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

by

Greg Iacobini

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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.

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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

Ac	Acetyl
AIBN	*azo-bis*-Isobutyronitrile
Ar	Aryl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
br	broad
cat.	Catalytic
Cbz	Carbobenzyloxy
CPME	Cyclopentyl methyl ether
COD	Cyclooctadiene
conc.	Concentrated
COSY	Correlation Spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylidine acetone
DBB	4,4′-Di-*tert*-butylbiphenyl
DBU	1,3-Diazabicyclo[5.4.0]undecane
de	Diastereomeric excess
DIBAL	Di-iso-butylaluminium hydride
DMAc	Dimethylacetamide
DMAP	Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMEDA	*N,N'*-Dimethylethylenediamine
DMF	Dimethylformamide

DMSO	Dimethyl sulfoxide
EDTA	Ethylenediaminetetraacetic acid
ee	Enantiomeric excess
FT	Fourier Transform
h	hour
HIV	Human immunodeficiency virus
HMBC	Heteronuclear Multiple Bond Coherence
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear Multiple Quantum Coherence
HPLC	High-performance liquid chromatography
HRMS	High Resolution Mass Spectroscopy
IPA	Isopropyl alcohol
IR	Infrared
J	Coupling constant
lit.	Literature value
m-CPBA	*meta*-Chloroperoxybenzoic acid
mol.	Molar
M.p.	Melting point
Ms	Mesyl
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
nOe	nuclear Overhauser effect
PMP	*para*-Methoxyphenyl
rt	Retention time
TCNE	Tetracyanoethylene

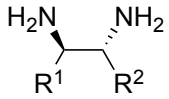
Temp.	Temperature
Tf	Triflate
THF	Tetrahydrofuran
tlc	Thin layer chromotography
TMS	Tetramethylsilane
Ts	Tosyl
TMEDA	Tetramethylethylenediamine
UV	Ultra violet

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.[1-5] We highlight work of most relevance to our studies in this chapter.

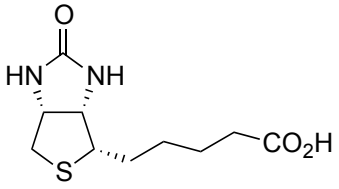


1,2-diamine
1

Figure 1.1

1.2 1,2-Diamines in Natural Products

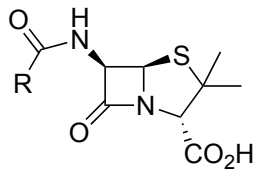
1,2-Diamines are found in a wide range of natural products, many of which have important biological functions.[2] For example, Biotin (vitamin H) **2** is an essential cofactor to carboxylase-catalysed reactions; it contains the 1,2-diamino moiety within an imidazolidinone ring (Figure 1.2).[6]



Biotin
2

Figure 1.2

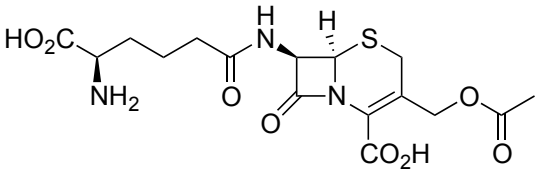
Penicillin **3**, the well-known family of antibiotics, contains a 2,3-diamino carboxylic acid unit within the penam skeleton (Figure 1.3).



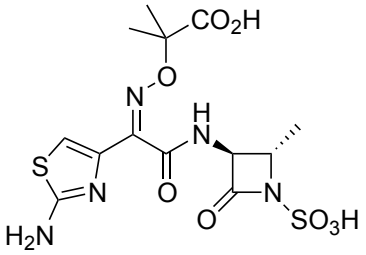
Penicillin
3

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

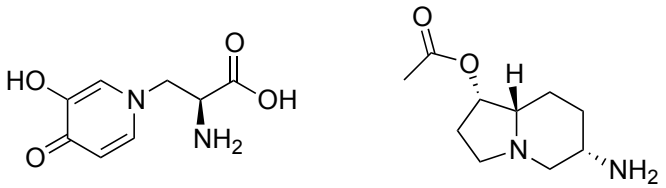


Aztreonam
5

Figure 1.4

Many natural products, in particular non-ribosomal peptides, possess a diamino carboxylate substructure.[7] These can be found within several families of antibiotics including edeines and tuberactomycin derivatives.[8] 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
6

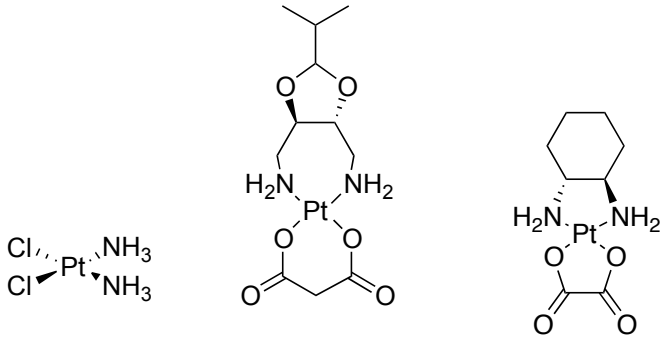
Slaframine
7

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.

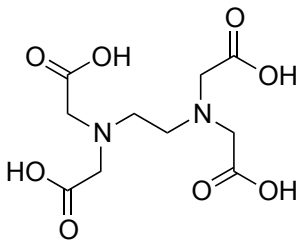
Cisplatin **8** was found to have anticancer properties by Rosenberg in the 1960s.[14] Since this discovery there has been a great deal of interest in developing diamine-platinum complexes that possess greater activity and fewer side effects than Cisplatin, as well as overcome drug resistance that can 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]



Cisplatin **8** | Heptaplatin **9** | Oxaliplatin **10**

Figure 1.6

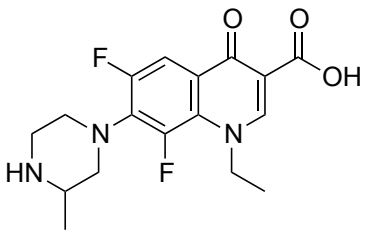
Ethylenediaminetetraacetic acid (EDTA) **11** is a synthetic 1,2-diamine that has found use both within industry and medicine due to its ability to bind to metal ions. It is commonly used in chelation therapy for the removal of excess iron in the body as well as for conditions such as mercury and lead poisoning (Figure 1.7). [17]



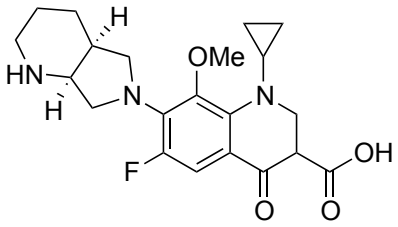
EDTA **11**

Figure 1.7

The quinolones are a family of synthetic broad-spectrum antibiotics, a number of which contain vicinal diamines within heterocyclic substituents.[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).[19,20]



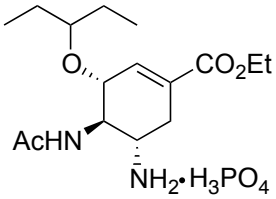
Lomefloxacin
12



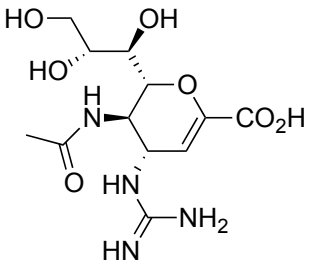
Moxifloxacin
13

Figure 1.8

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]



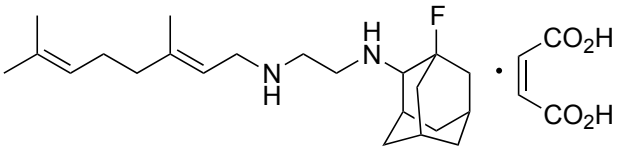
Oseltamivir (Tamiflu™)
14



Zanamivir (Relenza™)
15

Figure 1.9

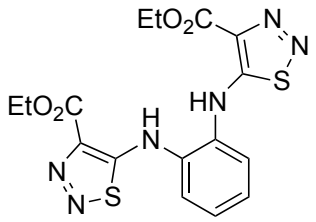
In 2009 Yao *et al*. identified a number of 1,2-diamines, such as **16**, that possess potent antituberculosis activity (Figure 1.10).[23] Tuberculosis remains one of the worlds most deadly infectious diseases and with the development of antibiotic-resistant strains, new medicines for its treatment are highly sought-after. [24]



16

Figure 1.10

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.[25]



17

Figure 1.11

1.4 Applications in Synthetic Chemistry

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.[2] 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.[26,27] 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).[28]

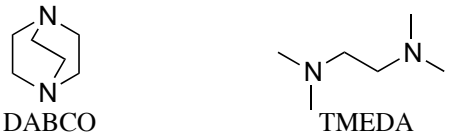
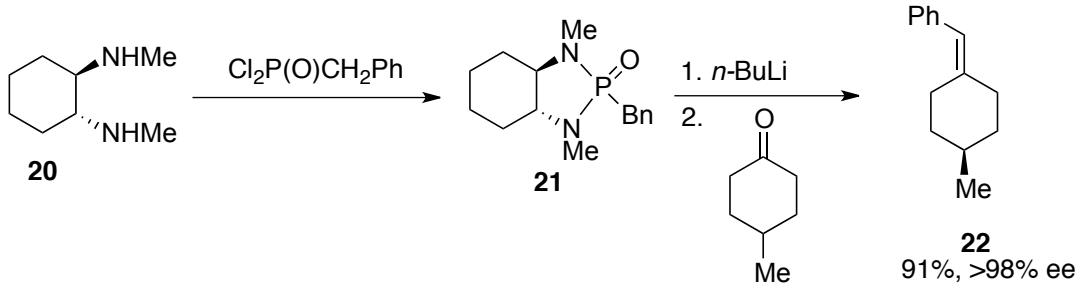


Figure 1.12

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

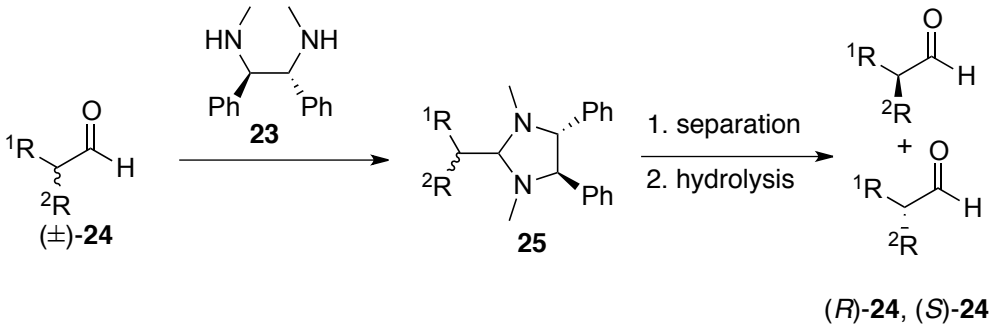
Chiral auxiliaries are used for incorporating temporary chirality into an otherwise achiral molecule, thus allowing asymmetric reactions to be carried out.[29] Since the introduction of chiral auxiliaries there has been much development in the area and in a number of cases, the 1,2-diamine moiety is present within the auxiliary.[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).[30]



Scheme 1.1

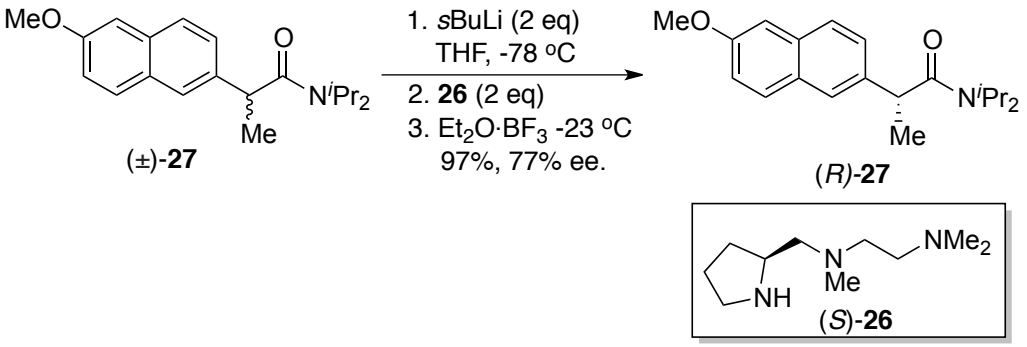
Mangeney *et al*. have shown that symmetrical 1,2-diamines such as **23** can act as simple but effective resolving agents for chiral aldehydes **24**.[31-33] Aminal

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

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]

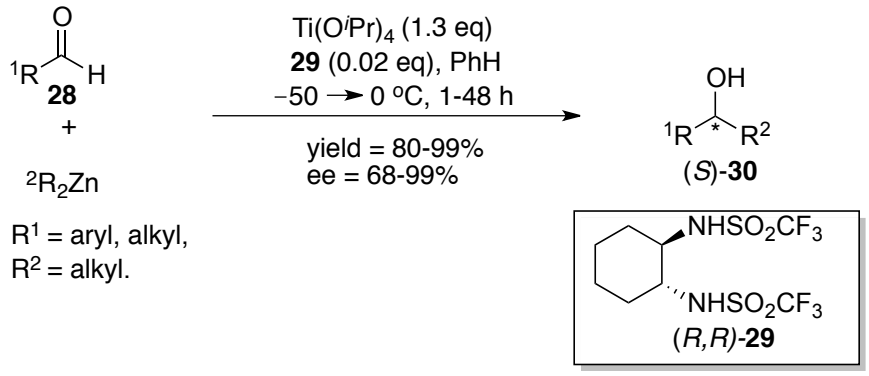


Scheme 1.3

1.4.2 1,2-Diamines as chiral ligands

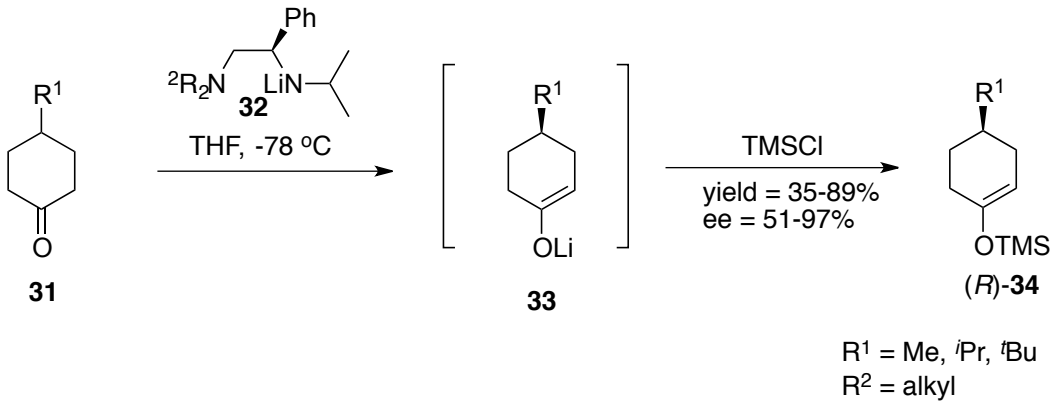
There has been an extensive amount of research into the use of chiral 1,2-diamine ligands for the stereoselective addition of organometallic reagents to aldehydes and ketones.[35-38] Knochel *et al*. have demonstrated this with the

addition of dialkylzinc reagents to aldehydes **28** in the presence of $Ti(O^iPr)_4$ and disulfonamide **29** to give excellent enantioselectivities of the resulting secondary alcohols **30** (Scheme 1.4).[39]



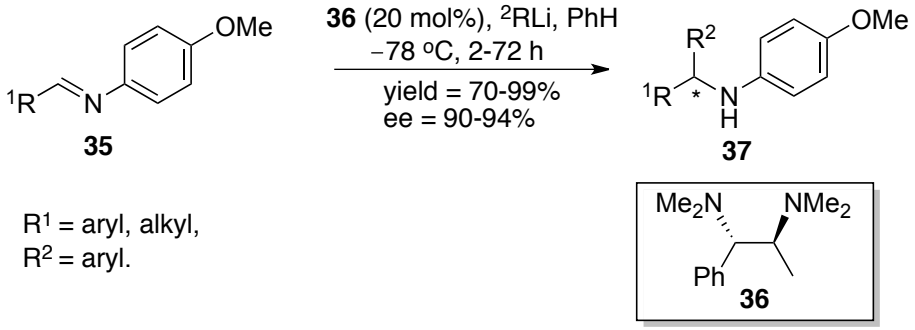
Scheme 1.4

In 1986, Koga and Simpkins first described independently the use of chiral lithium amide bases to stereoselectively deprotonate ketones.[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).[42]



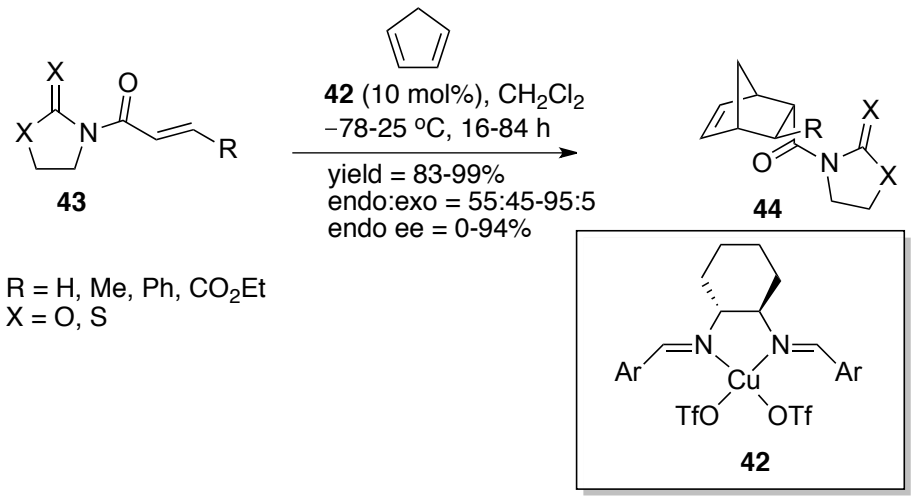
Scheme 1.5

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).[43]



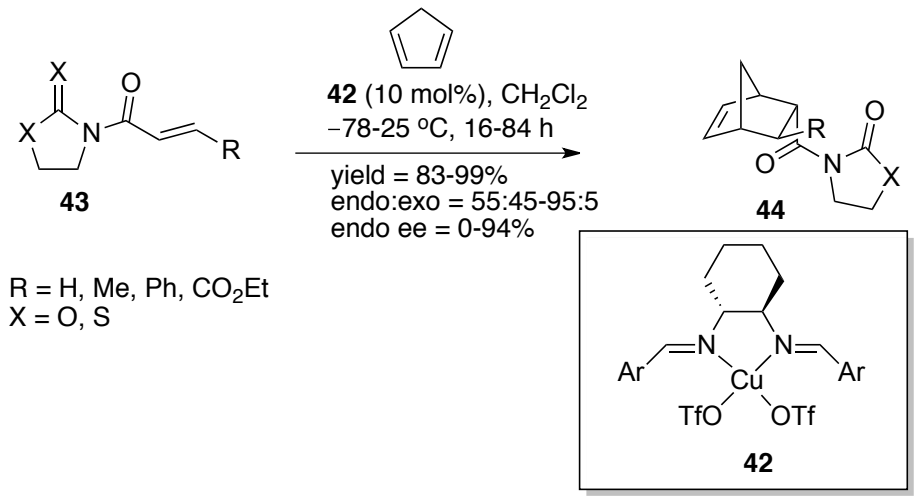
Scheme 1.6

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.[44-45] Cycloadduct **41**, formed from diene **39** and oxazolidinone **40**, is an important intermediate for prostaglandin synthesis (Scheme 1.7).[46]



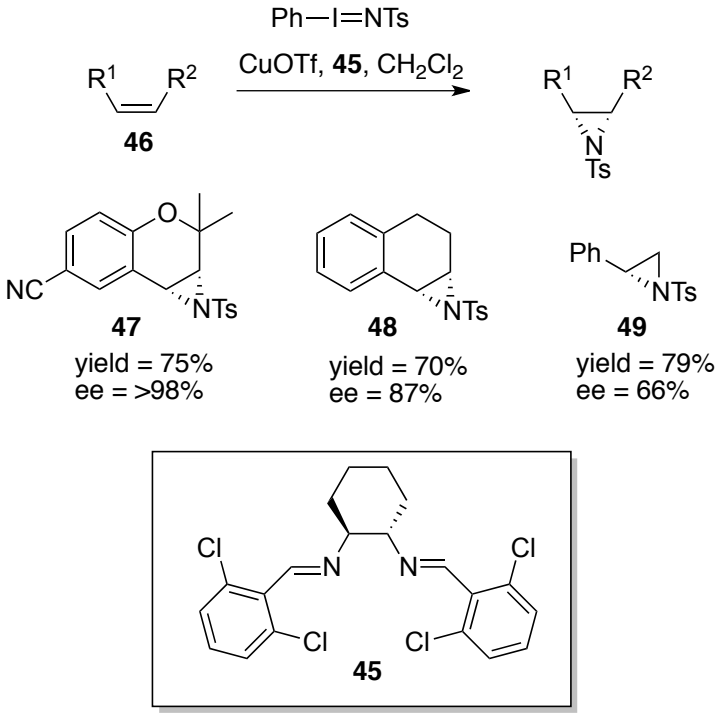
Scheme 1.7

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).[47]



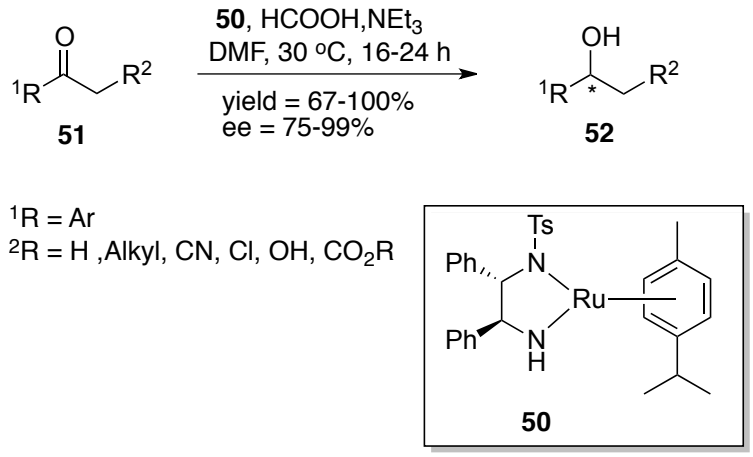
Scheme 1.8

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).[48]



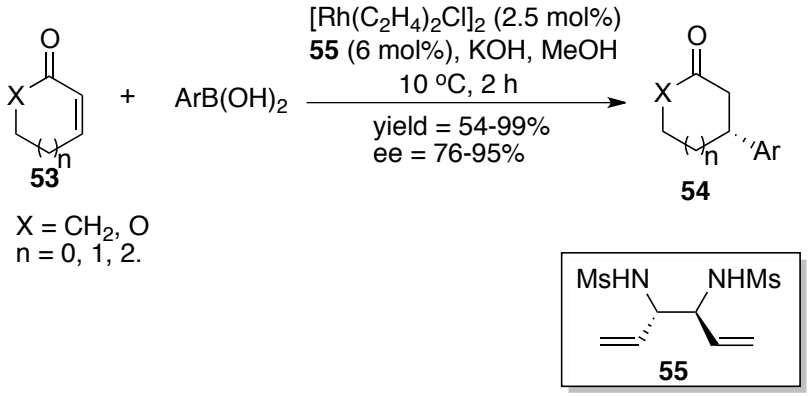
Scheme 1.9

Asymmetric hydrogenation is arguably one of the most important and widely used enantioselective reactions.[49,50] In particular, asymmetric transfer hydrogenation reactions have received much attention in recent years.[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 **50**, can reduce a wide range of ketones **51** to the corresponding alcohols **52** with excellent enantioselectivities (Scheme 1.10).[52]



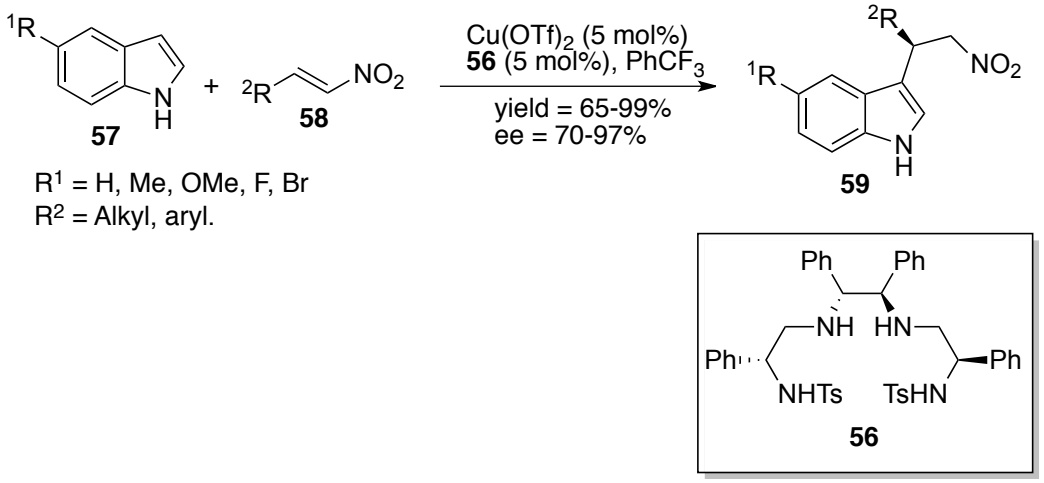
Scheme 1.10

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

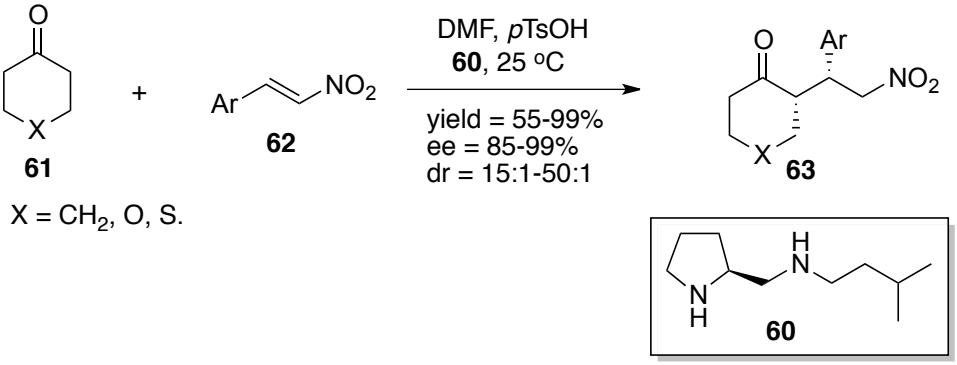
More recently, Wan *et al*. have utilised 1,2-diamine **56** as a ligand for a copper-catalysed asymmetric Friedel-Crafts alkylation of indoles **57** with nitroalkenes **58** to give substituted indoles **59** with excellent yields and enantioselectivities (Scheme 1.12).[54]



