

A stock solution of LiDBB in THF was prepared as follows: Freshly cut pellets of lithium (66 mg, 9.40 mmol) were placed in a flask containing 4,4'-di-tert-butylbiphenyl (500 mg, 1.88 mmol). The tube was evacuated and filled with argon 3 times. 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. To a solution of 1,2-diazetididine (1 molar equiv.) in THF at -78 °C was added the solution of LiDBB until the dark green colour persisted for more than a minute. The reaction mixture was stirred for a further 30 minutes and then quenched by the addition of saturated aqueous NH₄Cl (1 mL). After warming to room temperature, Et₂O (2 mL) was added. The layers were separated and the aqueous layer extracted with Et₂O (3 × 10 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification on silica gel (ethyl acetate in hexane) afforded the desired product.

**[(S)-Diethyl propane-1,2-diylbiscarbamate ((S)-290)](N\_N\_R\_CO\_2Et)\_EtO\_2CHN\_NHCO\_2Et**

((S)-290) was synthesised according to General Procedure 5 with the following: (S)-280 (87 mg, 0.40 mmol), THF (2 mL) and stock LiDBB solution (2.7 mL, 1.1 mmol approx.). Purification on silica gel (25% ethyl acetate in hexane) afforded (S)-290 (56 mg, 64%) as a white crystalline solid. \([\alpha]^{30}_D = -11.1\)
(EtOAc); M.p 131.9-132.6 °C; IR (neat) 3308 (N-H), 2980 (C-H), 1681 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 5.28 (1H, br s, NH), 5.02-5.11 (1H, br m, NH), 4.02-4.10 (4H, m, CO₂CH₂CH₃), 3.77 (1H, br m, H-2), 3.15-3.29 (2H, m, H-1), 1.19 (6H, t, J = 7.1 Hz, CO₂CH₂CH₃), 1.12 (3H, d, J = 6.7 Hz, H-3); ¹³C NMR (100 MHz, CDCl₃) 157.4 (1C, CO₂CH₂CH₃), 156.6 (1C, CO₂CH₂CH₃), 60.9 (1C, CO₂CH₂CH₃), 60.7 (1C, CO₂CH₂CH₃), 47.6 (1C, C-2), 46.4 (1C, C-1), 18.4 (1C, C-3), 14.6 (2C, CO₂CH₂CH₃); MS (ES⁺) m/z = 241 [M+Na]⁺, HRMS (ES⁺) m/z calculated for C₉H₁₈N₂O₄Na [M+Na]⁺: 241.1159; found: 241.1157.

**Diethyl (3-phenylpropane-1,2-diyl)biscarbamate (291)**

![Chemical Structure](image)

291 was synthesised according to General Procedure 5 with the following: 282 (64 mg, 0.21 mmol), THF (2 ml) and stock LiDBB solution (1.8 mL, 0.7 mmol approx.). Purification on silica gel (20% ethyl acetate in hexane) afforded 291 (44 mg, 69%) as a white crystalline solid. [α]³⁰ D = +24.0 (EtOAc); M.p 87.1-87.9 °C; IR (neat) 3322 (N-H), 2980 (C-H), 1684 (C=O), 751 (ArH) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.18 (5H, m, ArH), 4.94 (2H, br s, NH), 4.05-4.13 (4H, m, CO₂CH₂CH₃), 3.87-3.97 (1H, br m, H-2), 3.31 (1H, dt, J = 4.7, 14.0 Hz, H-1), 3.16-3.24 (1H, br m, H-1), 2.84-2.93 (1H, br m, H-3), 2.76 (1H, dd, J = 7.2, 13.9 Hz, H-3), 1.23 (3H, t, J = 7.2 Hz, CO₂CH₂CH₃), 1.21 (3H, t, J = 7.2 Hz, CO₂CH₂CH₃); ¹³C NMR (150 MHz, CDCl₃) 157.4 (1C, CO₂CH₂CH₃), 156.6 (1C, CO₂CH₂CH₃), 137.3 (1C, ArC), 129.2 (2C, ArCH), 128.7 (1C, ArCH), 126.7 (2C, ArCH), 126.7 (2C, ArCH), 61.1 (1C, CO₂CH₂CH₃), 53.1 (1C, C-2), 53.1 (1C, C-2).
CO₂CH₂CH₃); MS (ES⁺) m/z = 295 [M+H]⁺, HRMS (ES⁺) m/z calculated for C₁₅H₂₃N₂O₄ [M+H]⁺: 295.1652; found: 295.1647.

**Diethyl 1[(3’-phenyl-1’,2’-oxazol-5’-yl)methyl]hydrazine-1,2-dicarboxylate (300)**

![Chemical structure of 300](image)

To a stirred solution of 251 (100 mg, 0.47 mmol), in CH₂Cl₂ (3 mL) was added phenyl hydroximoyl chloride (87 mg, 0.56 mmol) in CH₂Cl₂ (2 mL). The reaction was allowed to reach room temperature, stirred for 24 h then concentrated in vacuo. Purification on silica gel (20% ethyl acetate in hexane) afforded 300 (87 mg, 56%) as a white crystalline solid. M.p 57.1-58.1 °C; IR (neat) 3286 (N-H), 2978 (CH₃), 1681 (C=O), 1208 (N-O), cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.74-7.79 (2H, br m, ArH), 7.38-7.47 (3H, br m, ArH), 6.90-7.19 (1H, br m, NH), 6.57 (br s, 1H, H-4’), 4.85 (2H, br s, NCH₂Ar), 4.15-4.25 (4H, br m, CO₂CH₂CH₃), 1.25 (6H, br m, CO₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) 168.2 (1C, C-5’), 162.6 (2C, CO₂CH₂CH₃), 155.8 (1C, C-3’), 130.1 (1C, ArCH) 128.9 (2C, ArCH), 128.8 (1C, ArC), 126.8 (2C, ArCH), 101.5 (1C, C-4’), 63.2 (1C, CO₂CH₂CH₃), 62.3 (1C, CO₂CH₂CH₃), 45.5 (1C, NCH₂Ar), 14.4 (2C, CO₂CH₂CH₃); MS (ES⁺) m/z = 356 [M+Na]⁺, HRMS (ES⁺) m/z calculated for C₁₆H₁₉N₃O₅Na [M+Na]⁺: 356.1217; found: 356.1221.
General Procedure 6

To a solution of 3-methylene-1,2-diazetidine (1 molar equiv.) in CH₂Cl₂ at 0 °C was added tetracyanoethylene (1 molar equiv.). The solution was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was concentrated in vacuo and the crude product was recrystallised from ethyl acetate.

Diethyl 5,5,6,6-tetracyano-1,2-diazaspiro[3.3]heptane-1,2-dicarboxylate

(303)

303 was synthesised according to General Procedure 6 with the following: 251 (0.05 g, 0.23 mmol), tetracyanoethylene (0.03 g, 0.23 mmol) and CH₂Cl₂ (3 mL). Recrystallisation from ethyl acetate afforded 303 (0.067 g, 98%) as a white crystalline solid. M.p. 184.3-185.1 °C; IR (neat) 2985 (CH₃), 1718 (C=O), 1269 (C=O) cm⁻¹; ¹H NMR (400 MHz, CD₃CN), 4.57 (1H, d, J = 17.7 Hz, H-3), 4.54 (1H, d, J = 17.8 Hz, H-3), 4.17-4.41 (5H, m, H-7, 2 x CO₂CH₂CH₃), 3.71 (1H, d, J = 15.9 Hz, H-7), 1.35 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃), 1.31 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃); ¹³C NMR (100 MHz, CD₃CN) 159.1 (1C, CO₂CH₂CH₃), 155.2 (1C, CO₂CH₂CH₃), 111.2 (1C, CN), 110.7 (1C, CN), 108.4 (1C, CN), 90.7 (1C, CN).

¹Only one carbon observed for C-5/C-6
107.8 (1C, CN), 68.3 (1C, C-4), 63.3 (1C, CO₂CH₂CH₃), 62.7 (1C, CO₂CH₂CH₃), 57.7 (1C, C-3) 40.6 (1C, C-7), 31.4 (1C, C-5 or C-6), 13.3 (1C, CO₂CH₂CH₃), 13.3 (1C, CO₂CH₂CH₃); MS (ES⁺) m/z = 365 [M+Na]⁺, HRMS (ES⁺) m/z calculated for C₁₅H₁₄N₆O₄Na [M+Na]⁺: 365.0969; found: 365.0967.