Scheme 1.12

1.4.3 1,2-Diamines as organocatalysts

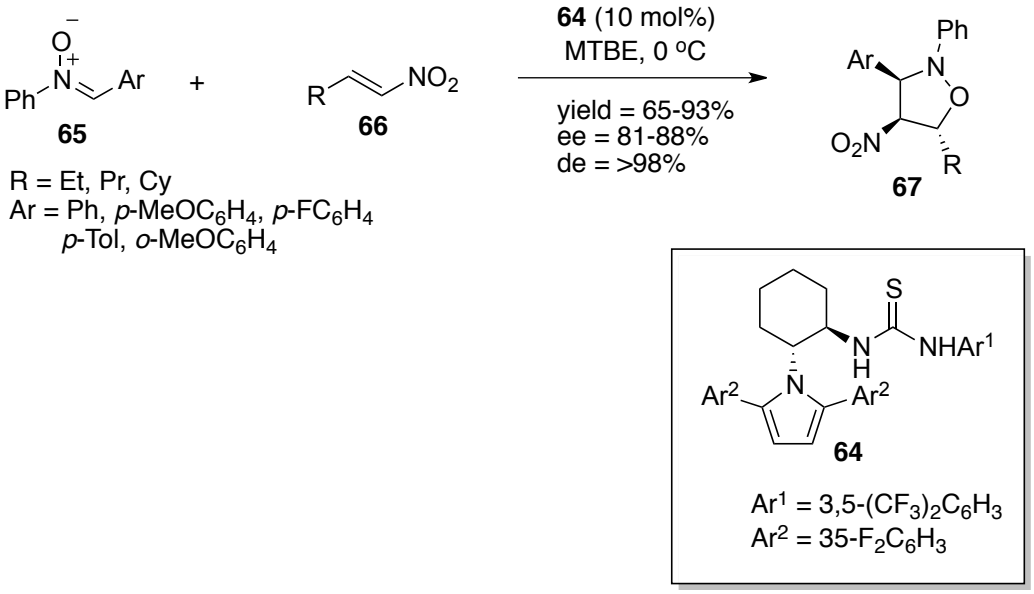
In recent years there have been many reports of reactions that utilise 1,2-diamines as catalysts themselves.[55] For example, Pansare and Pandya have demonstrated that proline-derived 1,2-diamine **60** is capable of catalysing the asymmetric Michael addition of cyclic ketones **61** to nitroalkenes **62** to yield **63** with excellent enantioselectivities (Scheme 1.13).[56]



Scheme 1.13

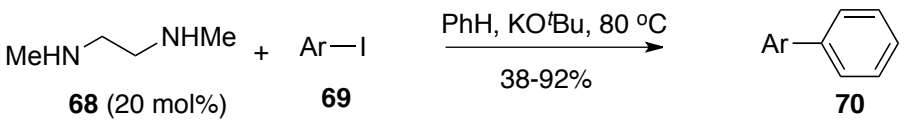
The asymmetric catalysis of cycloadditions with 1,2-diamines have also been developed. For example Chen and co-workers have reported organocatalyst **64**,

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 enantioseletivity and excellent diastereoselectivity (Scheme 1.14).[57]



Scheme 1.14

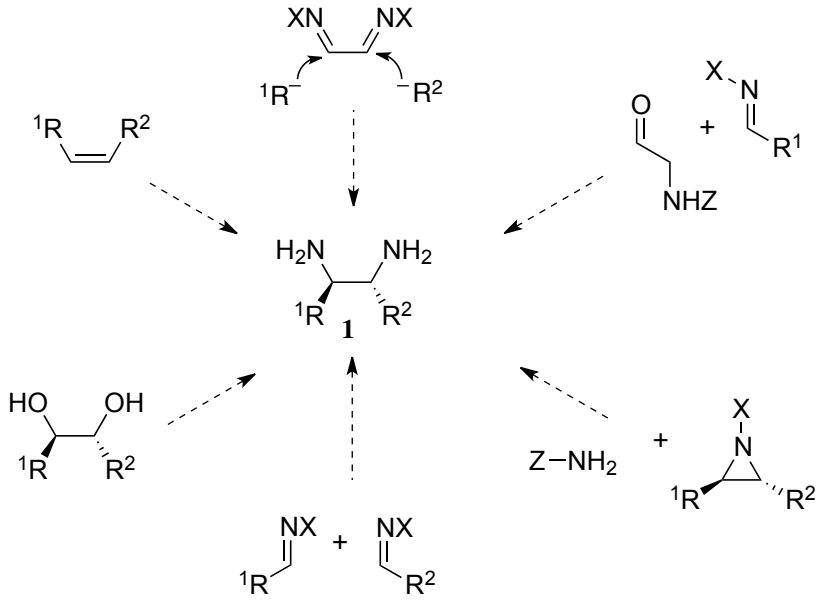
In 2010, Lei and co-workers described the use of *N,N'*-dimethylethylenediamine (DMEDA **68**) as a catalyst to promote C-H arylation of unactivated benzene with aryl iodides **69**.[58] The mechanism is believed to involve an aryl radical anion intermediate and offers considerable scope for coupling reactions of substrates that are sensitive to transition metal-based catalysts (Scheme 1.15).



Scheme 1.15

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.[2-3] 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.

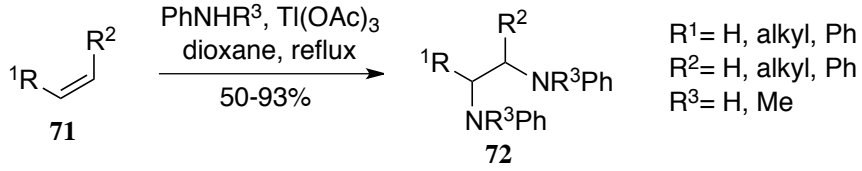


Scheme 1.16

1.5.1 Diamination of alkenes

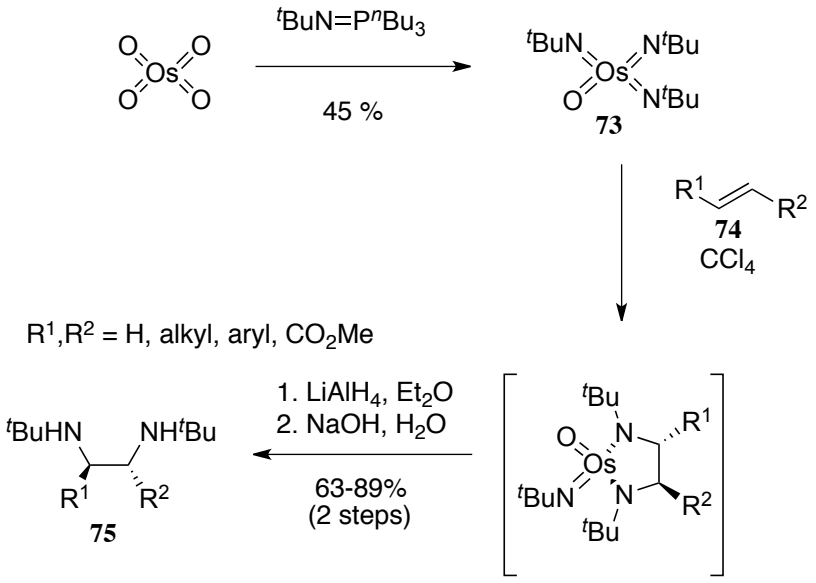
The direct addition of two nitrogen atoms across an olefin can be considered to be one of the most attractive routes for the synthesis of 1,2-diamines. However, unlike the analogous dihydroxylation reaction, which has enjoyed much success, the diamination of alkenes has received relatively little attention.[59]

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]



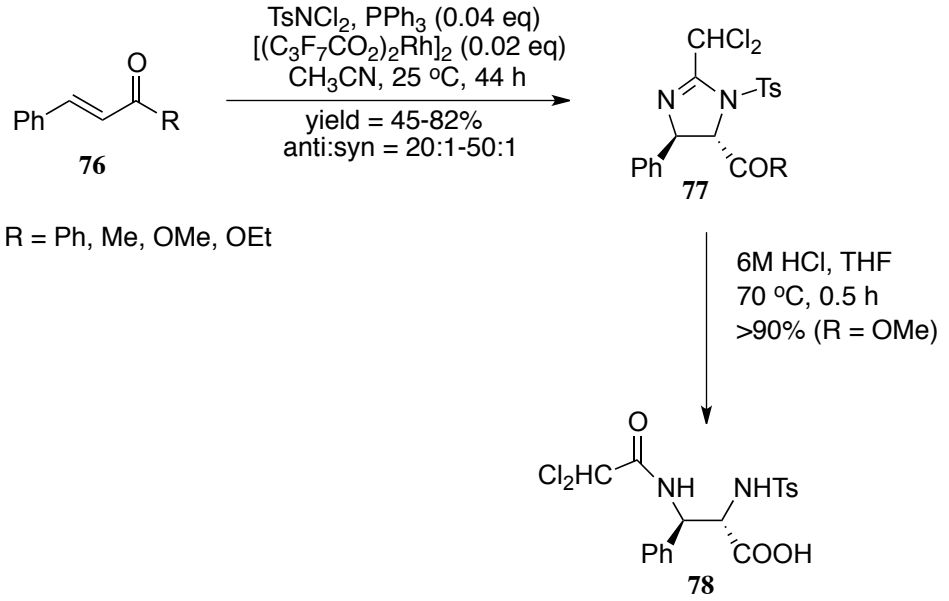
Scheme 1.17

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 OsO_4. In addition, this synthesis is only compatible with *E*-alkenes and no absolute stereochemical control is possible (Scheme 1.18).



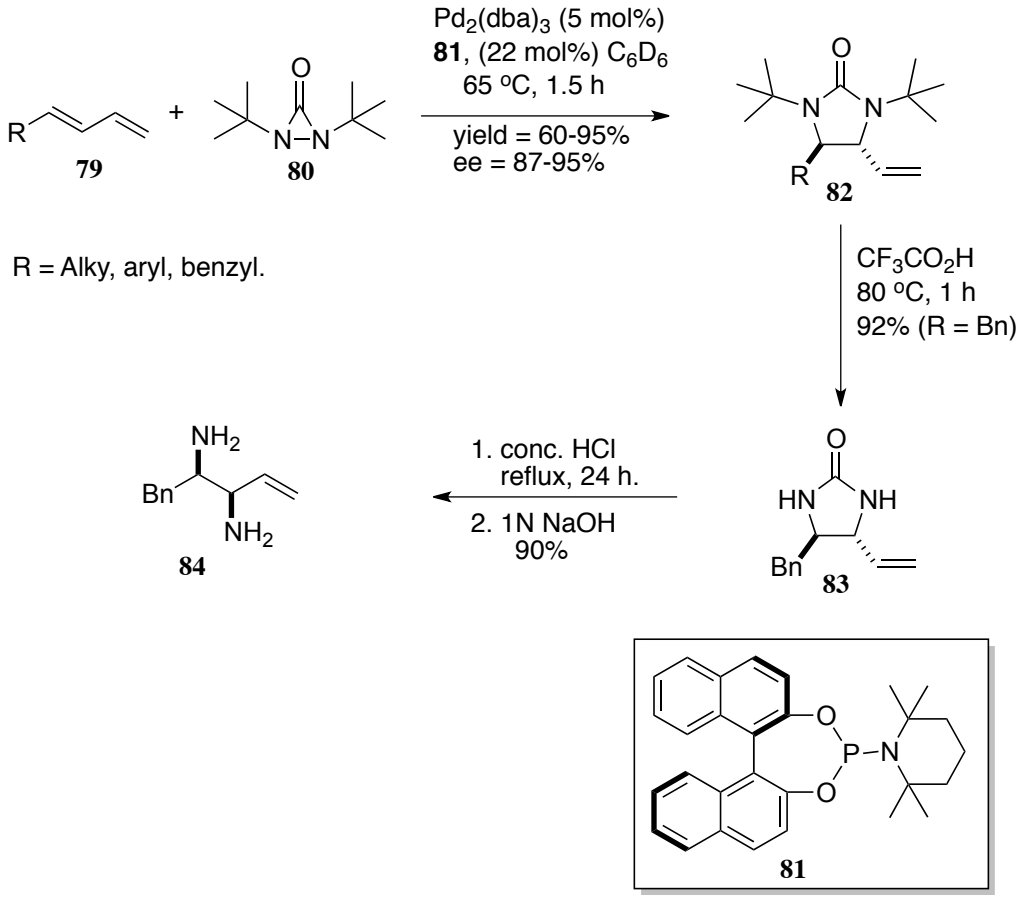
Scheme 1.18

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]



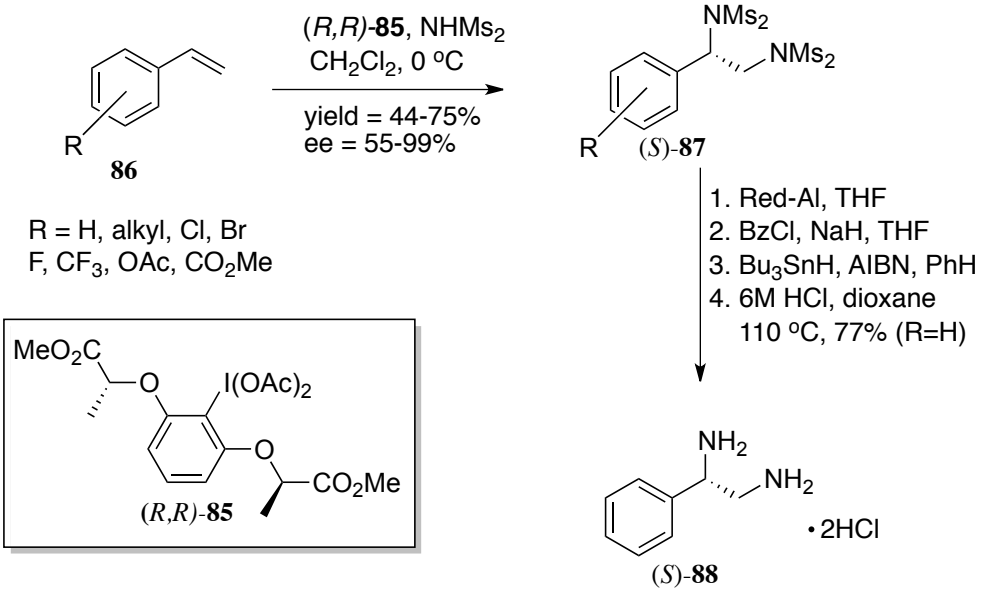
Scheme 1.19

Since Li's findings there has been increased interest in the area and several groups have reported the enantioselective diamination of olefins.[63-66] For example, in 2007 Shi *et al*. demonstrated the asymmetric diamination of dienes **79** with di-*tert*-butyldiaziridinone (**80**) using $Pd_2(dba)_3$ as a catalyst and BINOL-based ligand **81**.[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

More recently Muniz and co-workers have reported the use of chiral hypervalent iodine complex **85** for the diamination of styrene derivatives **86**.[68] 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).

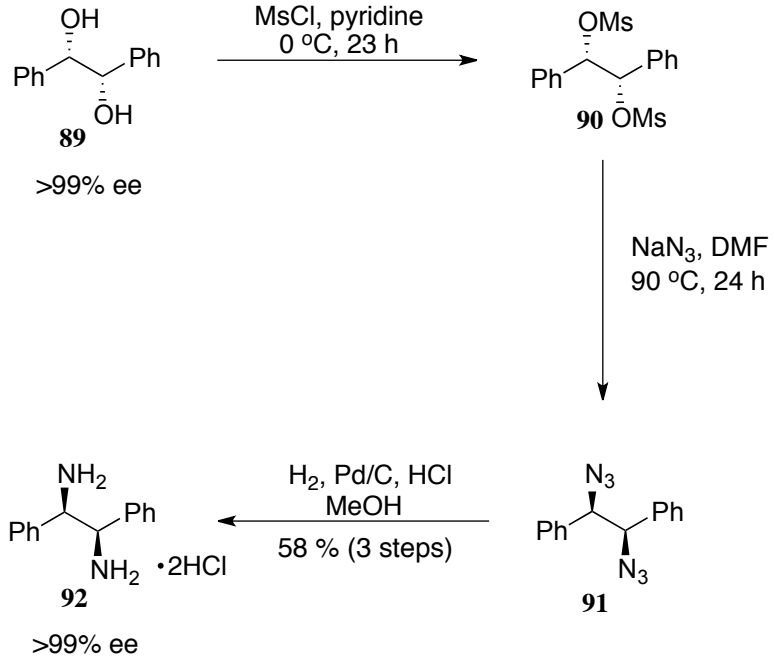


Scheme 1.21

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

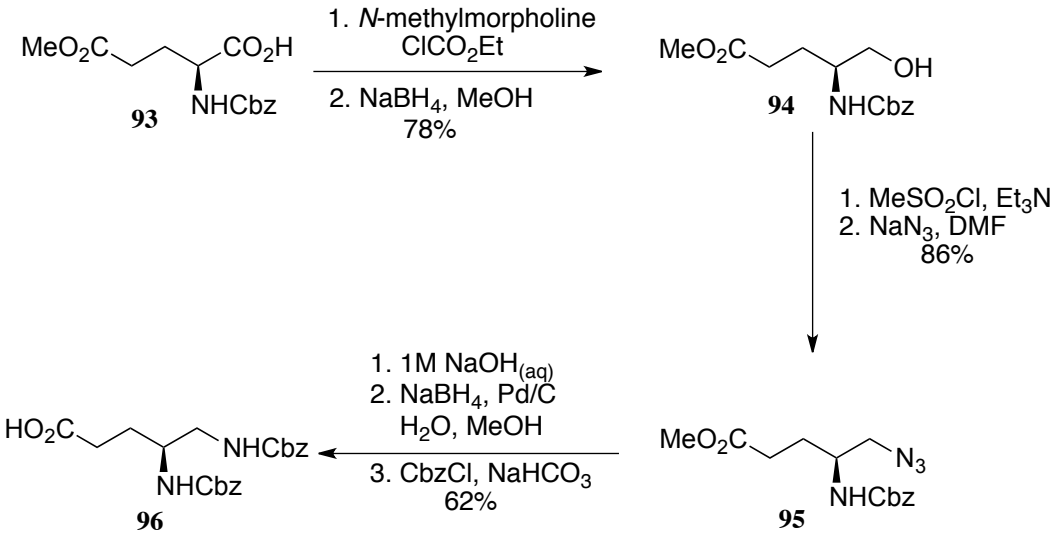
The enantioselective syntheses of 1,2-diols and *β*-amino alcohols have received much attention and there are now a variety of effective methods available for their preparation.[69-75] In addition, there are a number of optically active *β*-amino acids available from the chiral pool.[76] As such, their 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).[71]



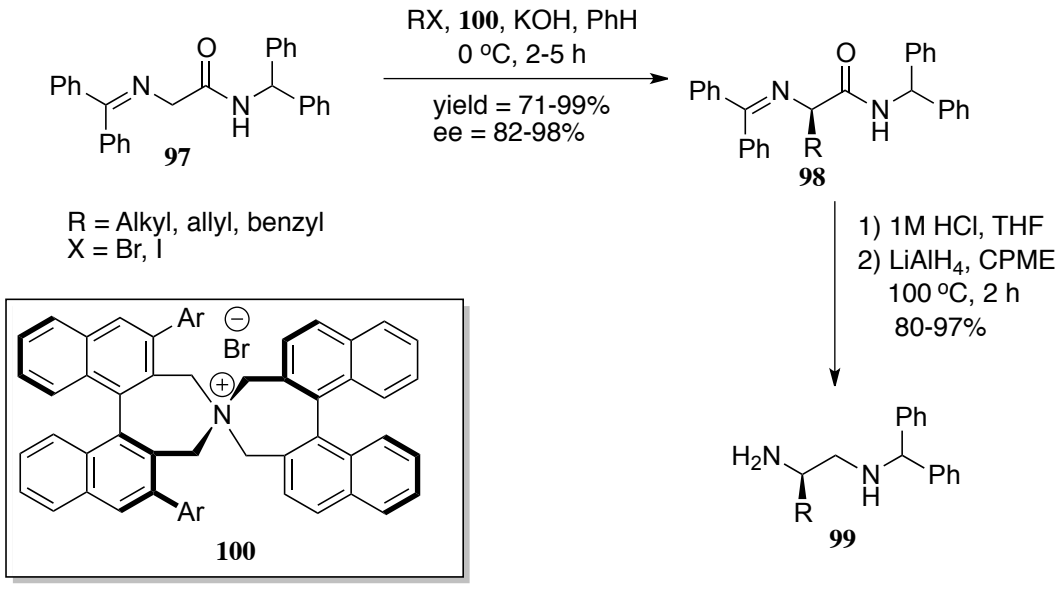
Scheme 1.22

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).



Scheme 1.23

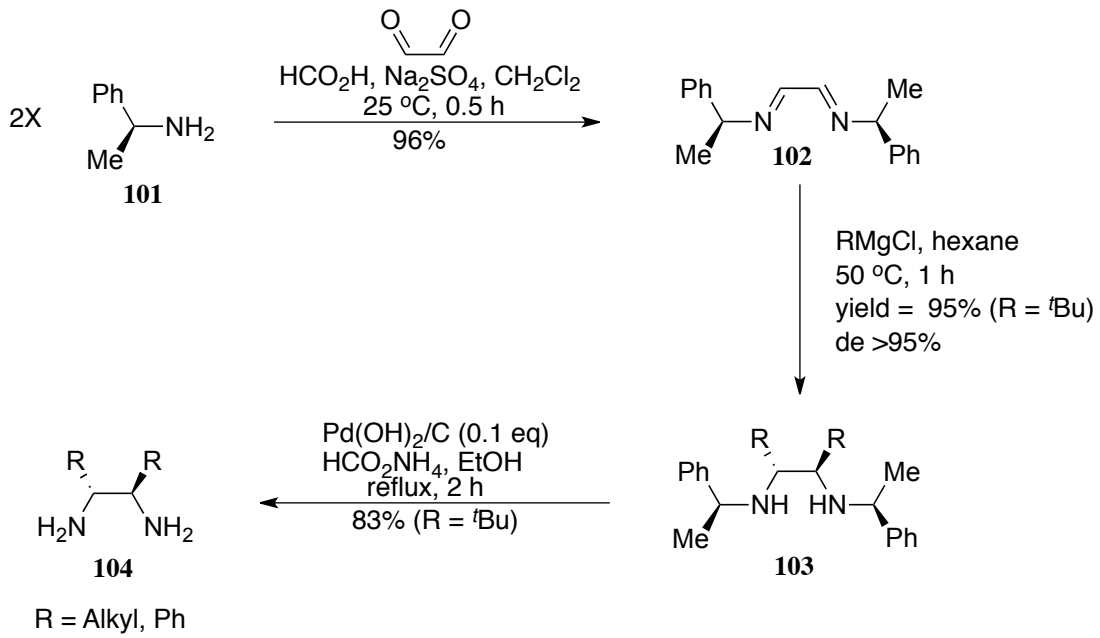
In 2004, Maruoka *et al*. reported a highly enantioselective synthesis of 1,2-diamines **99** from protected α-amino acid amides **97** using a phase-transfer-catalysed alkylation.[78] This method utilises chiral ammonium salt **100** as the catalyst and leads to **99** in 2 steps (Scheme 1.24).



Scheme 1.24

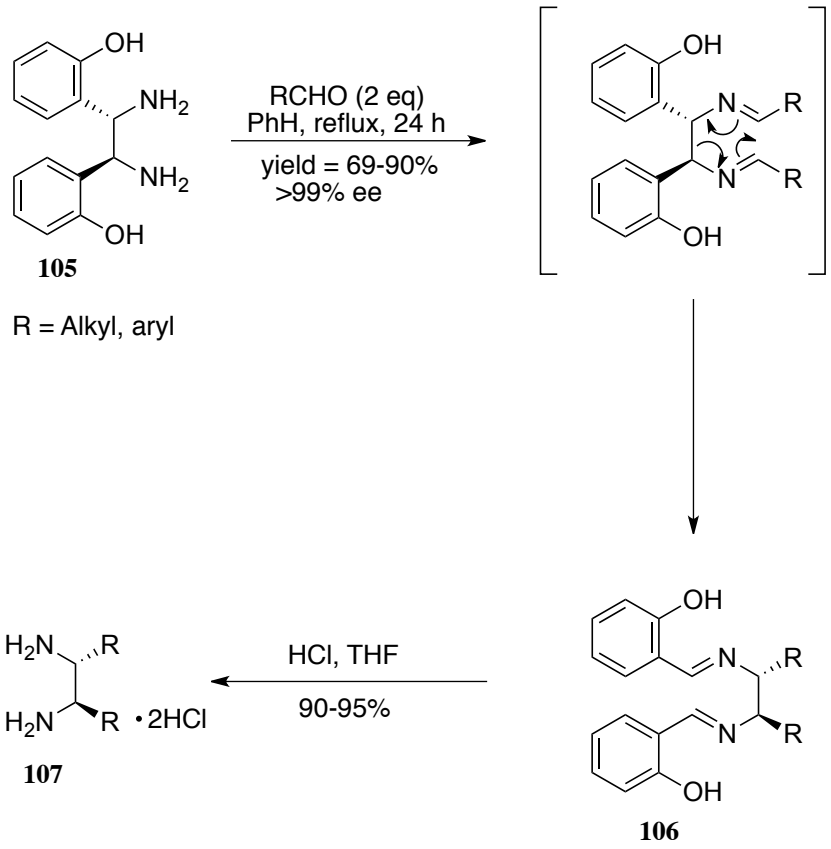
1.5.3 1,2-Diamines from bis-imines

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 α-methyl-benzylamino groups to induce stereochemistry.[79] Subsequent hydrogenation affords 1,2-diamine **104** in good yield and excellent diastereoselectivity.



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]



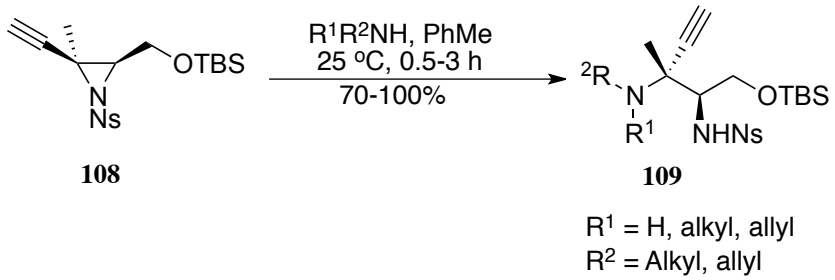
Scheme 1.26

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.

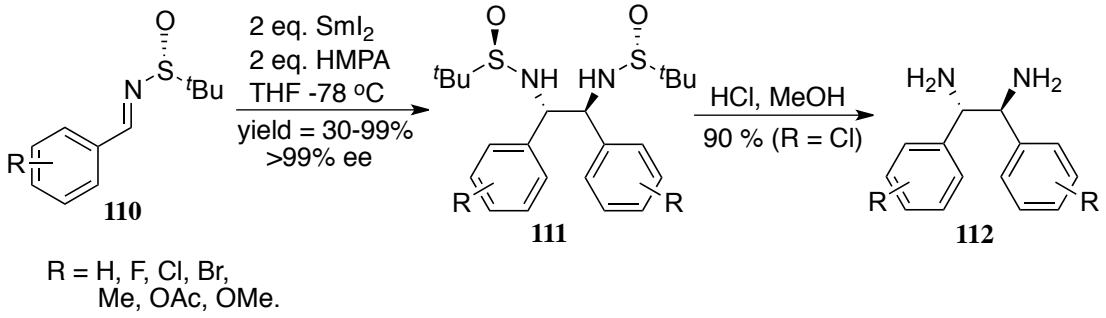
There are numerous well-established methods for the enantioselective synthesis of aziridines.[81-84] As such, it comes as no surprise that the ring opening of aziridines with nitrogen-based nucleophiles has been employed for the synthesis of 1,2-diamines. The example in Scheme 1.27 demonstrates the ring 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

1.27).[84] 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

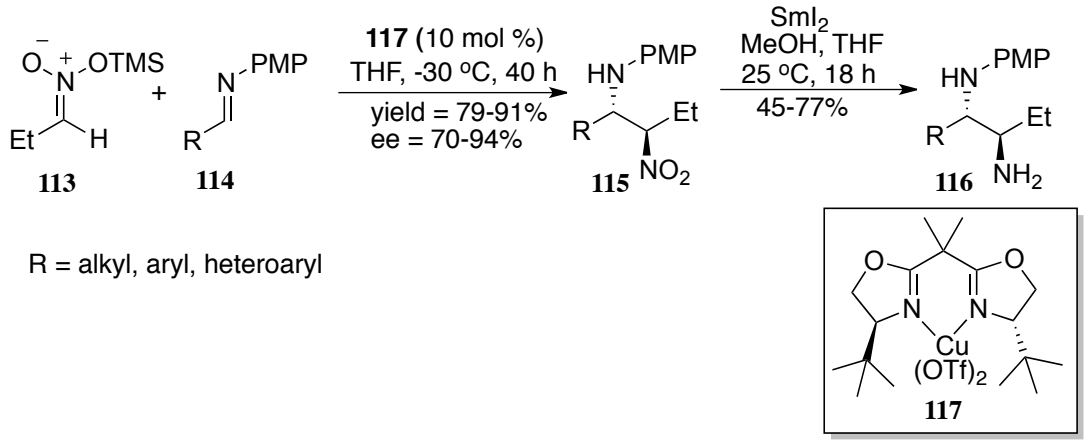
In 2004, Xu and co-workers reported the asymmetric synthesis of 1,2-diamines **112** via a reductive homocoupling of aromatic N-*tert*-butanesulfinyl imines **110** in the presence of SmI_2 and HMPA, followed by deprotection with HCl in methanol.[85] This process offers a straightforward route to a range 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

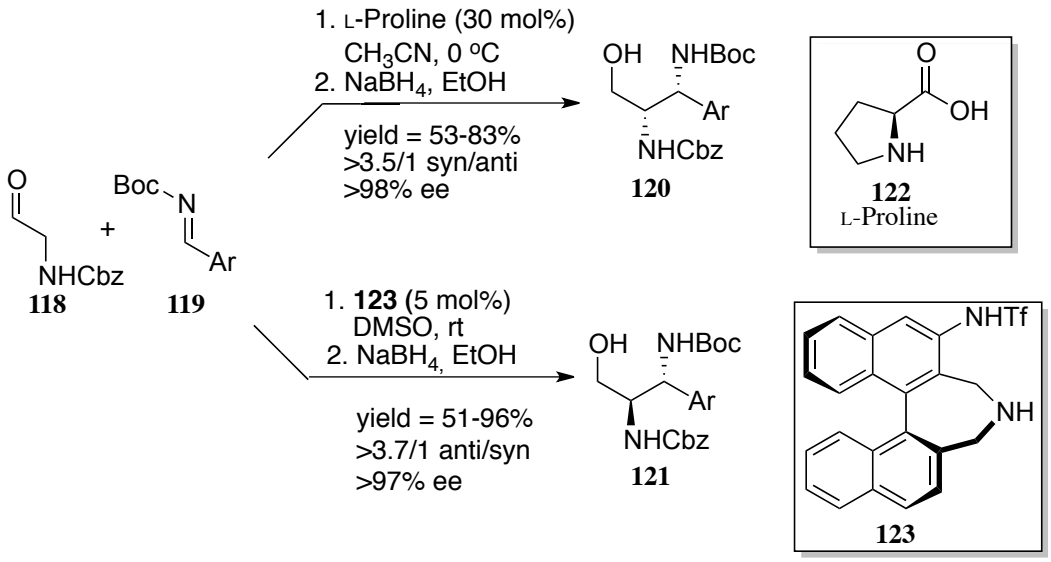
Anderson *et al*. have recently utilised an asymmetric nitro-Mannich reaction for the synthesis of *β*-nitroamines **115** using copper catalyst **117** with trimethylsilylnitropropanate (**113)** and a variety of imines **114**.[86] These products

can then undergo reduction with SmI_2 to yield a variety of enantiomerically enriched 1,2-diamines **116** (Scheme 1.29).[87]



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 α-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).



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 efficent 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

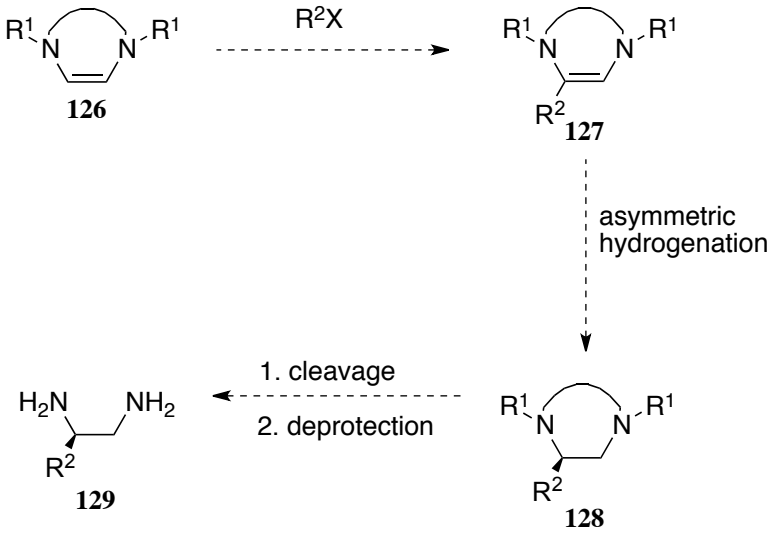
In this thesis, we explore an alternative approach to the synthesis of 1,2-diamines based upon the use of a variety of heterocyclic templates containing two vicinal nitrogen atoms. In this chapter, we describe efforts to use 1,2-diazetine **124** and imidazolin-2-one **125** systems for this purpose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

124
1,2-diazetine

125
imidazolin-2-one

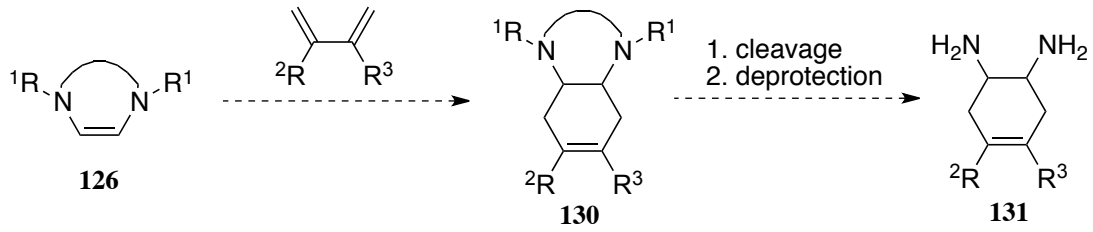
Figure 2.1

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)



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

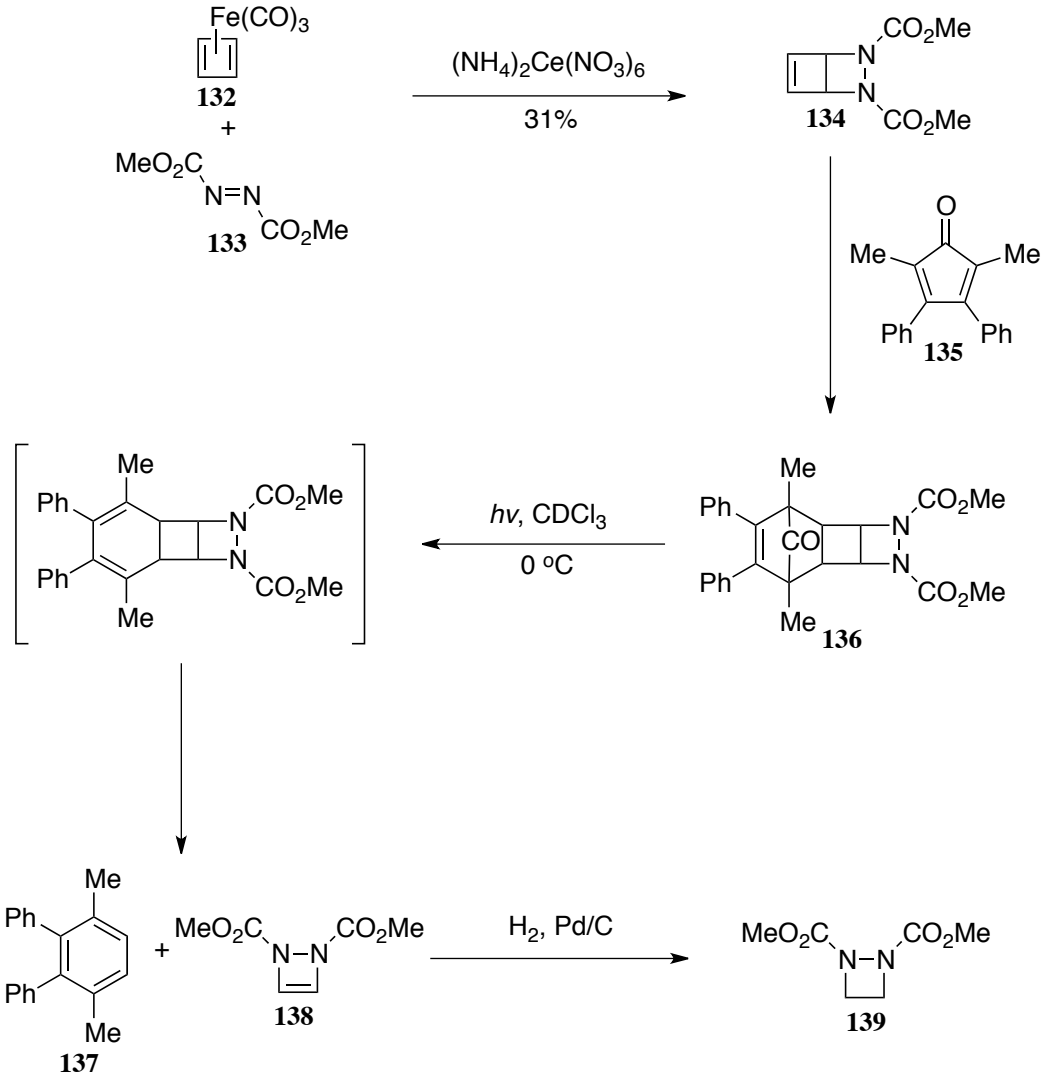
2.2.1 Introduction

There are very few reports of 1,2-diazetines in the literature, as their synthesis poses a significant challenge.[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.[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.

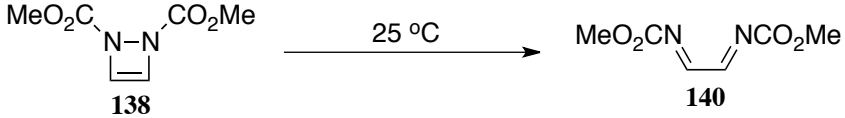
2.2.2 Background

To our knowledge, Warrener and Nunn reported the first known synthesis of a 1,2-diazetine in 1972.[93] Synthesis of **138** was achieved beginning with a cycloaddition between dimethylazodicarboxylate (**133**) and *in situ* generated cyclobutadiene via oxidation of the corresponding $Fe(CO)_3$ complex **132,** to yield diazabicyclohexane **134**, which undergoes a second cycloaddition with 2,5-dimethyl-3,4-diphenylcyclo**-**penta-2,4-dienone (**135**) to furnish tricycle **136**. Irradiation of **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 (**137**) and 1,2-diazetine **138**. In this instance, **138** was converted to the corresponding 1,2-diazetidine **139** by catalytic hydrogenation using palladium on carbon (Scheme 2.3).



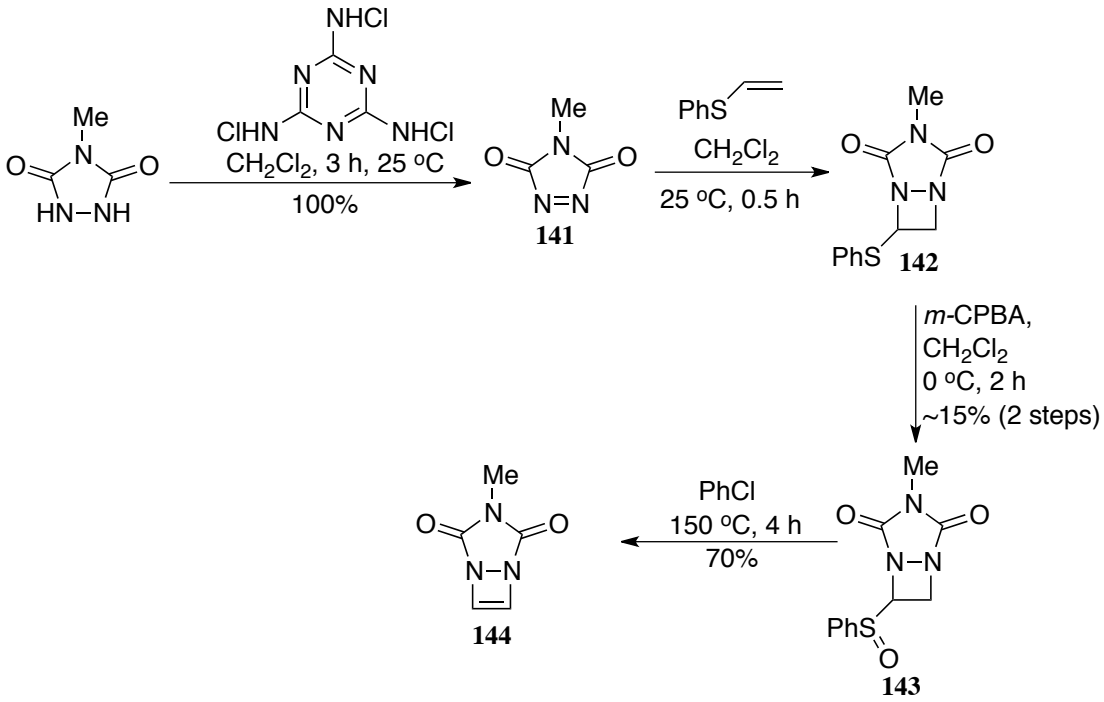
Scheme 2.3

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 °C (Scheme 2.4).



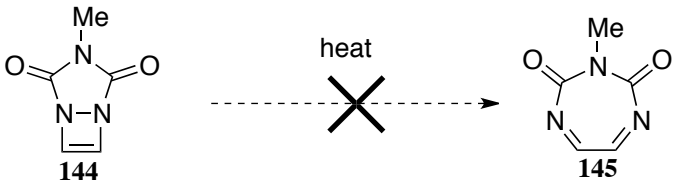
Scheme 2.4

More recently, Breton *et al*. have reported the thermally stable, bicyclic diazetine **144**.[89] Its synthesis is achieved by oxidation of *N*-methyl urazole with trichloromelamine 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).



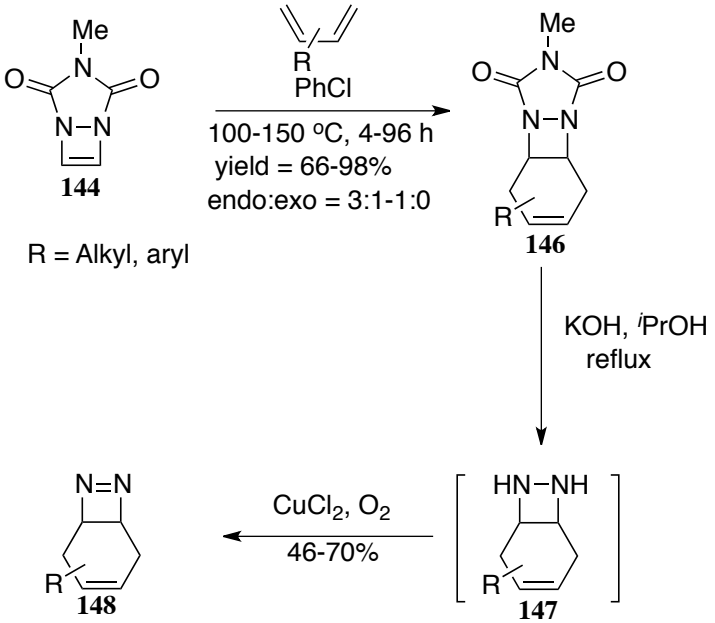
Scheme 2.5

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).



Scheme 2.6

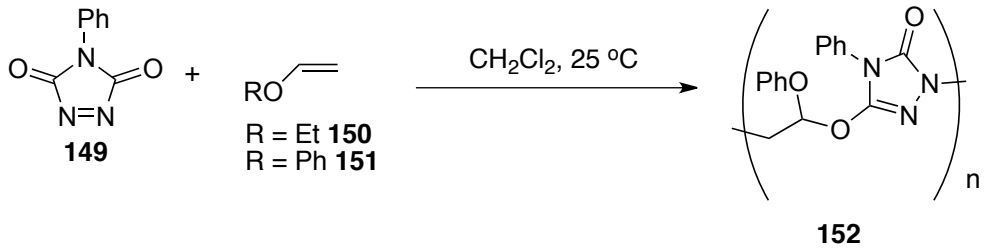
Breton has also demonstrated that **144** can act as a suitable dienophile for Diels-Alder reactions with a variety of dienes. Yields range from modest to excellent, with high selectivity for *endo* products. In addition, it was shown that the products could be converted to Δ^1-1,2-diazetines **148** 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).



Scheme 2.7

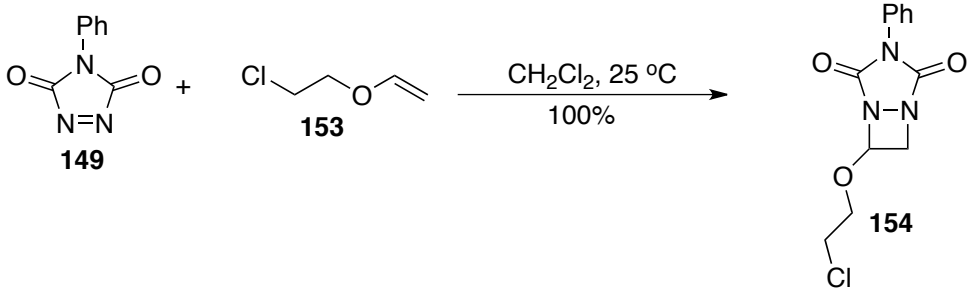
Based on Breton's pioneering work, it was felt that 1,2-diazetines such as **144**, could serve as excellent building blocks for the synthesis of 1,2-diamines. However, its synthesis suffers from poor overall yields, limiting its utility

(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.[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).[97]



Scheme 2.8

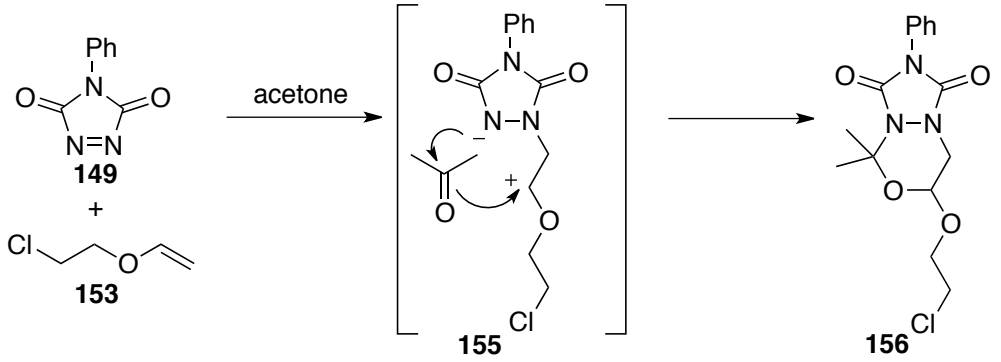
In contrast, the reaction of 2-chloroethyl vinyl ether (**153**) with **149** is reported to furnish diazetidine **154** in quantitative yield (Scheme 2.9).



Scheme 2.9

Hall's characterisation of copolymer **152** is limited to the observation of very broad peaks in the ^{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).

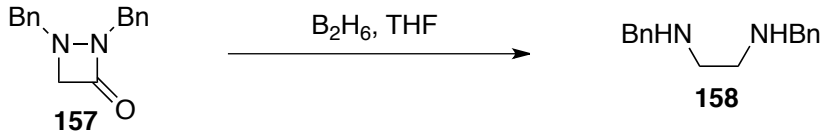


Scheme 2.10

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. $ClCH_2CH_2O$-) 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**.