**Di-iso-propyl 5,5,6,6-tetracyano-1,2-diazaspiro[3.3]heptane-1,2-dicarboxylate (305)**

305 was synthesised according to General Procedure 6 with the following: 273 (0.05 g, 0.21 mmol), tetracyanoethylene (0.026 g, 0.21 mmol) and CH₂Cl₂ (3 mL). Recrystallisation from ethyl acetate afforded 305 (59 mg, 80%) as a white crystalline solid. M.p. 172.1-172.9 °C; IR (neat) 2986 (CH₃), 1704 (C=O), 2365 (-CN) 1285 (C-O) cm⁻¹; ¹H NMR (400 MHz, CD₃CN) 5.12 (1H, sept, J = 6.4 Hz, CO₂C(CH₃)₂), 4.99 (1H, sept, J = 6.3 Hz, CO₂CH(CH₃)₂), 4.56 (1H, d, J = 15.3 Hz, H-3), 4.54 (1H, d, J = 15.3 Hz, H-3), 4.22 (1H, d, J = 15.8 Hz, H-7), 3.69 (1H, d, J = 15.8 Hz, H-7), 1.36 (6H, t, J = 6.2 Hz, CO₂CH(CH₃)₂), 1.31 (6H, t, J = 6.3 Hz, CO₂CH(CH₃)₂); ¹³C NMR (400 MHz, CD₃CN) 158.8 (1C, CO₂CH(CH₃)₂), 154.4 (1C, CO₂CH(CH₃)₂), 111.2 (1C, CN), 110.8 (1C, CN), 108.5 (1C, CN), 107.3 (1C, CN), 72.1 (1C, CO₂CH(CH₃)₂), 71.0 (1C, CO₂CH(CH₃)₂), 68.4 (1C, C-4), 57.9 (1C, C-3), 40.6 (1C, C-7), 31.2 (1C, C-5 or C-6), 20.7 (2C, CO₂CH(CH₃)₂), 20.6 (2C, CO₂CH(CH₃)₂); MS (ES⁺) m/z = 393 [M+Na]⁺, HRMS (ES⁺) m/z calculated for C₁₅H₁₄N₆O₄Na [M+Na]⁺: 393.1282; found: 393.1284.
Di-\textit{tert}-butyl-5,5,6,6-tetracyano-1,2-diazaspiro[3.3]heptane-1,2-
dicarboxylate (304)

304 was synthesised according to General Procedure 6 with the following: 252 (50 mg, 0.19 mmol), tetracyanoethylene (24 mg, 0.19 mmol) and CH$_2$Cl$_2$ (3 mL). Recrystallisation from ethyl acetate afforded 304 (52 mg, 71%) as a white crystalline solid. M.p. 145.8-146.4 ºC; IR (neat) 2981 (CH$_3$), 1705 (C=O), 1367 (C-O) cm$^{-1}$; $^1$H NMR (400 MHz, CO(CD$_3$)$_2$) 4.91 (1H, d, $J = 10.4$ Hz, H-3), 4.65 (1H, d, $J = 10.4$ Hz, H-3), 4.35 (1H, d, $J = 15.1$ Hz, H-7), 4.02 (1H, d, $J = 15.2$ Hz, H-7), 1.58 (9H, s, C(CH$_3$)$_3$), 1.53 (9H, s, C(CH$_3$)$_3$); $^{13}$C NMR$^1$ (100 MHz, CO(CD$_3$)$_2$) 159.9 (1C, CO$_2$C(CH$_3$)$_3$), 154.7 (1C, CO$_2$C(CH$_3$)$_3$), 112.6 (1C, CN), 112.1 (1C, CN), 110.3 (1C, CN), 109.3 (1C, CN), 84.9 (1C, CO$_2$C(CH$_3$)$_3$), 83.5 (1C, CO$_2$C(CH$_3$)$_3$), 70.1 (1C, C-4), 59.6 (1C, C-3), 42.2 (1C, C-7), 32.2 (1C, C-5 or C-6), 28.2 (3C, CO$_2$C(CH$_3$)$_3$), 28.1 (3C, CO$_2$C(CH$_3$)$_3$); MS (ES$^+$) $m/z = 421$ [M+Na]$^+$; HRMS (ES$^+$) $m/z$ calculated for C$_{19}$H$_{22}$N$_6$O$_4$Na [M+Na]$^+$: 421.1595; found: 421.1593.