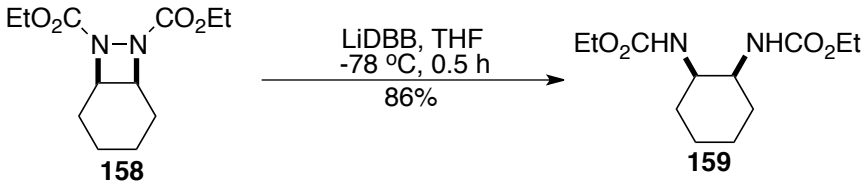
There are a number of known methods for the cleavage of N–N bonds, many of which utilise reductive conditions such as lithium and liquid ammonia.[98] Moody and co-workers have reported the conversion of aza-β-lactam **157** to 1,2-

diamine **158** using diborane for both carbonyl reduction and N–N bond cleavage (Scheme 2.11).[99]



Scheme 2.11

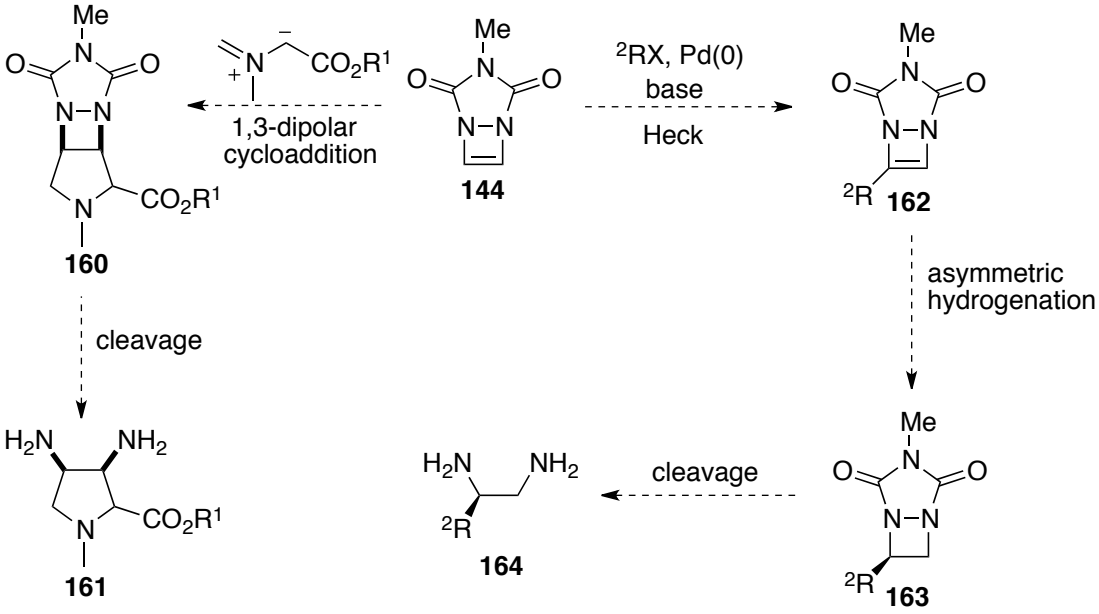
More recently, Shipman and co-workers have demonstrated N–N bond cleavage of 1,2-diazetidine **159** with LiDBB in good yield (Scheme 2.12).[100]



Scheme 2.12

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).

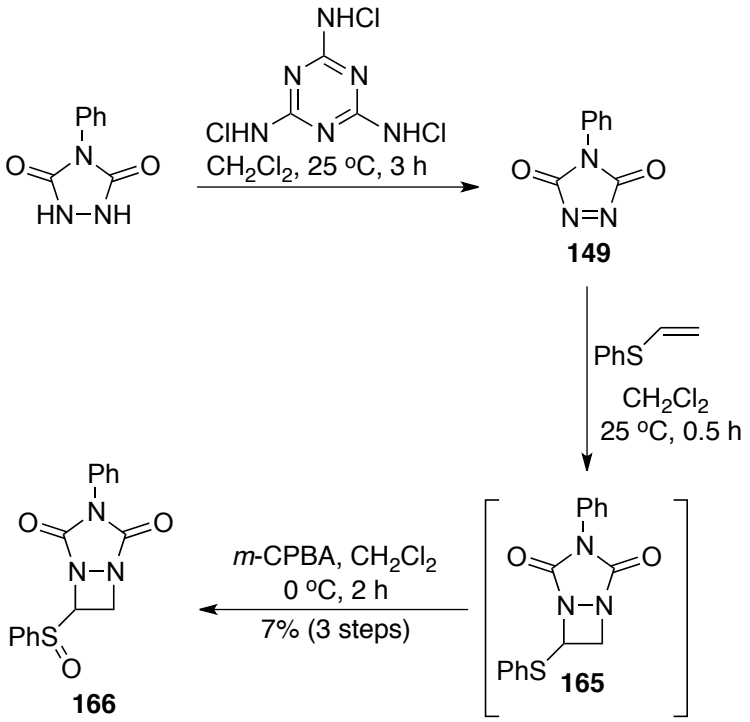


Scheme 2.13

2.2.3 Synthesis of 1,2-diazetines

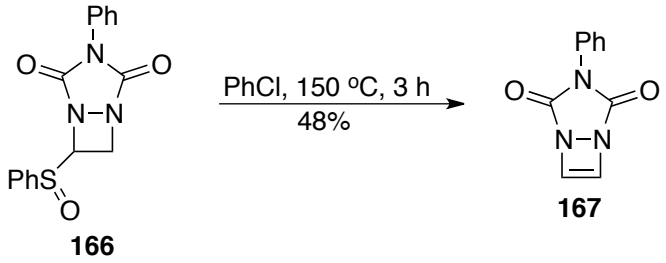
We wished to begin by repeating the synthesis of the 1,2-diazetine **144** using the procedure described by Breton. However *N*-methyl urazole, the precursor to *N*-methyl-1,2,4-triazolinedione (**141**), was found to be highly costly, and so *N*-phenyl urazole was used as an alternative. This was oxidised 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 ^{1}H 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

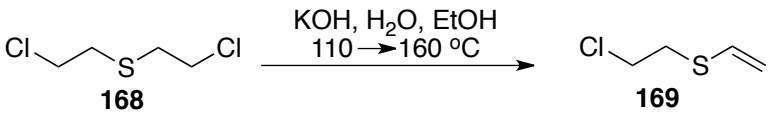
Next, novel 1,2-diazetine **167** was obtained by heating **166** in a sealed tube in chlorobenzene (Scheme 2.15). ^{1}H NMR spectroscopy was diagnostic for the characterisation of **167**, as the ABX pattern of **166** was no longer present and a new singlet at 6.74 ppm, corresponding to the two diazetine 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.



Scheme 2.15

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.[97]

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**).[101] Indeed, to our knowledge all the known procedures for the synthesis of **169** require bis(2-chloroethyl) sulfide as a precursor (Scheme 2.16).[102]



Scheme 2.16

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).

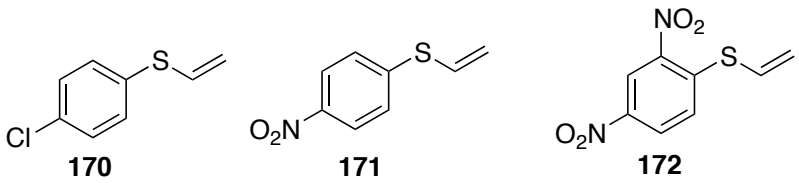
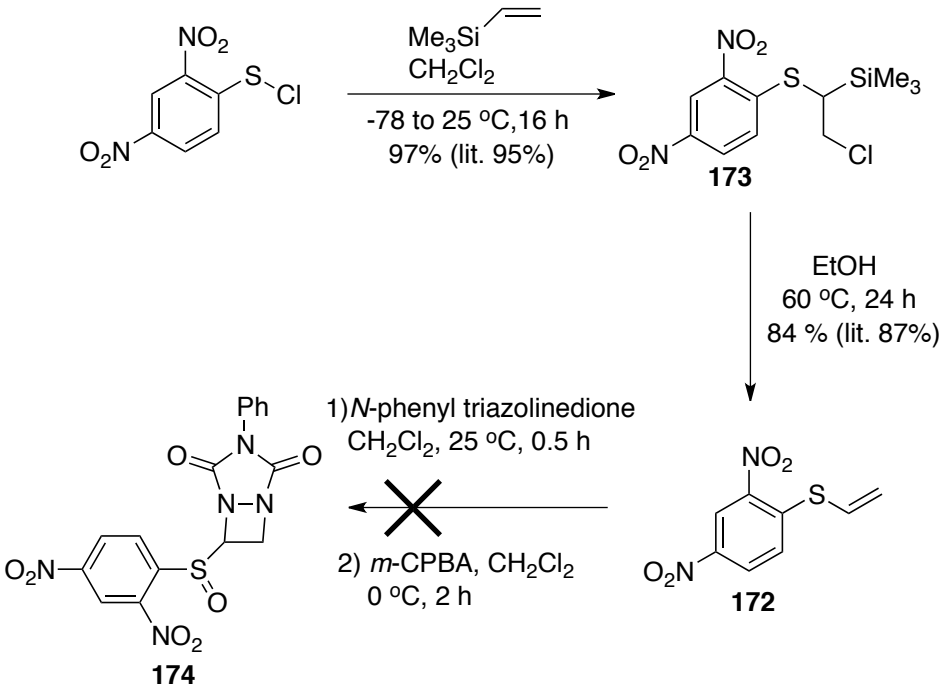


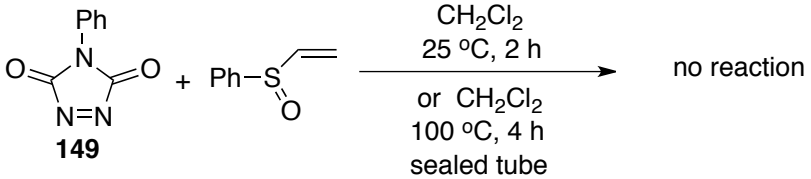
Figure 2.2

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).[103] 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).



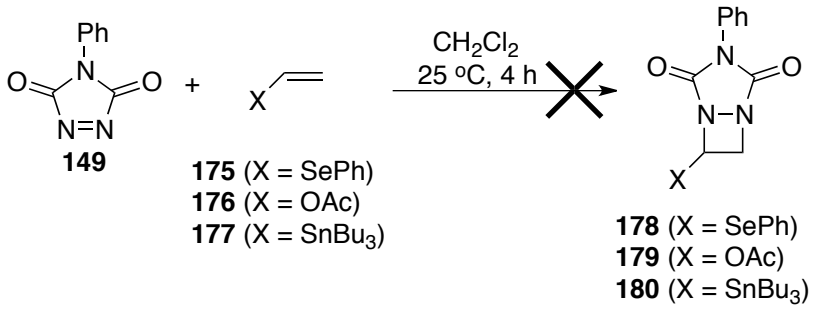
Scheme 2.17

It is possible that a less electron-withdrawing alternative such as **170** or **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 **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).



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

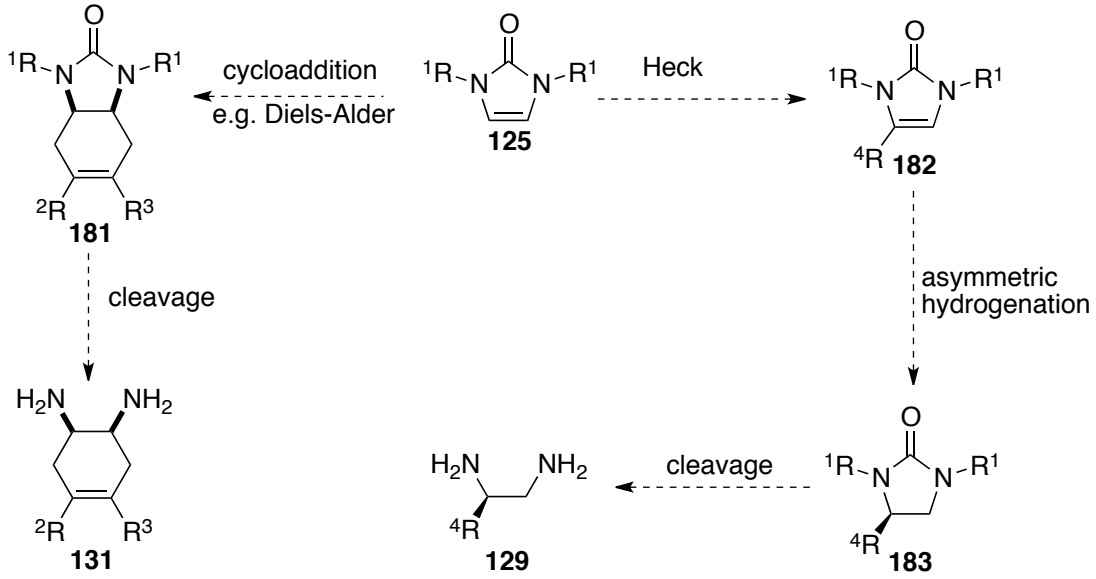
2.2.4 Conclusions

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.[104-108] Reports for the synthesis of such compounds, both functionalised and unfunctionalised go back over a century.[109] 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).

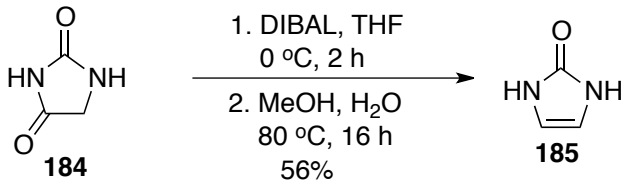


Scheme 2.20

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.

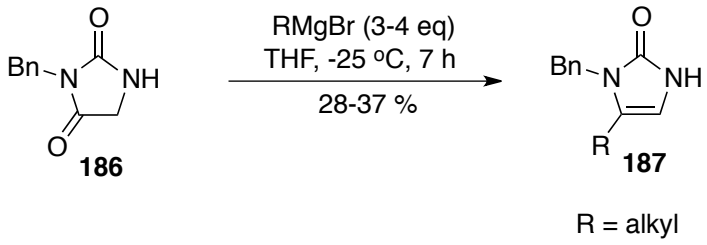
2.3.2 Background

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).[108]



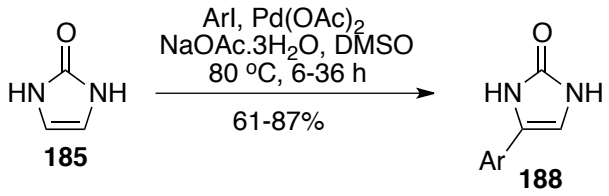
Scheme 2.21

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).[110]



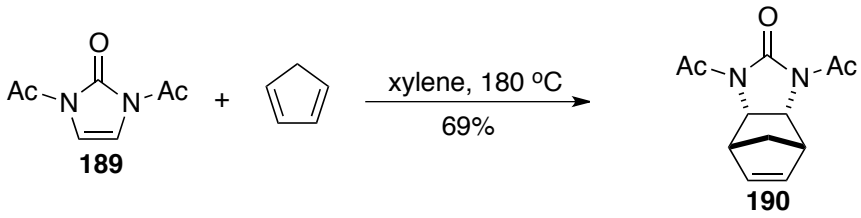
Scheme 2.22

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).[111]



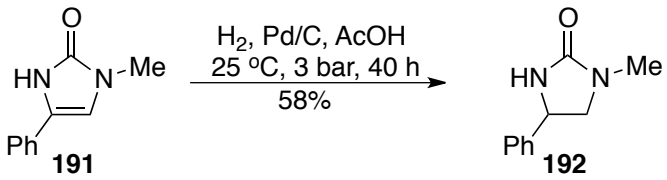
Scheme 2.23

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).[108, 112-114]



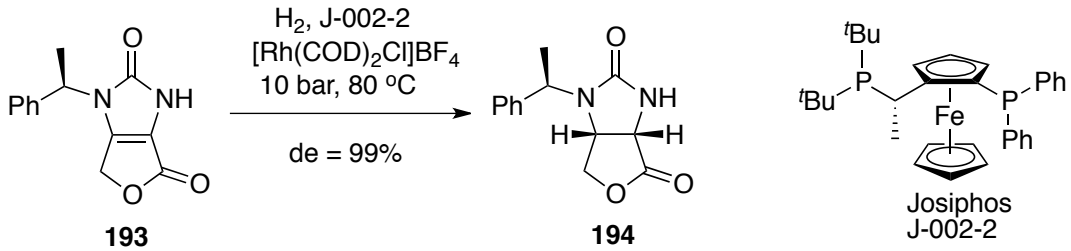
Scheme 2.24

Duschinsky and Kohn have both reported the hydrogenation of imidazolinone **191** (Scheme 2.25).[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.



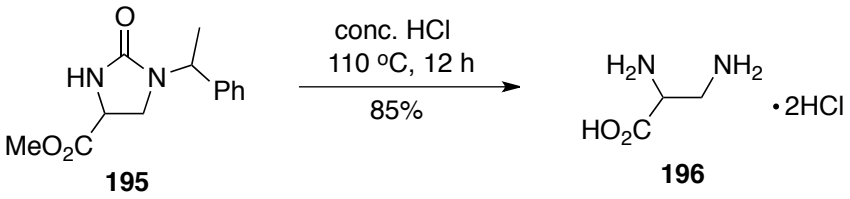
Scheme 2.25

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.[117] In this case, the electronics of the double bond are likely influenced by the adjacent carbonyl group (Scheme 2.26).

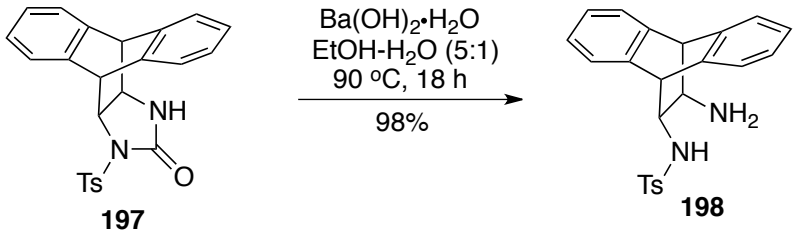


Scheme 2.26

There are many of examples in the literature for the hydrolysis of imidazolidinones to the corresponding 1,2-diamines.[115, 118-121] 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).[119,122]



Scheme 2.27

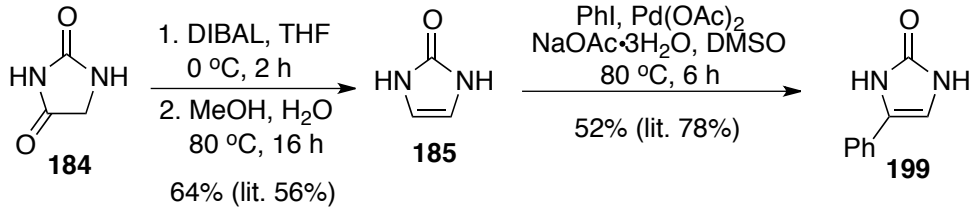


Scheme 2.28

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.

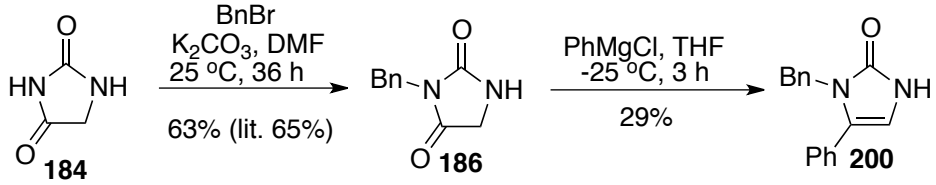
2.3.3 Synthesis and reactions of imidazolin-2-ones

Imidizadolinone **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).



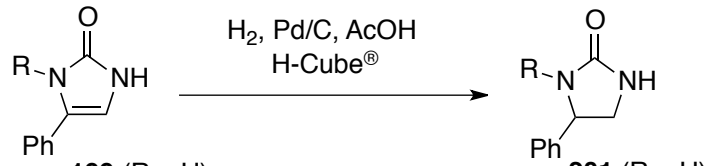
Scheme 2.29

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).



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).



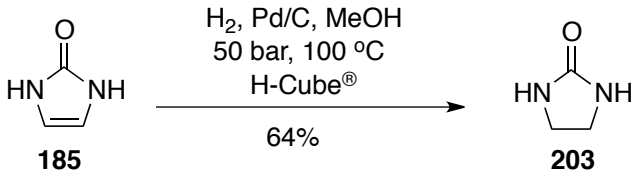
199 (R = H)
200 (R = Bn)

201 (R = H)
202 (R = Bn)

entry	substrate	R	temp. (°C)	pressure (bar)	outcome
1	**199**	H	25	1	No reaction
2	**200**	Bn	25	1	No reaction
3	**199**	H	25	20	No reaction
4	**199**	H	50	50	No reaction
5	**199**	H	100	100	**201** (53%)
6	**200**	Bn	100	100	No reaction

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).[115,116] 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).



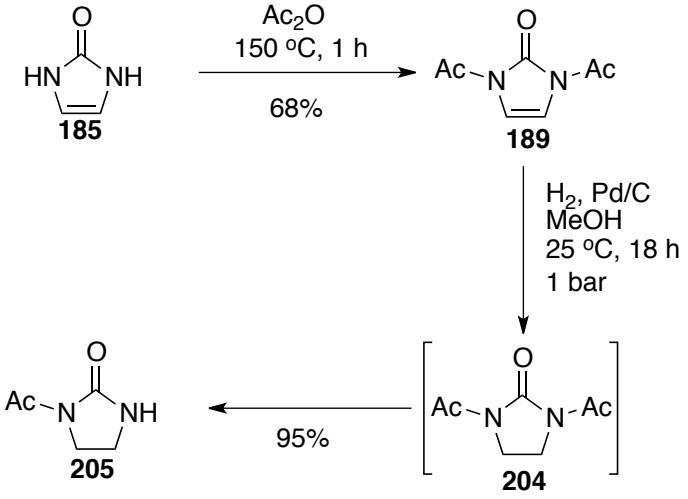
Scheme 2.31

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).

Scheme 2.32

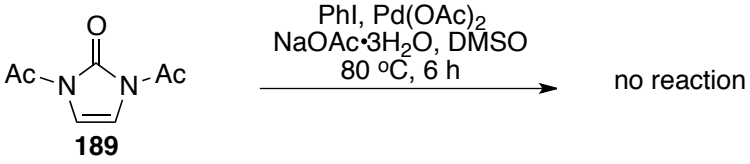
By removing the lone pairs from the ring, by introduction of electron-withdrawing substituents on N, the aromatic character of the heterocycle should be reduced. In this way, the reactivity towards hydrogenation might be significantly increased. To explore this idea, the hydrogenation of the diacetylated 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).



Scheme 2.33

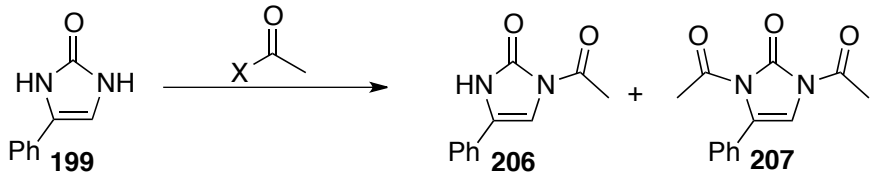
In light of these results, we began to investigate the synthesis of other *N*-substituted imidazolinones. It was hoped that diacetylated imidazolinone **189** could be functionalised directly by Heck-type processes, as depicted in Scheme 2.34, but unfortunately no reaction occurred under the conditions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



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 ºC (Table 2.2).



entry	X	additives	solvent	time (h)	temp. (ºC)	**206** (%)	**207** (%)
1	OAc	-	-	4	150	5	trace
2	OAc	Et_3N, DMAP	DMSO	48	80	25	trace
3	Cl	Et_3N, DMAP	DMSO	16	80	-	-
4	Cl	Et_3N, DMAP	DMF	3	80	42	trace
5	Cl	Et_3N	DMF	3	80	43	trace

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).

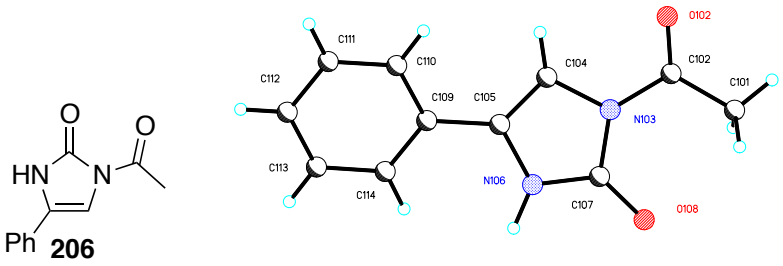
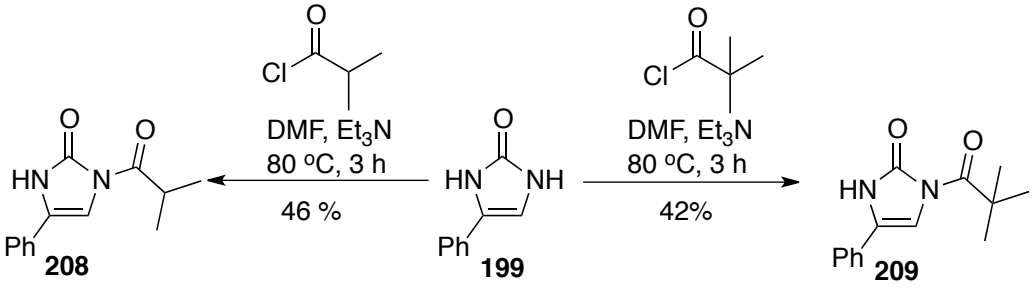


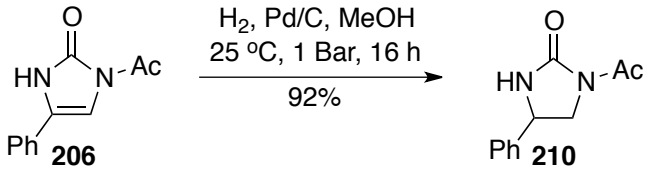
Figure 2.3

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).



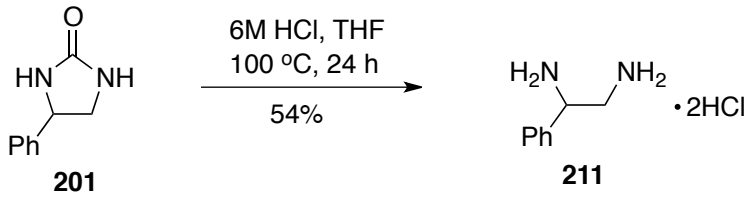
Scheme 2.35

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

Phenyl substituted derivative **201** was readily hydrolysed to corresponding diamine **211** under acidic conditions in accordance with literature precedent.[119] The yield for this reaction was not optimised at this time (Scheme 2.37).