$^1$Only one carbon observed for C-5/C-6
Diethyl 5,5,6,6-tetracyano-7,7-dimethyl-1,2-diazaspiro[3.3]heptane-1,2-dicarboxylate (306)

306 was synthesised according to General Procedure 6 with the following: 274 (50 mg, 0.21 mmol), tetracyanoethylene (26 mg, 0.21 mmol) and CH₂Cl₂ (3 mL). Recrystallisation from ethyl acetate afforded 306 (30 mg, 39%) as a white crystalline solid. M.p. 137.7-138 °C; IR (neat) 2989 (CH₃), 2333 (-CN), 1756 (C=O), 1270 (C-O) cm⁻¹; ¹H NMR (400 MHz, CD₃CN) 4.38-4.50 (3H, m, CO₂CH₂CH₃, H-3), 4.22-4.31 (3H, m, CO₂CH₂CH₃, H-3), 1.72 (3H, s, >C(CH₃)₂), 1.63 (3H, s, >C(CH₃)₂), 1.35 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃), 1.31 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃); ¹³C NMR (100 MHz, CD₃CN) 159.2 (1C, CO₂CH₂CH₃), 153.8 (1C, CO₂CH₂CH₃), 109.8 (1C, CN), 109.5 (1C, CN), 109.1 (1C, CN), 107.3 (1C, CN), 76.3 (1C, C-4), 63.0 (1C, CO₂CH₂CH₃), 62.9 (1C, CO₂CH₂CH₃), 53.9 (1C, C-3), 53.1 (1C, C-7), 44.7 (1C, C-5 or C-6), 43.8 (1C, C-5 or C-6), 24.2 (1C, >C(CH₃)₂), 20.9 (1C, >C(CH₃)₂), 13.3 (1C, CO₂CH₂CH₃), 13.2 (1C, CO₂CH₂CH₃); MS (ES⁺) m/z = 393 [M+Na]+, HRMS (ES⁺) m/z calculated for C₁₇H₁₉N₆O₄ [M+Na]⁺: 371.1462; found: 371.1465.
Firstly, a solution of DMDO in acetone was prepared as follows: a 250 mL 3-necked round bottomed flask fitted with a condenser was connected to a 50 mL receiving flask cooled to -78 °C. NaHCO$_3$ (12 g, 143 mmol), acetone (13 ml, 177 mmol) and water (20 ml, 1.11 mol) were added to the 3-necked flask and cooled to 0 °C. Oxone (25 g, 164 mmol) was added to the flask portion-wise with vigourous stirring. A sheet of aluminium foil containing dry ice was then wrapped around the condenser followed by the attachment of a water aspirator. The reaction was then stirred under these conditions for 1 h whereby several mL of solution had been collected within the 50 mL flask. The concentration of the solution was determined to be approximately 0.05 M using iodometric titration. The freshly prepared solution of DMDO (4 mL, 0.02 mmol approx.) was added to a stirred solution of 251 (24 mg, 0.11 mmol) in CH$_2$Cl$_2$ (1 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 1 h and then concentrated in vacuo to afford 310 (25 mg, 96%) as a colourless oil. IR (neat) 2983 (CH$_3$), 1698 (C=O), 1102 (C-O) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 4.58 (1H, d, $J = 10.0$ Hz, H-3), 4.44 (1H, d, $J = 10.1$ Hz, H-3), 4.15-4.32 (4H, m, CO$_2$CH$_3$CH$_3$), 3.69 (1H, d, $J = 4.0$ Hz, H-6), 2.85 (1H, d, $J = 3.9$ Hz, H-6), 1.30 (3H, t, $J = 7.1$ Hz, CO$_2$CH$_2$CH$_3$), 1.29 (3H, t, $J = 7.1$ Hz, CO$_2$CH$_2$CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) 160.8 (1C, CO$_2$CH$_2$CH$_3$), 156.8 (1C, CO$_2$CH$_2$CH$_3$), 71.2 (1C, C-4), 63.2 (1C, CO$_2$CH$_2$CH$_3$), 62.9 (1C, CO$_2$CH$_2$CH$_3$), 56.4 (1C, C-3), 47.5 (1C, C-6), 14.3 (1C, CO$_2$CH$_2$CH$_3$), 14.3 (1C, CO$_2$CH$_2$CH$_3$); MS (ES$^+$) $m/z$