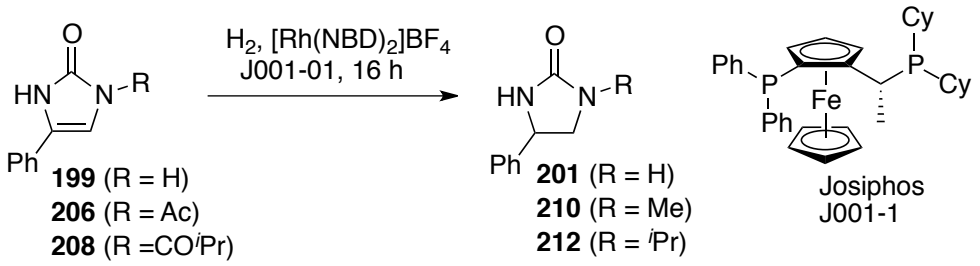
201 **211**

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]ethyldicyclohexyl-phosphine (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).



entry	substrate	solvent	pressure (bar)	temp. (ºC)	outcome
1	**206**	MeOH	1	25	no reaction
2	**206**	MeOH	10	25	no reaction
3	**206**	MeOH	10	50	**199**
4	**208**	MeOH	100	100	**199**
5	**199**	MeOH	100	100	no reaction
6	**206**	EtOAc	10	50	no reaction
7	**206**	EtOAc	20	50	no reaction
8	**206**	EtOAc	50	25	no reaction
9	**206**	THF	50	50	no reaction
10	**206**	EtOAc	50	100	over reduction
11	**206**	EtOAc	50	50	over reduction
12	**206**	EtOAc	30	50	no reaction

Table 2.3

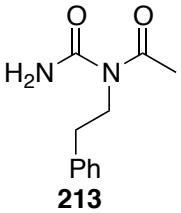
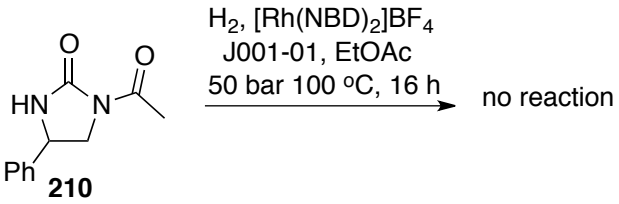


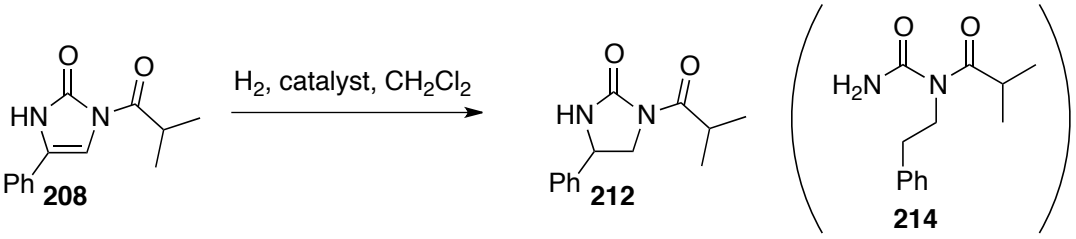
Figure 2.4

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

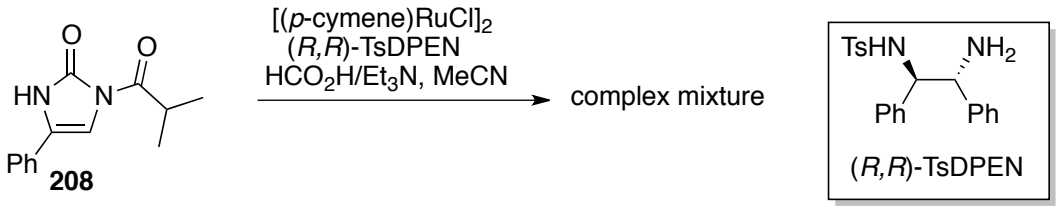
In light of these results it appeared that the catalyst and ligand choice were not suitable and so alternatives were considered. Rather than screen numerous combinations of catalysts and chiral ligands, it was decided that it would be appropriate to determine first that the required selective reduction could be achieved with an achiral homogeneous catalyst. Wilkinson's catalyst $[Rh(PPh_3)_3Cl]$ and Crabtree's catalyst ($[Ir(COD)(PCy_3)(Py)]PF_6$) were selected for this investigation. No reaction was observed when **208** was treated with $[Rh(PPh_3)_3Cl]$ 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 ^{O}C, a complex mixture was obtained which contained no evidence for the presence of **212** by either ^{1}H 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 $[Ir(COD)(PCy_3)(Py)]PF_6$ gave similar complex mixtures, again displaying mass spectrometry evidence for over-reduction, even under 1 bar of hydrogen (entries 4 and 5).



entry	catalyst	pressure (bar)	time (h)	temp. (°C)	outcome
1	$[Rh(PPh_3)_3Cl]$	1	16	25	no reaction
2	$[Rh(PPh_3)_3Cl]$	50	16	25	no reaction
3	$[Rh(PPh_3)_3Cl]$	50	16	50	over reduction
4	$[Ir(COD)(PCy_3)(Py)]PF_6$	1	2	25	over reduction
5	$[Ir(COD)(PCy_3)(Py)]PF_6$	1	0.5	25	over reduction

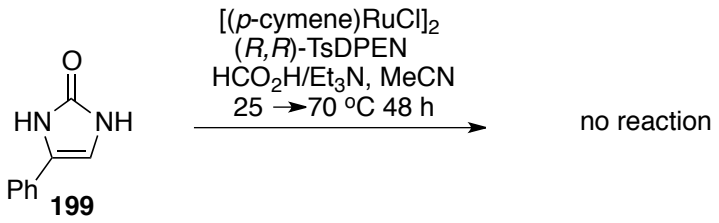
Table 2.4

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.[123] 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).



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

2.4 Conclusions

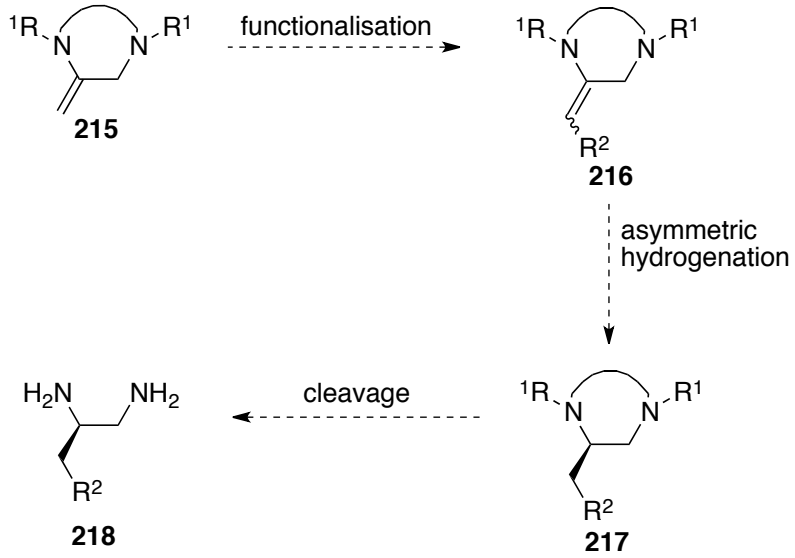
During these studies we have successfully synthesised racemic 1,2-diamine **211** via hydrogenation of phenyl-substituted imidazolinone **199** and subsequent hydrolysis with hydrochloric acid (Schemes 2.36 and 2.37). It was discovered that hydrogenation reactions of these compounds are highly sensitive 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

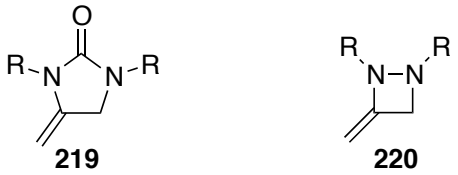
3.1 Introduction

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).



219 **220**

Figure 3.1

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

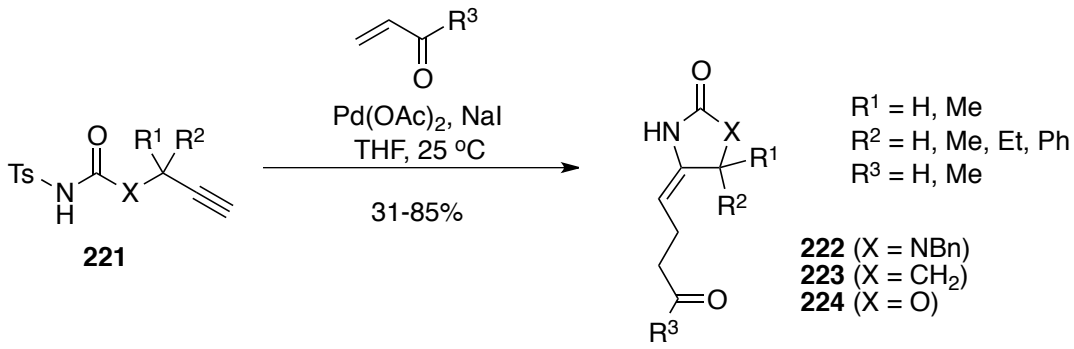
3.2.1 Introduction

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

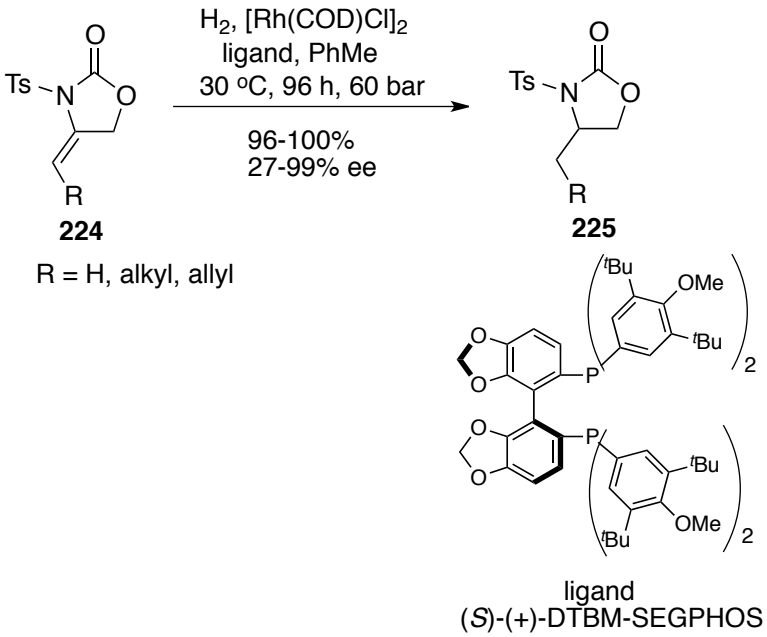
In 2000 Lei and Lu reported the synthesis of a variety of imidazolidinones **222**, lactams **223** and oxazolidinones **224** using a tandem intramolecular

aminopalladation of alkynes **221** with alkene insertion.[126] The entire process allows the synthesis and functionalisation of the heterocycles in a single step (Scheme 3.2)



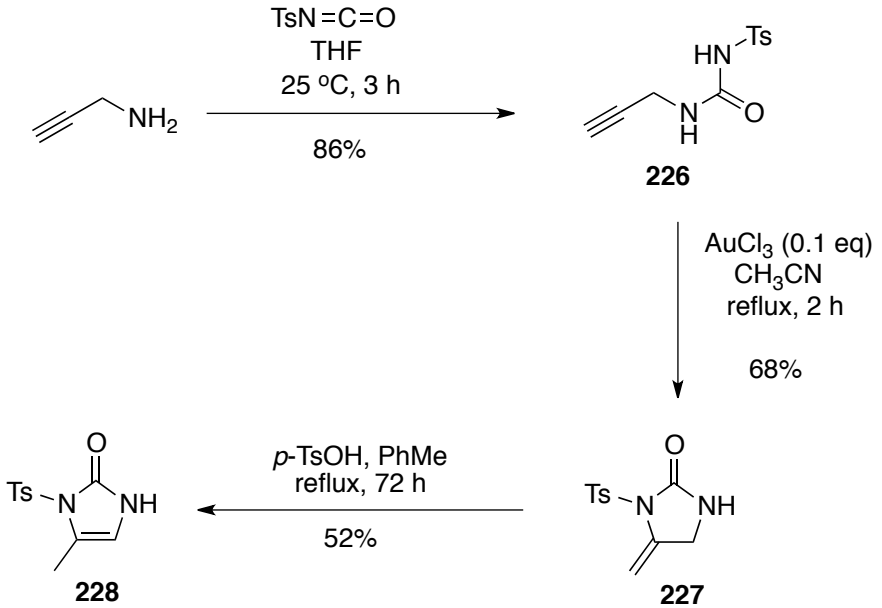
Scheme 3.2

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).[127] 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.



Scheme 3.3

More recently, Padwa and co-workers have reported the cyclisation of *N*-(*p*-toluenesulfonyl)-*N*'-(2-propyn-1-yl)urea (**226**) with $AuCl_3$ 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).

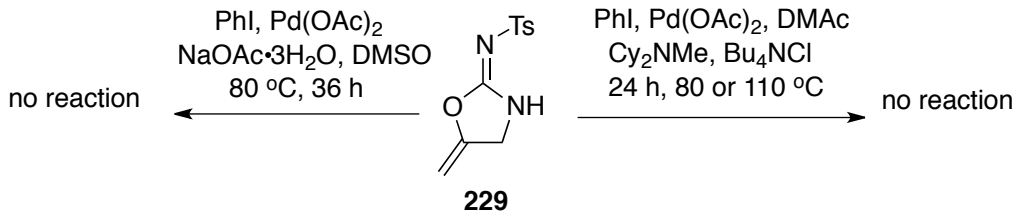


Scheme 3.4

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.

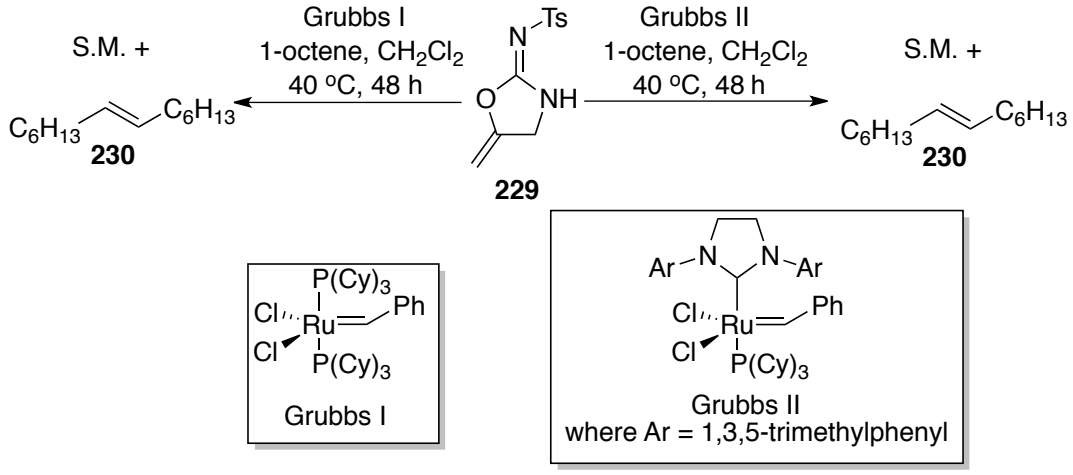
3.2.3 Reactions of *N*-tosyl-methyleneimidazolidinone

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 ºC, 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

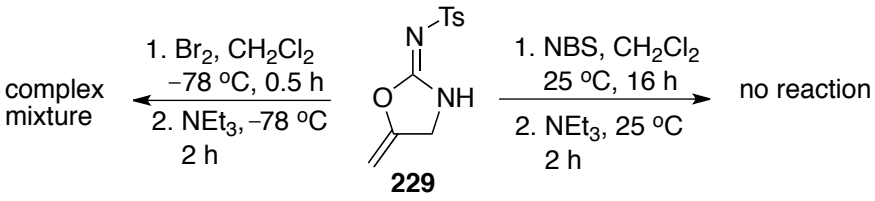
As initial palladium catalysed cross-couplings were proving unsuccessful, we decided to explore a different approach to functionalisation of the alkene terminus. Cross metathesis reactions with Grubbs I and II catalysts could provide a general route to such compounds.[131,132] To test this idea, 1-octene was selected as an appropriate substrate due to its good reactivity in cross-metathesis.[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

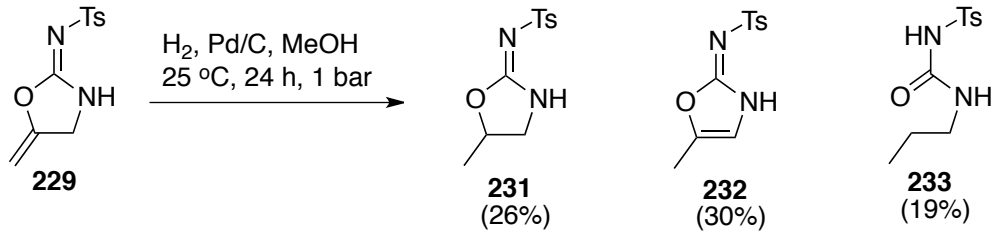
As a result of the apparent lack of reactivity of what was assumed to be **227** towards metathesis, we considered bromination of the double bond and subsequent coupling with a boronic acid by way of Suzuki cross-couplings.

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).



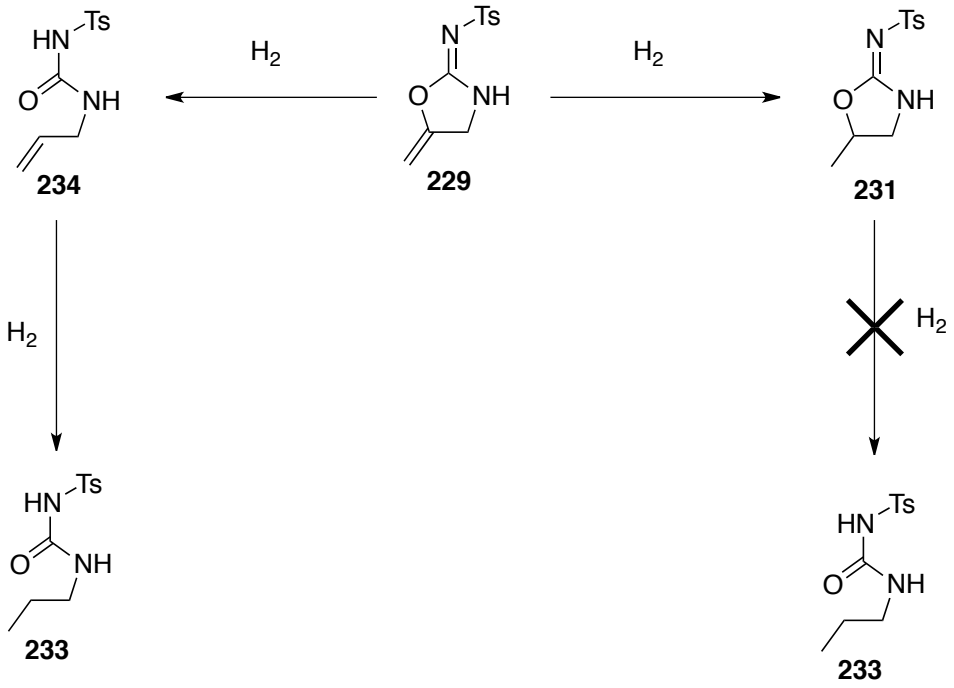
Scheme 3.7

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).[128] 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).

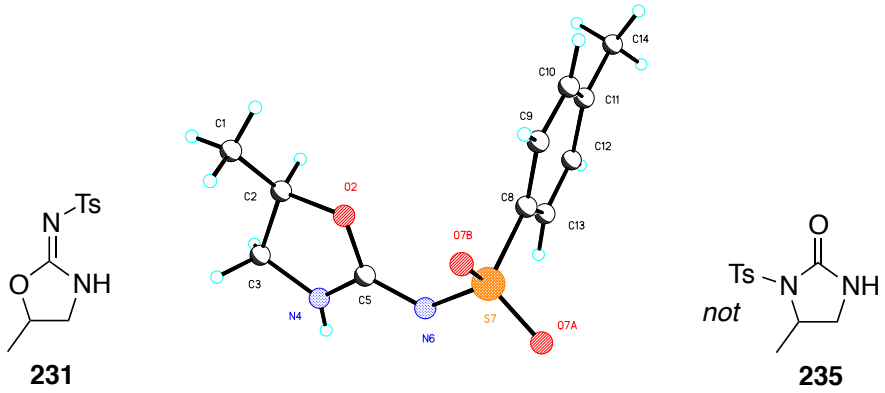
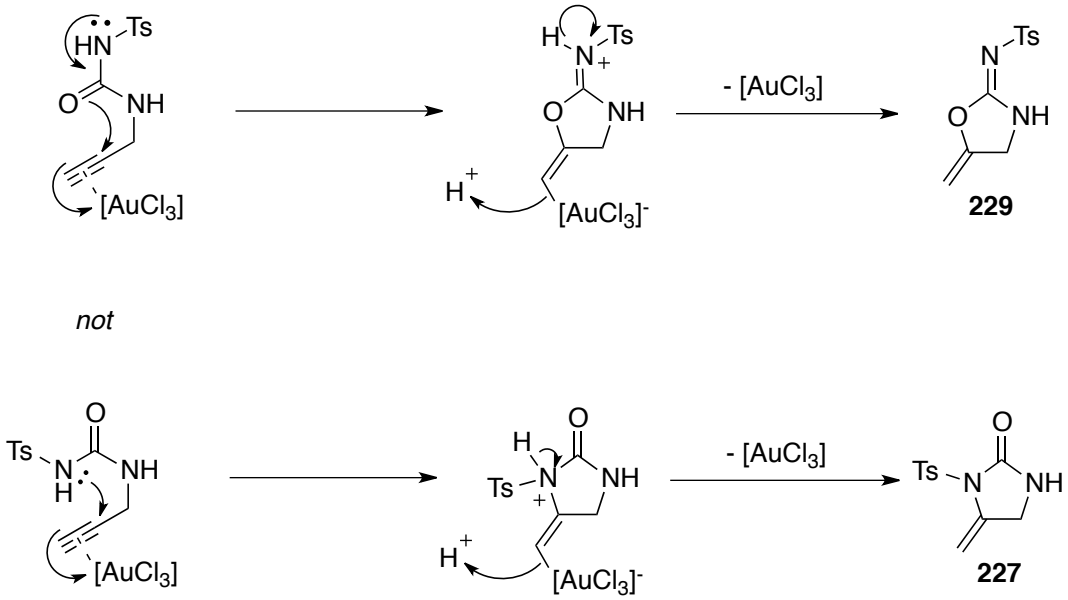


Figure 3.2

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).



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).

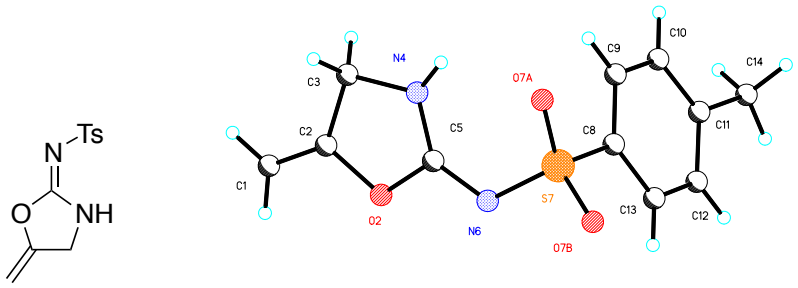
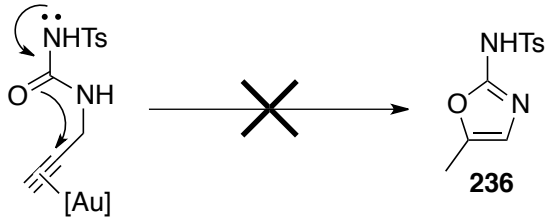


Figure 3.3

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).[128] This is presumably because he anticipated the tautomer **236**, which did not match the ^{1}H 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**.



Scheme 3.11

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).

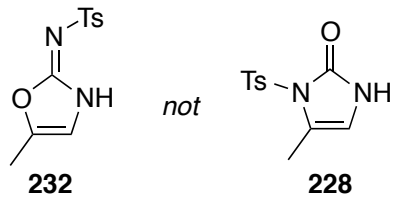
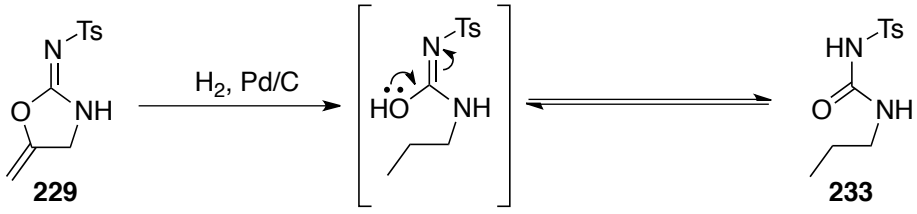


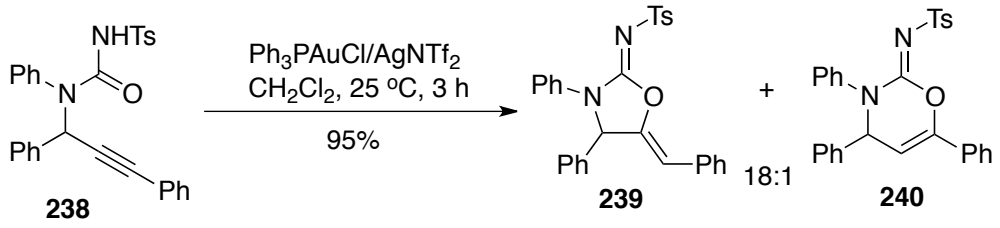
Figure 3.4

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

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).

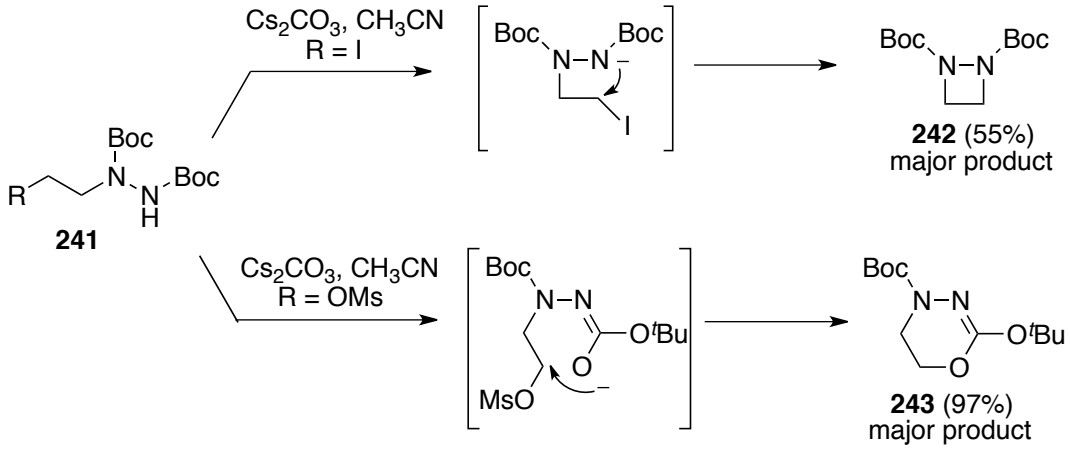


Scheme 3.13

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

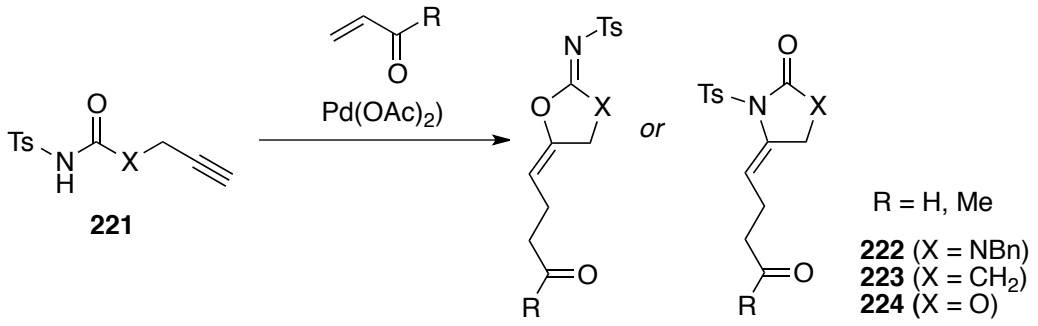
leaving group had a profound effect on the cyclisation of **241**, with either 1,2-diazetidine **242** or **243** afforded as the major product, depending on the leaving group R. The structures of both **242** and **243** have been confirmed by X-ray crystallography (Scheme 3.14).[137]



Scheme 3.14

These observations would suggest that the coordination of $AuCl_3$ to alkyne **226** creates a "hard" electrophile that favours ring-closure through oxygen, as previously described in Scheme 3.10.

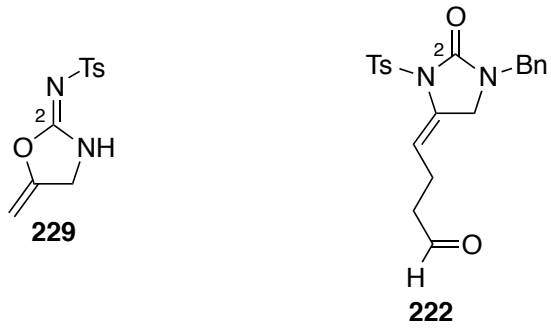
It would be of interest to determine whether or not this preference for closure through oxygen rather than nitrogen is witnessed in other, non-gold catalysed reactions. For instance, one could imagine a similar preference for ring closure through oxygen with the reactions reported by Lu (Scheme 3.15).[126]



221

Scheme 3.15

It was hoped that we could compare our ^{13}C NMR data for **229** with that of Lu's for methyleneimidazolodinone **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).

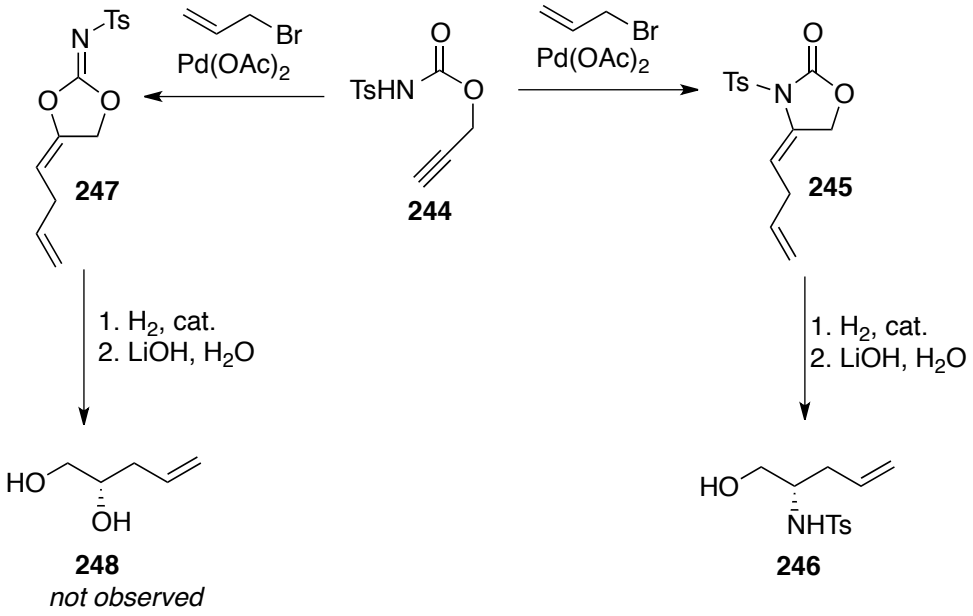


229 **222**

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

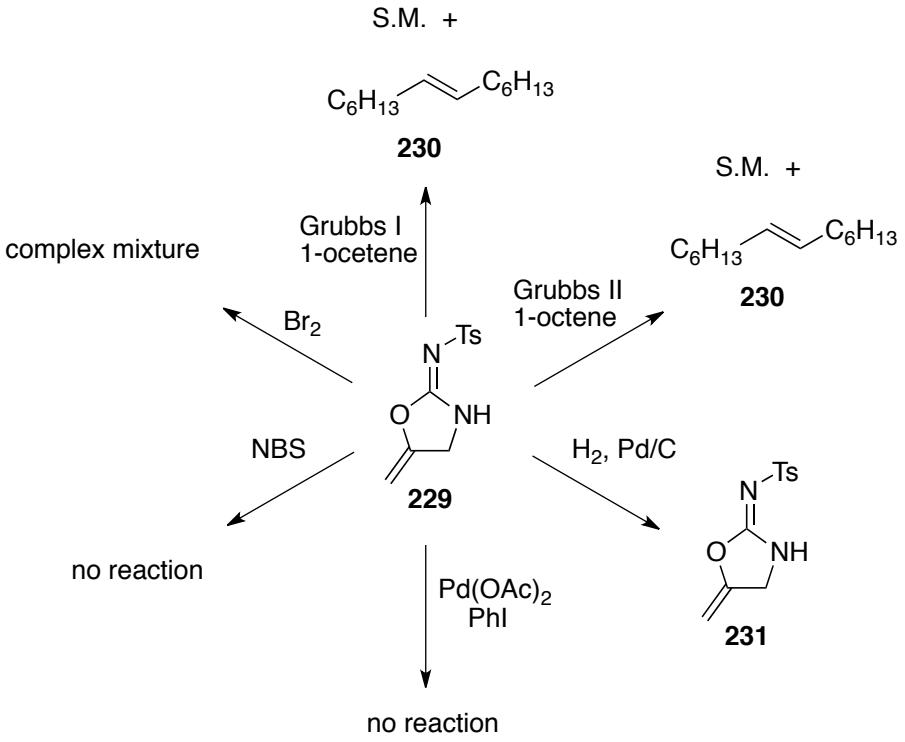
charaterisation of the product. Indeed, Lu's spectroscopic data is in accordance with other published data for **246**.[136]



Scheme 3.16

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 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.



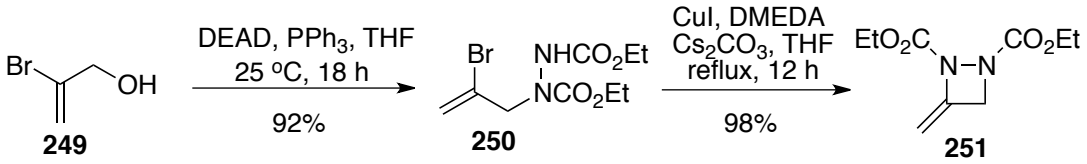
Scheme 3.17

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.[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).



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).

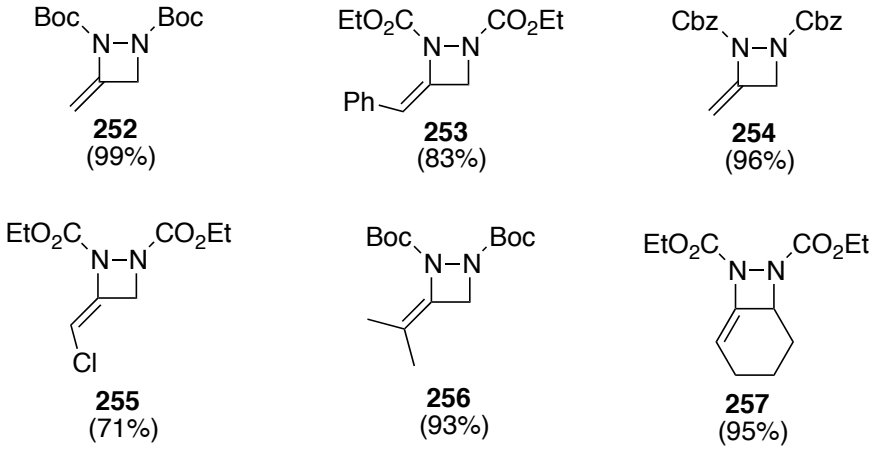
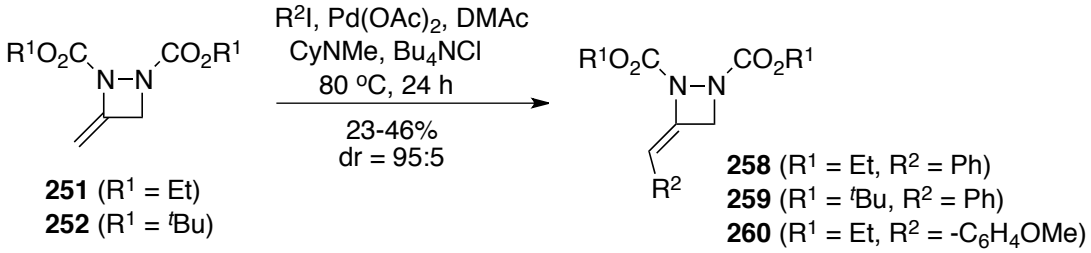


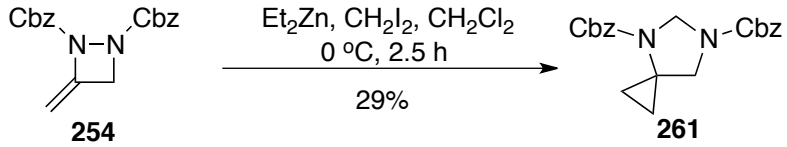
Figure 3.5

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 iodides. Although the reported yields are low, the reaction shows excellent diastereoselectivity, with the *E* isomer being the major product (Scheme 3.19).[100]



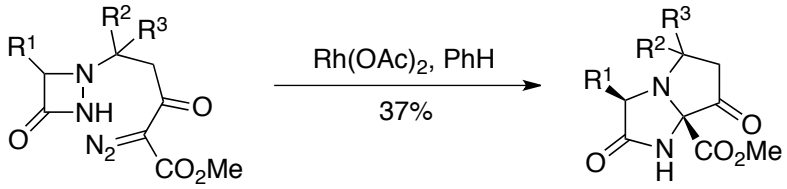
Scheme 3.19

Mike Brown has also shown that cyclopropanation of **254** produces expanded cyclopropane **261**.[137] 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).



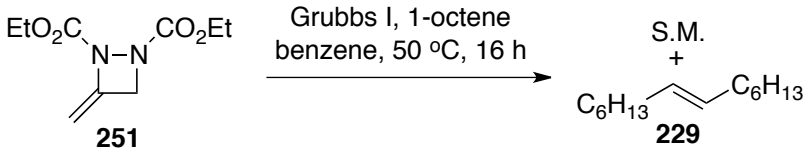
Scheme 3.20

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 β-lactam analogues (Scheme 3.21).[138]



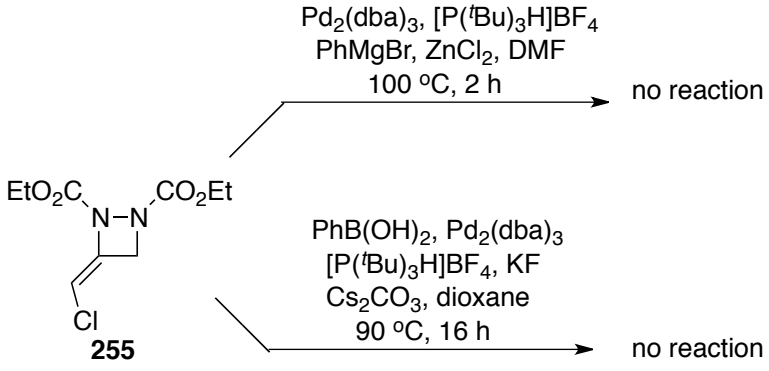
Scheme 3.21

Other efforts by Mike Brown to functionalise **251** were less successful. For example, Grubbs metathesis with 1-octene led only to starting material and *E*-7-tetradecene (**229**) (Scheme 3.22).[137]



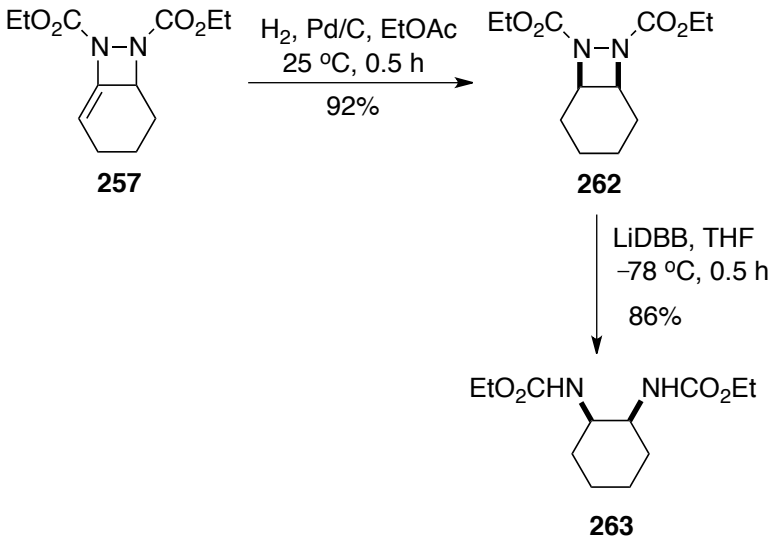
Scheme 3.22

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]



Scheme 3.23

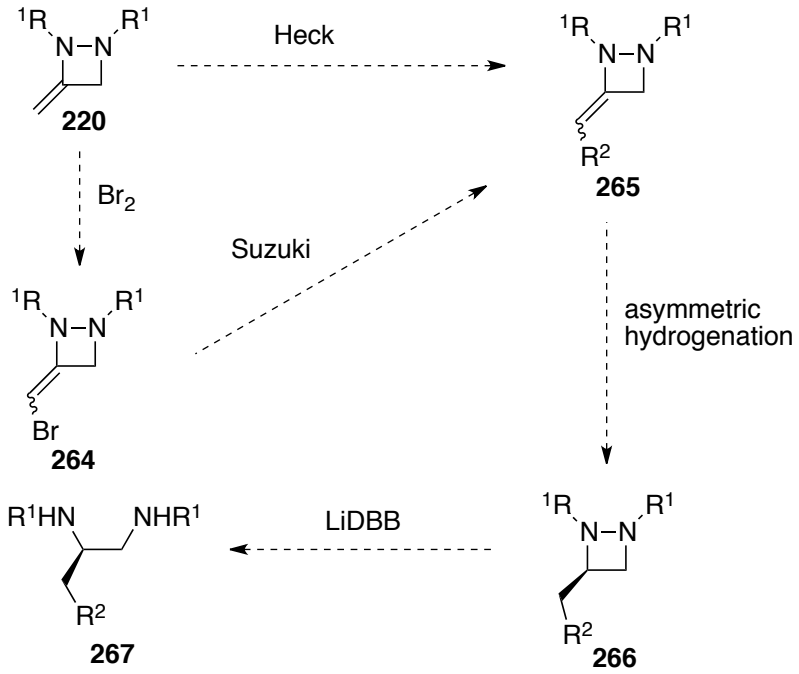
Preliminary hydrogenation studies of methylenediazetidines were also undertaken. Bicycle **257** was easily hydrogenated to diazetidine **262** under standard palladium on carbon conditions with excellent yield. It was deduced that this reaction proceeded to give exclusively the *syn* product. Subsequent reduction of **262** with LiDBB provided the protected diamine **263** in good yield (Scheme 3.24).[100]



Scheme 3.24

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-

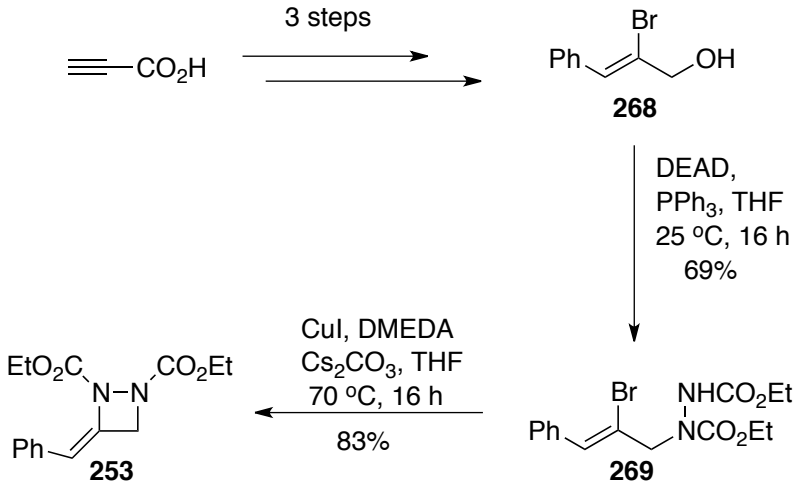
methylene-1,2-diazetidines **265**. The asymmetric hydrogenation of these substrates followed by N–N bond cleavage to yield a range of enantiomerically enriched 1,2-diamines **267** could then be investigated (Scheme 3.25).



Scheme 3.25

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

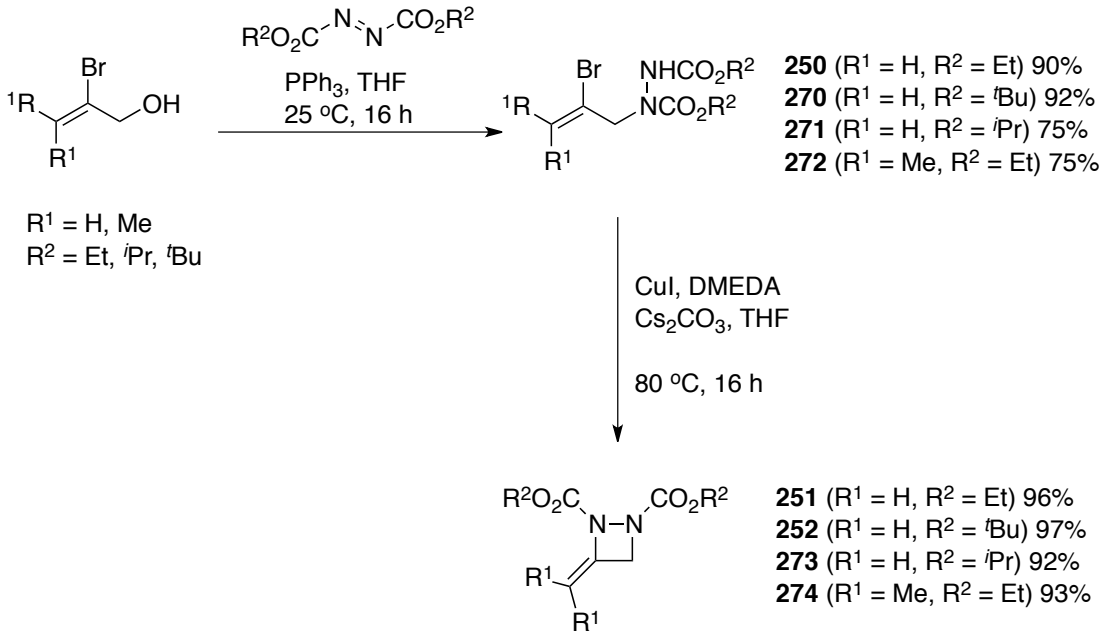
It has already been shown that 3-methylene-1,2-diazetidines are able to undergo Heck-type reactions with aryl iodides, albeit in modest yields (Scheme 3.19).[100] In addition, it is possible to incorporate certain functionalities prior to ring-closure. This however is considered an undesirable method, as the synthesis of the precursor itself then requires several steps, as illustrated for the synthesis of alkene **268** (Scheme 3.26).[137]



Scheme 3.26

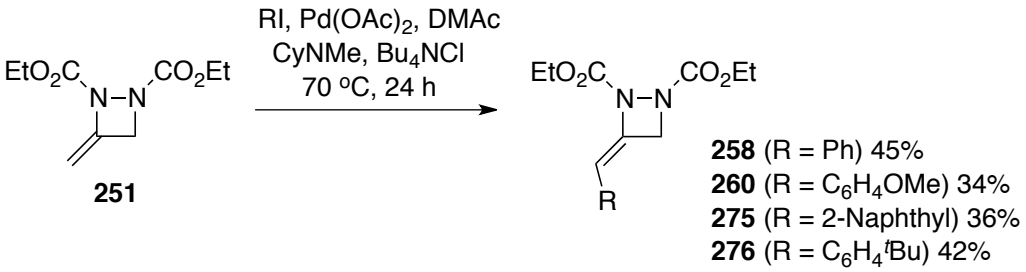
As a result, we decided to investigate alternative methods for the functionalisation of 3-methylene-1,2-diazetidines. In turn, this would provide us with a variety of suitable substrates for hydrogenation studies.

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).



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).[100] 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 ^{1}H 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 ^{1}H 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**.

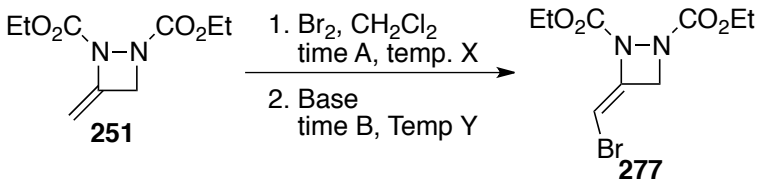


Scheme 3.28

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.



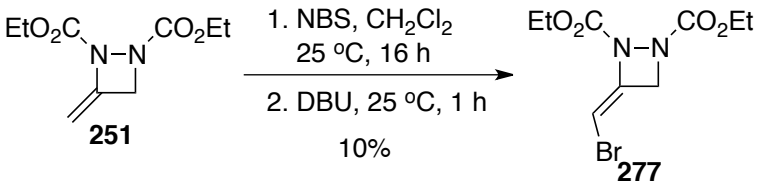
entry	time A[1] (h)	temp. X (°C)	base	time B[1] (h)	temp. Y (°C)	Outcome
1	1	0	DBU	4	25	degradation
2	1	0	DBU	1	0	degradation
3	1	-78	DBU	4	-78->25	mixture
4	1	-78	Et_3N	4	-78->25	mixture
5	1	-78->25	DBU	4	25	degradation
6	1	-78->-50	DBU	4	-50	**277** (42%)
7	1	-78->-60	DBU	4	-60	**277** (12%)
8	1	-78->-40	DBU	4	-40	**277** (7%)

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.

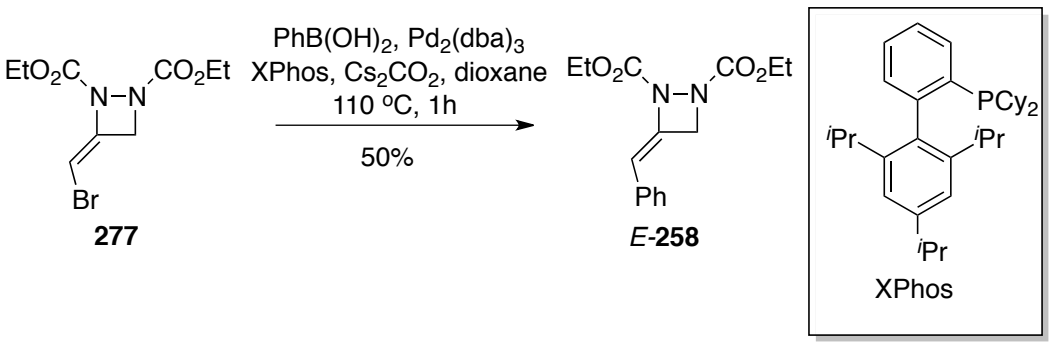
The synthesis of **277** was also achieved with *N*-bromosuccinimide (NBS), however this also led to a complex mixture of products and **277** was only

obtained in very low yield. Lowering the reaction temperature led to only traces of product (Scheme 3.29).