**Ethyl ([1-[(ethoxycarbonyl)amino]cyclopropyl]methyl)carbamate (312)**

![Ethyl ([1-[(ethoxycarbonyl)amino]cyclopropyl]methyl)carbamate (312)](image)

To a stirred solution of 251 (150 mg, 0.70 mmol) in CH₂Cl₂ (4 mL), was added CH₂Cl₂ (282 µL, 3.5 mmol) followed by ZnEt₂ (3.5 mL, 3.5 mmol, 1M in hexanes) and the reaction was stirred at 25 °C for 24 h. The reaction was quenched with NH₄Cl (aq) (2 mL) and extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were dried over magnesium sulphate and concentrated *in vacuo*. The residue was taken up in THF (2 mL) and 1M HCl (3 mL) and stirred at 80 °C for 4 h. Upon cooling, the reaction mixture was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over magnesium sulphate and concentrated *in vacuo*. Purification on silica gel (30% ethyl acetate in hexane) afforded 312 (34 mg, 21%) as a white solid. ¹H NMR (400 MHz, CDCl₃) 5.61 (1H, br s, NH), 5.10 (1H, br s, NH), 4.07-4.13 (4H, m, CO₂CH₂CH₃), 3.28 (2H, br m, H-2), 1.24 (6H, t, J = 7.0 Hz, CO₂CH₂CH₃), 0.83 (4H, br s, 4H, CH₂CH₂); MS (ES⁺) m/z = 253 [M+Na]⁺, HRMS (ES⁺) m/z calculated for C₁₀H₁₉N₂O₄ [M+H]⁺: 231.1339; found: 231.1430.
References


78. T. Ooi, M. Takeuchi, D. Kato, Y. Uematsu, E. Tayama, D. Sakai, K. Maruoka, 


   16370.


   **9**, 351.


   2005, **70**, 5665.

   9932.

   **134**, 7516.

   2001, **3**, 3185.

   2010, **51**, 382.


Appendix
Appendix 1

$^1$H NMR spectra (400 MHz) of 235
Appendix 2

$^1$H NMR Spectra (400 MHz) of (±)-290 in the presence (S)-(+) 1-(9-Anthryl)-2,2,2-trifluoroethanol (focused on methyl group splitting).

(±)-290

Pirkle's alcohol
(S)-(+) 1-(9-Anthryl)-2,2,2-trifluoroethanol
Appendix 2

$^1$H NMR Spectra (400 MHz) of (R)-290 in the presence (S)-(+-) 1-(9-Anthryl)-2,2,2-trifluoroethanol spiked with (+)-290 (focused on methyl group splitting).

EtO$_2$CHN$\text{NHCO}_2$Et

(R)-290

Pirkle’s alcohol
(S)-(+-) 1-(9-Anthryl)-2,2,2-trifluoroethanol
Appendix 2

$^1$H NMR Spectra (400 MHz) of (S)-290 in the presence (S)-(+) - (9-Anthryl)-2,2,2-trifluoroethanol (focused on methyl group splitting).

![NMR Spectra Image](image-url)
Appendix 3

$^1$H NMR (400 MHz) spectra of 300
Appendix 4

$^1$H NMR Spectrum of 308

![NMR Spectrum Image]
Appendix 5

HPLC retention times using a solvent system of iPrOH in hexane on a Chiralcel AD column at 1.0 mL/min. UV absorbance was measured at 220 nm.

![Chemical structure](image_url)

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