Scheme 3.29

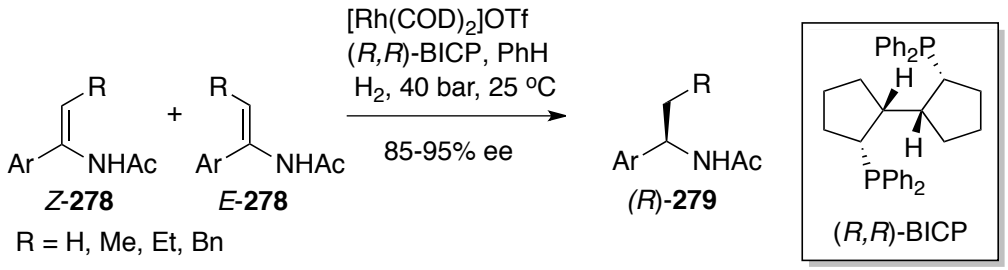
It had initially been hoped that the bromination and subsequent coupling of **277** with an appropriate boronic acid would allow us to synthesise functionalised methylenediazetidines in good yields. Unfortunately, as the bromination step was proving to be particularly difficult, this route did not appear to be suitable. Nevertheless, the Suzuki coupling of **277** and phenyl boronic acid afforded *E*-**258** in 50% yield without optimisation (Scheme 3.30).[140] ^{1}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.[141] Therefore we can only speculate that this reaction proceeded with retention of stereochemistry based on the ^{1}H NMR data, as previously discussed.



Scheme 3.30

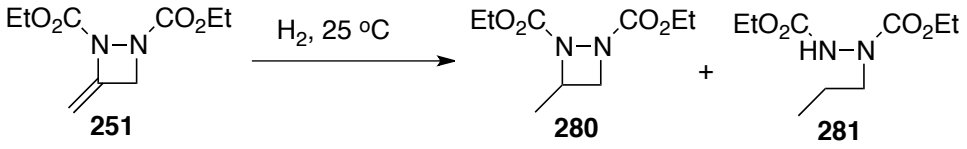
3.3.3 Hydrogenation Studies of 3-Methylene1,2-diazetidines

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).[100] 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.[127] In addition, there is a lot of research into the enantioselective hydrogenation of enamides.[142] 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).[143] 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.



Scheme 3.31

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).[144] Under the most effective conditions (entry 4) the reduced 1,2-diazetidine **280** was isolated in 70% yield.



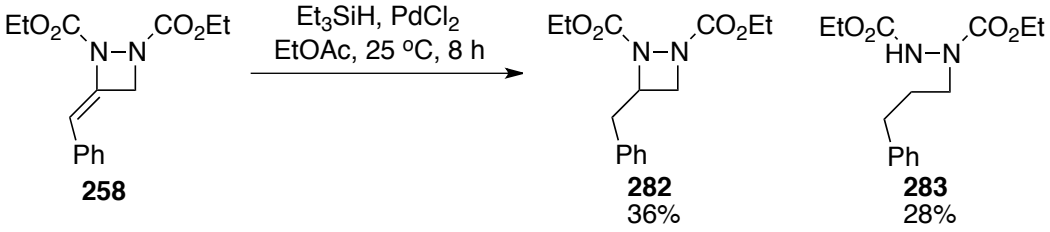
	H_2 source	catalyst	solvent	Time (h)	**280** (%)	**281** (%)
1	H_2 (1Bar)	Pd/C	EtOAc	24	68	5
2	H_2 (1Bar)	Pd/C	MeOH	16	54	23
3	Et_3SiH	$PdCl_2$	EtOH	2	62	29
4	Et_3SiH	$PdCl_2$	EtOAc	4	70	4

Table 3.2.

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

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

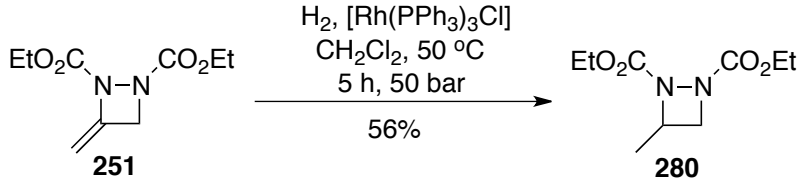


Scheme 3.32

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.

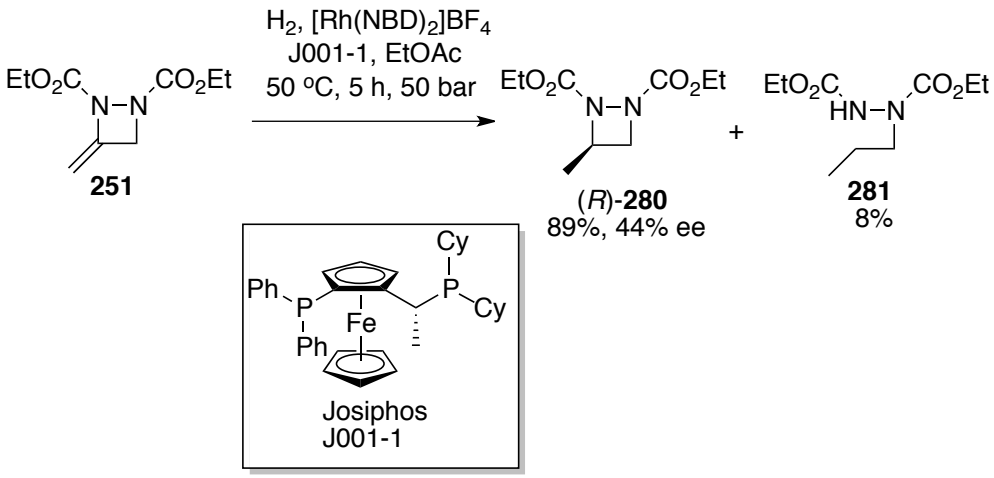
Before turning our attention to chiral catalysts, we wished to attempt a hydrogenation with Wilkinson's catalyst. As many asymmetric hydrogenation complexes are based on homogeneous rhodium complexes, we believed a hydrogenation with Wilkinson's catalyst would offer some initial insights into the reactivity 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).



Scheme 3.33

We began our study into the asymmetric hydrogenation of methylenediazetidines with the $[Rh(NBD)_2]BF_4$ 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).

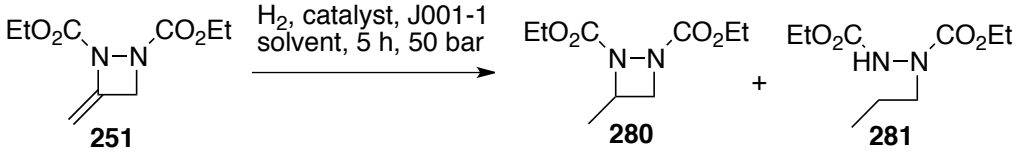


Scheme 3.34

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% [^{t}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 ºC 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).

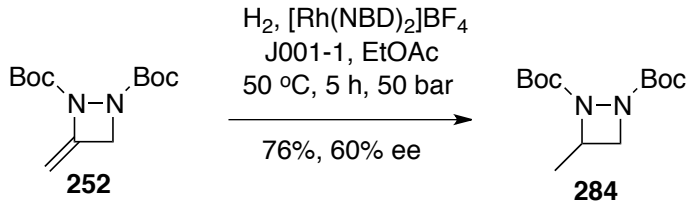


251 **280** **281**

entry	catalyst	solvent	temp (ºC)	**280** (%)	**281** (%)	ee (%)
1	$[Rh(NBD)_2]BF_4$	MeOH	50	63	10	4 (*S*)
2	$[Rh(NBD)_2]BF_4$	EtOAc	30	28	0	61 (*R*)
3	$[Rh(NBD)_2]BF_4$	CH_2Cl_2	30	8	0	53 (*R*)
4	$[Rh(COD)Cl]_2$	EtOAc	30	2	0	58 (*R*)
5	$[Rh(COD)Cl]_2$	CH_2Cl_2	30	8	0	49 (*R*)

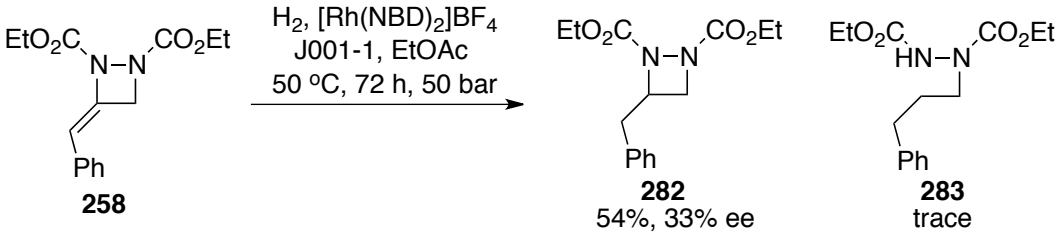
Table 3.3

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 ^{t}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

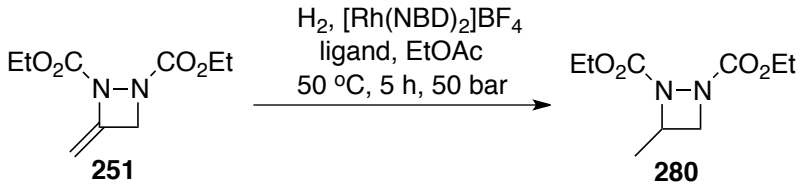
In addition, we also wished to investigate how effective these conditions were for the enantioselective hydrogenation of substituted methylenediazetidines, such as **258**. The presence of a phenyl substituent was found to decrease the rate of hydrogenation significantly, as only a trace of product was 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

Following on from these initial results, we turned our attention to variation of the chiral ligand with a view to improving the enantioselectivites. For the purposes of the study, methylenediazetidine **251** was chosen as the substrate.

Although higher enantioselectivies would likely be obtained at lower temperatures, for convenience, ligand screening was conducted at 50 ºC 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).

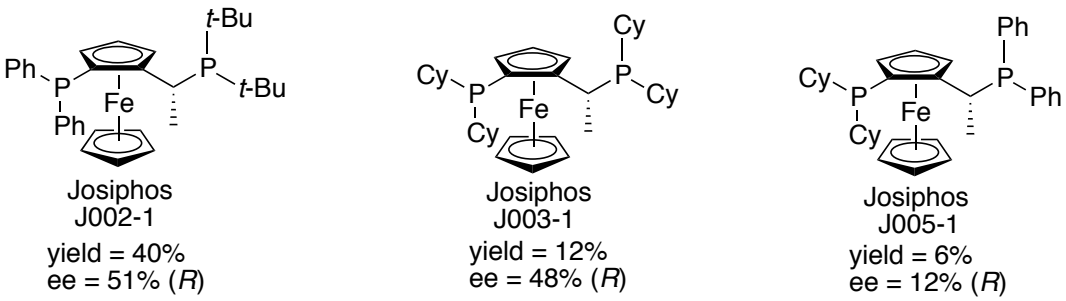
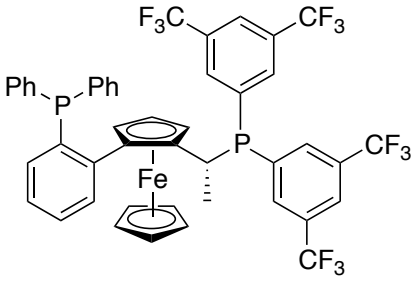
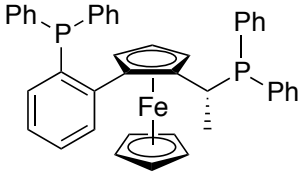


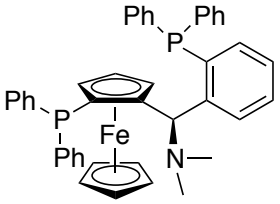
Figure 3.6



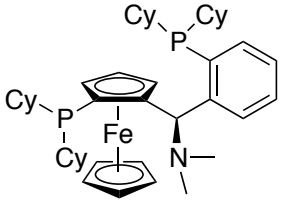
Walphos
W001-1
yield = 34%
ee = 70% (*S*)



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

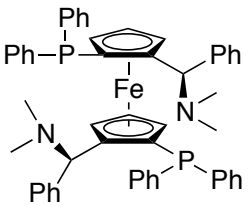


Taniaphos
T001-1
yield = 52%
ee = 25% (*R*)

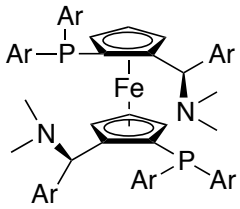


Taniaphos
T002-1
yield = 85%
ee = 27% (*S*)

Figure 3.7



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



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

where Ar =

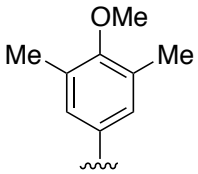


Figure 3.8

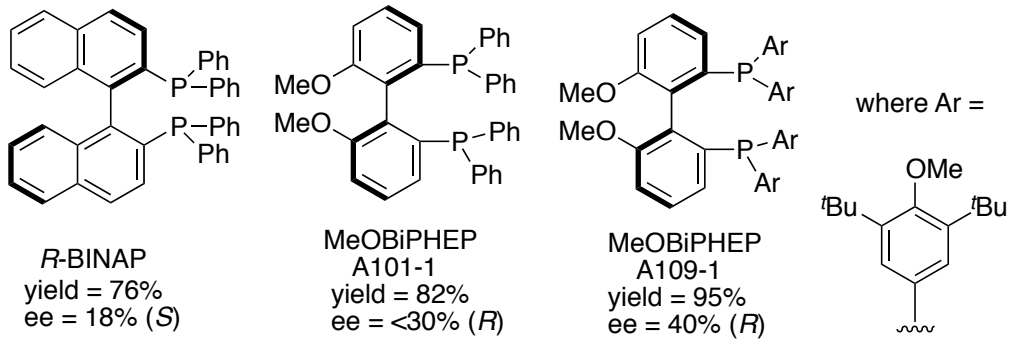
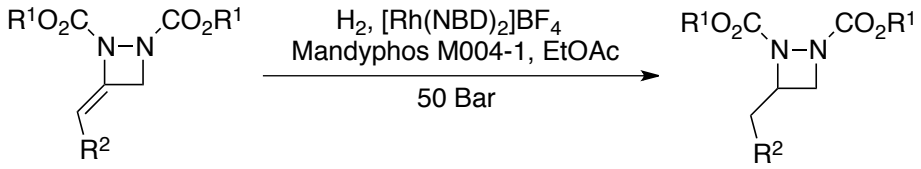


Figure 3.9

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.

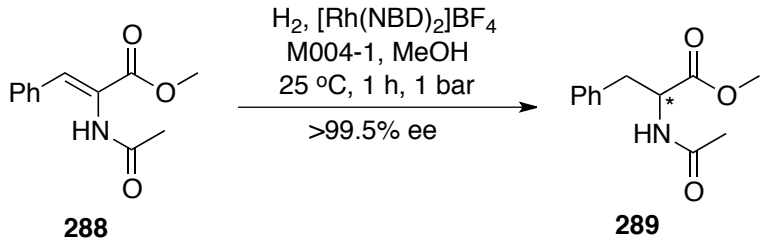
Hydrogenation of other methylenediazetidines was then investigated with these reaction conditions, as it was hoped Mandyphos M004-1 would prove to be a ligand of broad scope for this asymmetric transformation. Unfortunately this was not the case, and the enantioselectivities with substituted methylenediazetidines 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).



entry	substrate	R^1	R^2	temp (°C)	time (h)	product	ee (%)[i]
1	**251**	Et	H	50	5	**280** (98%)	89 (*S*)
2	**251**	Et	H	30	72	**280** (98%)	88 (*S*)
3	**252**	^{t}Bu	H	50	5	**284** (52%)	52
4	**258**	Et	Ph	50	72	**282** (89%)	8
5	**276**	Et	$C_6H_4{}^t$Bu	50	72	**285** (58%)	19
6	**275**	Et	Naphthyl	50	72	**286** (55%)	<30
7	**260**	Et	C_6H_4OMe	50	72	**287** (34%)	18

Table 3.4 [i] Determined by chiral HPLC (Appendix 5)

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.

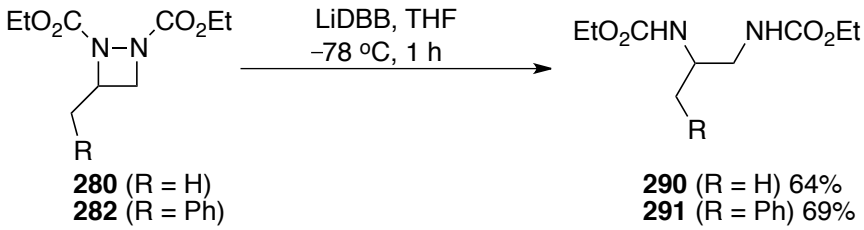


Scheme 3.38

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.

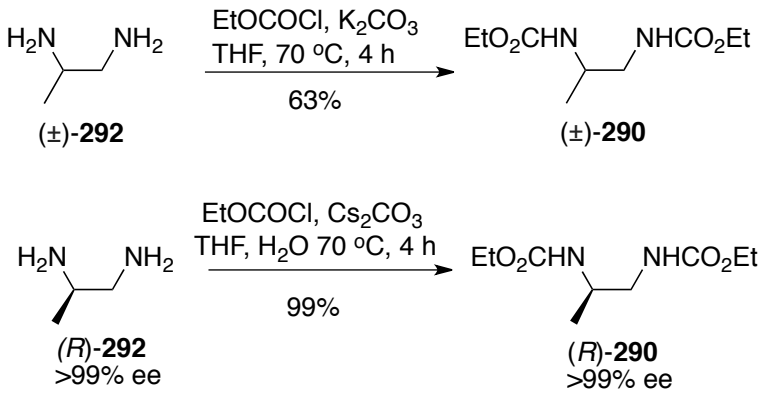
3.3.4 N–N bond cleavage and assignment of stereochemistry

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)



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.[146] 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).

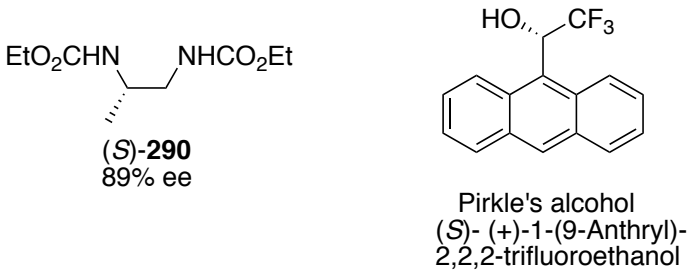
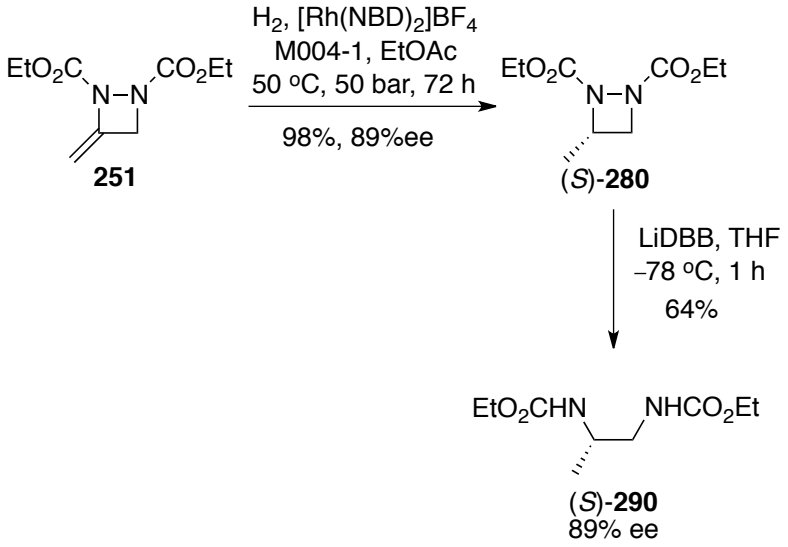


Figure 3.10

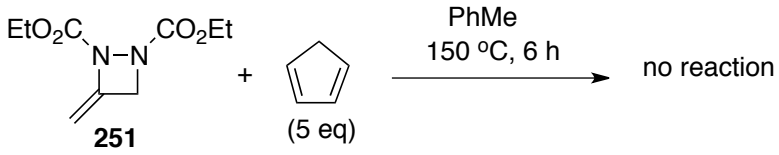
In summary we have demonstrated an efficient two-step synthesis of protected 1,2-diamine **290** from methylenediazetidine **251** with good yields and excellent enantioselectivity (Scheme 3.41).



Scheme 3.41

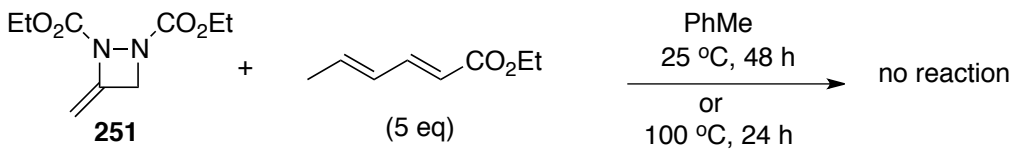
3.3.5 Other reactions of 3-methylene-1,2-diazetidines

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.[147] Methylenediazetidine **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).



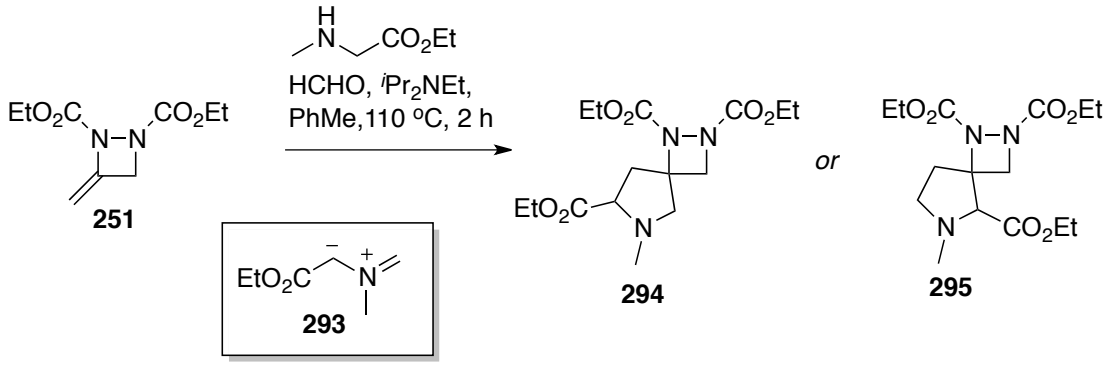
Scheme 3.42

The lack of reactivity with 1,3-cyclopentadiene suggests that the double bond of **251** is not electron-deficient and that an inverse electron demand Diels-Alder reaction might be more appropriate.[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).



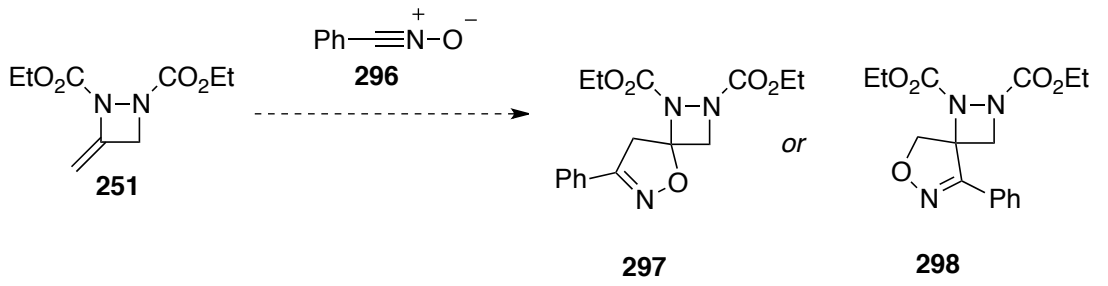
Scheme 3.43

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.[149] 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**).



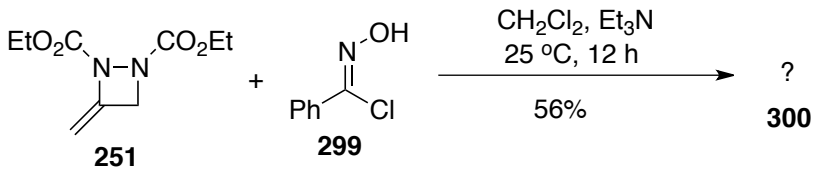
Scheme 3.44

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).[150]



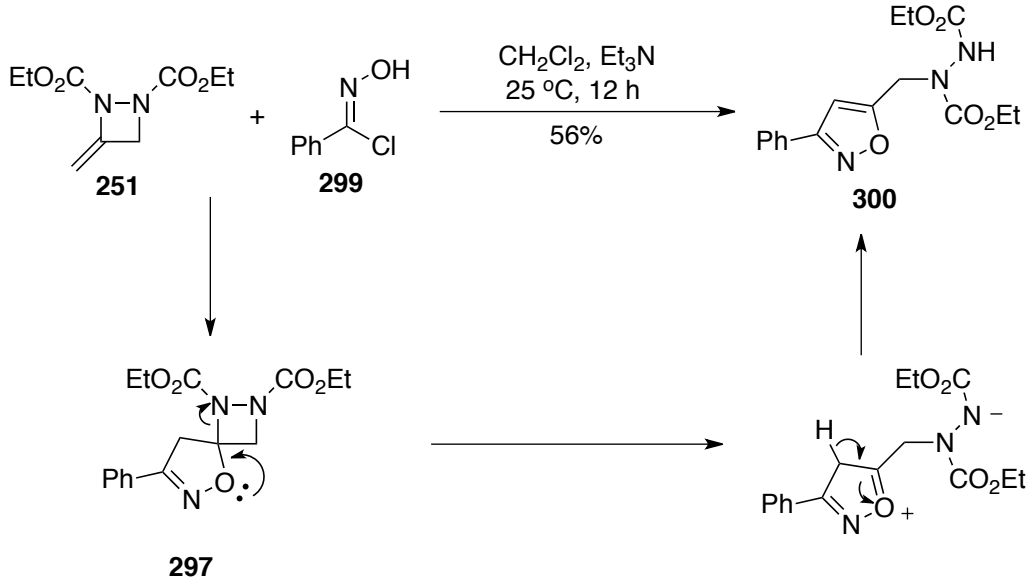
Scheme 3.45

296 was formed *in situ* by the deprotonation of **299**, which subsequently reacted with **251** to form unidentified product **300** (Scheme 3.46).



Scheme 3.45

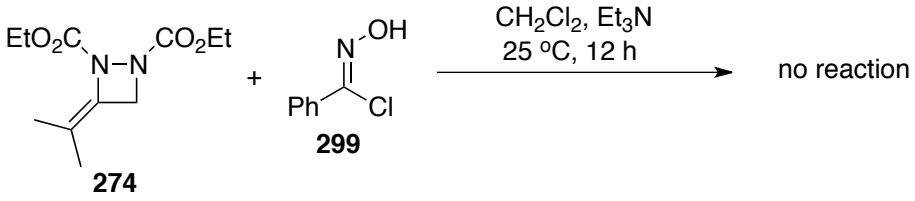
Unknown product **300** possessed the correct mass for both **297** and **298** (*m/z* = 356 $[M+Na]^+$), however the ^1H NMR spectrum was not convincing. Peaks corresponding to the phenyl ring, two ethyl chains, and what was initially thought to be two diazetidine ring hydrogens were present, but the 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).



Scheme 3.47

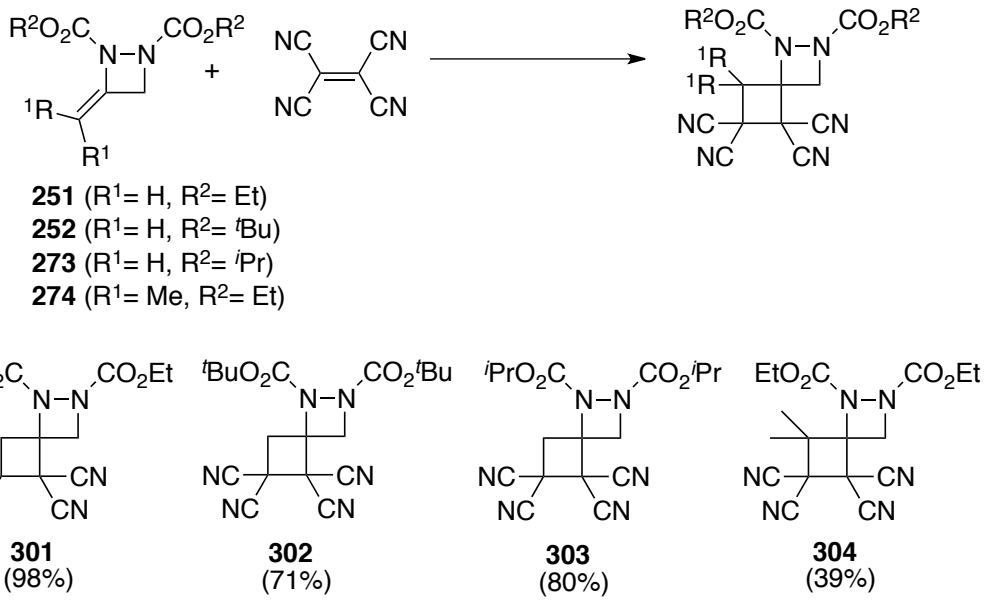
As it is unlikely that **298** would be able to undergo this ring-opening process, it is believed that **300** is the correct regioisomer for this reaction.

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**.[152] 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).



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).

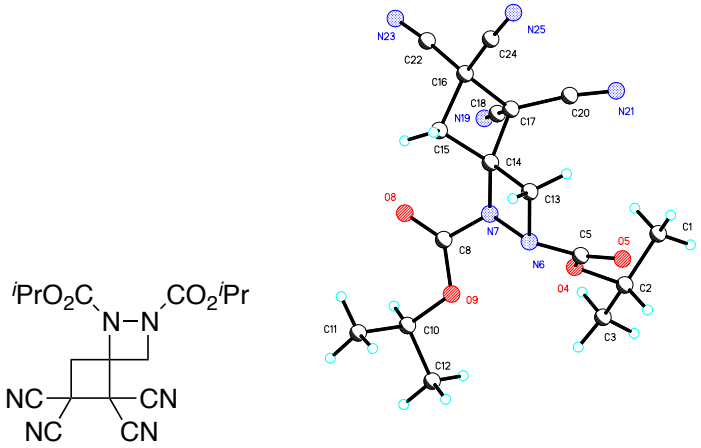
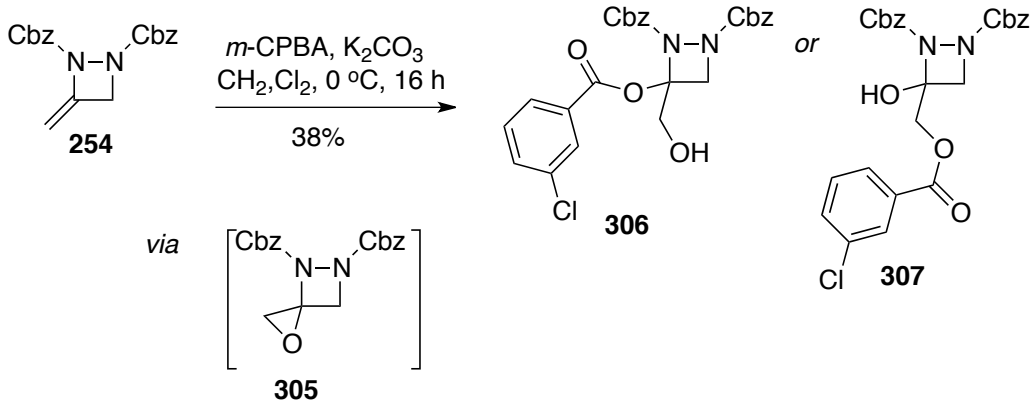


Figure 3.11

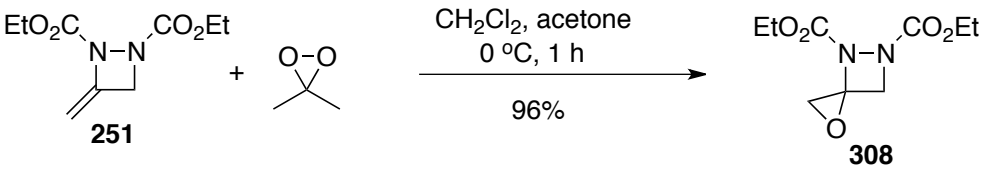
Mike Brown had previously attempted epoxidation of **254** with *m*-CPBA.[137] However, this led to ring-opened product, either **306** or **307**, which is expected

to arise from attack of the carboxylate onto the initially formed epoxide **305** (Scheme 3.50).



Scheme 3.50

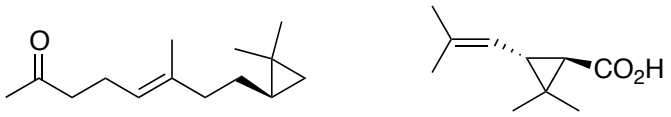
Although epoxide **305** was not obtained, the presence of the ring-opened compound suggests that its formation does occur. We therefore decided to investigate epoxidation with milder conditions. DMDO was selected as an oxidising agent, as no nucleophilic side-products are produced.[153] The reaction 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 $[M+Na]^+$) and the ^1H 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).



Scheme 3.51

The conditions used for the epoxidation of **251** were also applied to diazetidines **252**, **273** and **274**. Based on crude ^{1}H 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.[154] Noranthroplone (**309**) for example, exhibits cytotoxicity against B-16 melanoma cells whereas (+)-*E*-chrysanthemic acid (**310**) is a potent insecticide (Figure 3.12).[155,156]



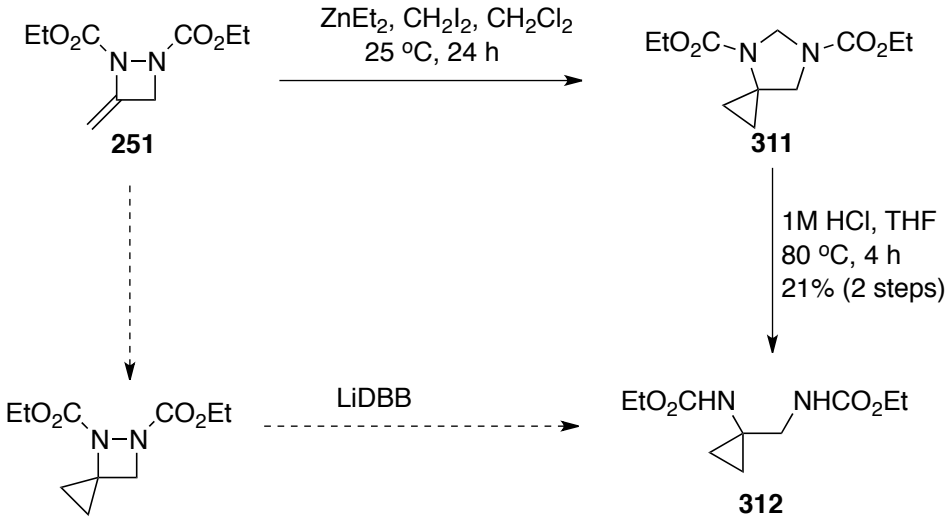
309
noranthroplone

310
(+)-*E*-chrysanthemic acid

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

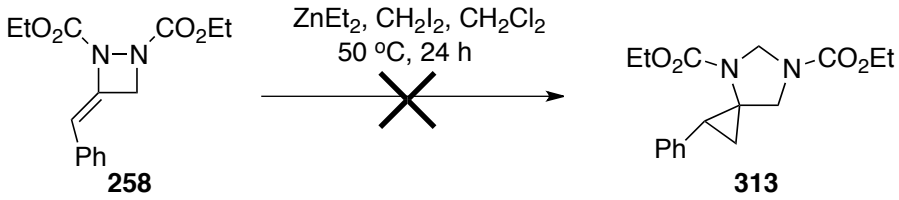
3.20).[137] It was expected however, that compounds such as **261** should be capable of hydrolysis under aqueous acidic conditions. This would provide an alternative route to the corresponding 1,2-diamines compared to direct N–N bond cleavage as previously discussed. Cyclopropanation of **251** led 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 ^{1}H 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 ^{1}H 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

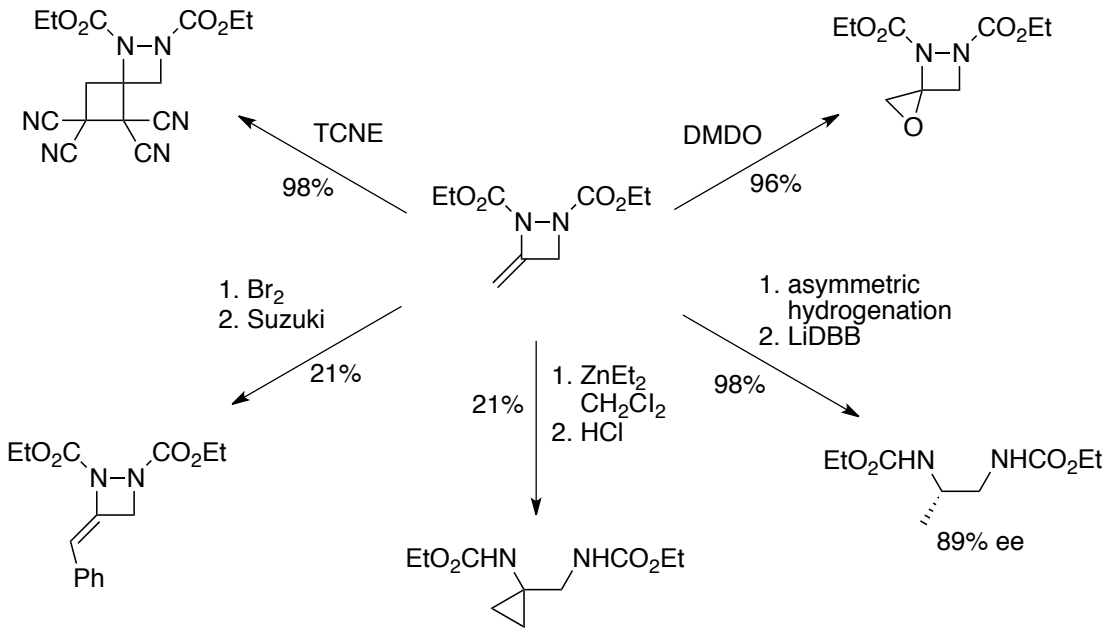
attempted, however no product was observed and only starting material was recovered. Increasing the reaction temperature did not yield any of expected product **313** (Scheme 3.53). Unfortunately due to time constraints, we were unable to pursue this chemistry further.



Scheme 3.53

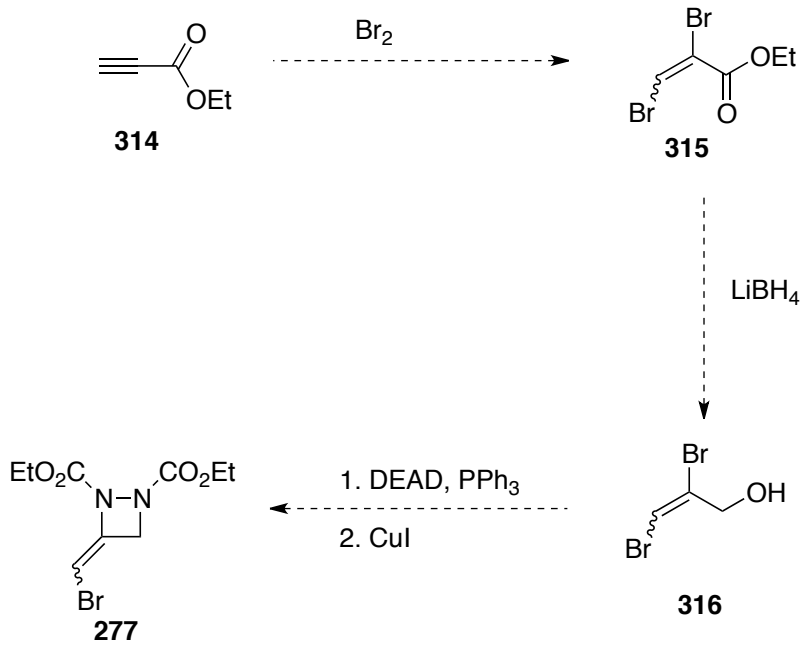
3. 4 Conclusions and Future Work

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 enantioselectivies 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).



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]



Scheme 3.55

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 enantioselectivies 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.

Chapter 4:

Experimental

General Information

Anhydrous solvents were purchased in Sure/Seal^{TM} 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 ºC. 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} deg cm^2 g^{-1}.

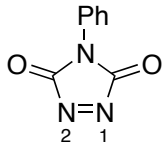
Infrared spectra were recorded on an Avatar 320 FT-IR or PerkinElmer Spectrum One FT-IR spectrometer with internal calibration. ^{1}H and ^{13}C spectra were recorded at 300 MHz and 75 MHz respectively on a Bruker DPX-300; at 400 MHz and 100MHz respectively on a Bruker DPX-400. Signals in the ^{1}H NMR 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.

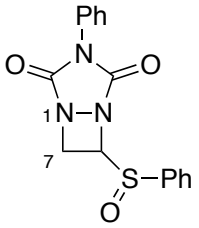
Chiral HPLC was conducted using a Gilson system using a Chiralcel AD column (1-5% ^{i}PrOH/*n*-hexane; 1.0 mL/min). UV absorbance was monitored at 220 nm by a Ranin Dynamax model UV-1. Racemic samples of the hydrogenation products were synthesised with Wilkinson's catalyst (Appendix 5).

4-Phenyl-1,2,4-triazoline-3,5-dione (149)



To a stirred solution of 4-phenylurazole (200 mg, 1.13 mmol) in CH_2Cl_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, C-3, C-5), 130.1 (1C, ArC), 129.5 (2C, ArCH), 129.1 (2C, ArCH), 125.2 (1C, ArCH); *m/z* (ES^+) 176 $[M+H]^+$. Data is in accordance with the reported values of Risi *et al*.[157]

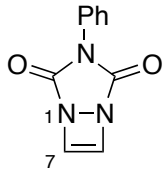
3-Phenyl-6-phenylsulfinyl-1,3,5-triazabicyclo[3.2.0]hepta-2,4-dione (166)



A solution of **149** (167 mg, 0.95 mmol) in CH_2Cl_2 (10 mL) was added to phenyl vinyl sulfide (0.13 mL, 0.95 mmol) in CH_2Cl_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 ºC and *m*CPBA (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 ºC; IR (film) 1712 (C=O), 1045 (S=O), 743 (ArH) cm^{-1}; ^1H 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[i] (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 $C_{16}H_{13}N_3O_3SNa$ $[M+Na]^+$: 350.0570; found: 350.0578.

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

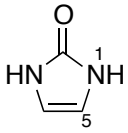


A solution of **166** (18 mg, 0.06 mmol) in chlorobenzene (3 mL) was placed in a high-pressure tube that was degassed and filled with nitrogen. The tube was heated to 150 ºC for 3 h, allowed to cool and the mixture was filtered through Celite®. The solvent was removed in *vacuo* to give a viscous brown oil. Column chromatography (10% ethyl acetate in petroleum ether) gave **167** (5 mg, 48%) as a white solid. M.p. 137.8-138.4 ºC; IR (film) 1728 (C=O), 1490 (Ar), 727 (Ar-H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.36 – 7.47 (5H, m, ArH), 6.74 (2H, s, H-

[i] Aromatic quaternary carbon is not observed

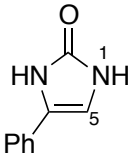
6, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) 155.0 (2C, C-2, C-4), 130.9 (1C, ArCH), 130.8 (1C, ArC), 129.5 (2C, ArCH), 129.3 (2C, ArCH), 125.4 (2C, C-6, C-7) *m/z* (ES$^+$) 224 [M+Na]$^+$; HRMS (ES$^+$) *m/z* calculated for $C_{10}H_8N_3O_2$ [M+H]$^+$: 202.0611; found: 202.0610.

1H-Imidazolin-2-one (185)



To a stirred suspension of hydantoin (4.00 g, 40.0 mmol) in THF (50 mL) at 0 ºC 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 ºC. 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 ºC; ^{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]

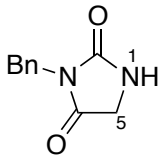
4-Phenyl-1H-imidazolin-2-one (199)



To a solution of **185** (1.00 g, 11.90 mmol), $Pd(OAc)_2$ (133 mg, 0.59 mmol) and $NaOAc.3H_2O$ (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 ºC for 6 h. Upon

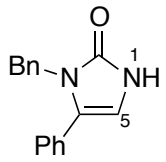
cooling, the solvent was removed via distillation. The crude product was recrystallised from IPA to yield **199** as a white crystalline solid (1.12 g, 52%). ^{1}H NMR (400MHz, DMSO-d_6) 10.50 (1H, s, NH), 10.04 (1H, s, NH), 7.49 (2H, d, J = 7.7 Hz, ArH) 7.31 (2H, t, J = 7.7 Hz, ArH), 7.16 (1H, t, J = 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)



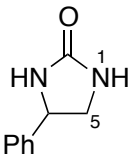
To a solution of hydantoin (1.00 g, 10 mmol) and potassium carbonate (5.52 g, 40 mmol) in DMF (25 mL) was added benzyl bromide (1.43 mL, 12 mmol) and stirred at 25 ºC for 36 h. The reaction mixture was then diluted with water (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers 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_2Ph) 3.98 (2H, s, H-5); (ES$^+$) m/z = 213 [M+Na]$^+$. Data is in accordance with Kohn and co-workers.[158]

3-Benzyl-4-phenylimidazolin-2-one (200)



To a solution of **186** (500 mg, 2.6 mmol) in THF (10 mL) at -25 ºC was added phenyl magnesium chloride (15.8 mL, 1M in Et_2O, 15.8 mmol). The solution was then allowed to warm to 25 ºC. After 16 h the reaction was quenched with methanol (2 mL) and diluted with Et_2O. The mixture was then washed with $NH_4Cl_{(aq)}$ (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. ^{1}H NMR (400 MHz, $CDCl_3$) 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, NCH_2Ph); (ES^+) *m/z* = 251 $[M+H]^+$. Data is in accordance with the values reported by Meanwell *et al*.[159]

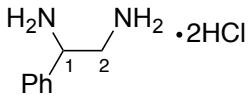
4-Phenylimidazolidin-2-one (201)



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 ºC 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. ^{1}H NMR (400 MHz, DMSO-d_6) 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,

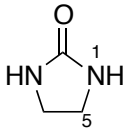
11.4 Hz, H-5); (ES$^+$) *m/z* = 162 [M+H]$^+$. Data is in accordance with the values reported by Kohn *et al*.[158]

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



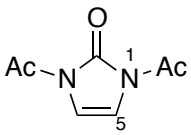
A solution of **201** (120 mg, 0.75 mmol) in THF (3 mL) and 4M HCl (2 mL) was stirred at 80 ºC for 6 h. Upon cooling, the reaction mixture was concentrated *in vacuo* and the resulting residue was washed with IPA to afford **211** (84 mg, 54%) as a white solid. M.p. = 300-301 ºC; ^{1}H NMR (400 MHz, 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)



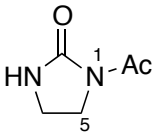
A solution of **185** (46 mg, 0.55 mmol) in methanol (5 mL) was passed through an H-Cube® loaded with a 10% palladium on carbon cartridge at 50 bar, 100 ºC until no starting material remained by LCMS. The solution was then concentrated *in vacuo*. Purification on silica gel (33% ethyl acetate in petroleum 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)



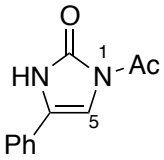
A solution of **185** (950 mg, 11.3 mmol) in acetic anhydride (10 mL) was stirred under reflux at 150 ºC for 1 h. The mixture was concentrated *in vacuo*. Recrystallisation from ethanol afforded **189** (1.29 g, 68%) as a white crystalline solid. ^{1}H NMR (300 MHz, DMSO-d_6) 7.15 (2H, s, H-4, H-5), 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)



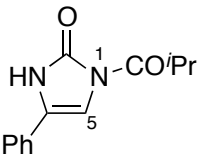
To a solution of **185** (75 mg, 0.45 mmol) in methanol (2 mL) was added 10% palladium on carbon (8 mg) and the suspension was stirred under a hydrogen atmosphere at 25 ºC for 18 h. the reaction mixture was filtered over a plug of Celite®, washed through with methanol (20 ml) and concentrated *in vacuo*. 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)



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 ºC for 3 h. Upon cooling, the solution was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were then washed with water (5 x 150 mL), dried over $MgSO_4$ 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 ºC; IR (film) 3151 (N-H) 1698 (C=O), 1357 (C-O), 730 (Ar-H) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) 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, $COCH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) 167.8 (1C, C-2), 152.0 (1C, N*C*OCH_3), 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, CO*C*H_3); (ES^+) m/z = 225 $[M+Na]^+$; HRMS (ES^+) m/z calculated for $C_{11}H_{10}N_2O_2Na$ $[M+Na]^+$: 225.0634; found: 225.0635.

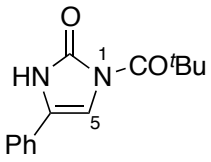
1-(2-Methylpropanoyl)-4-phenyl-imidazolin-2-one (208)



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 ºC for 3 h. Upon cooling, the

solution was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were then washed with water (5 x 150 mL), dried over $MgSO_4$ 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 ºC; IR (film) 3150 (NH), 2970 (CH), 1694 (C=O), 728 (Ar-H); ^{1}H NMR (400 MHz, DMSO-d_6) 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, NCOC*H*$(CH_3)_2$), 1.24 (6H, d, J = 6.8 Hz, NCOCH(C*H*$_3)_2$); ^{13}C NMR (100 MHz, DMSO-d_6) 175.0 (1C, C-2), 151.5 (1C, N*C*OCH$(CH_3)_2$), 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, NCO*C*H$(CH_3)_2$), 18.5 (2C, NCOCH(*C*H$_3)_2$); (ES$^+$) m/z = 253 [M+Na]$^+$; HRMS (ES$^+$) m/z calculated for $C_{13}H_{14}N_2O_2Na$ [M+Na]$^+$: 253.0947; found: 253.0947.

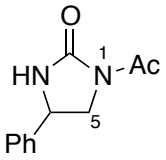
1-(2,2-Dimethylpropanoyl)-4-phenyl-imidazol-2-one (209)



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 ºC for 3 h. Upon cooling, the solution was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were then washed with water (5 x 150 mL), dried over $MgSO_4$ 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 ºC; 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, N*C*OC(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*C*(CH_3)$_3$), 25.9 (3C, NCOC(*C*H$_3$)$_3$); (ES$^+$) *m/z* = 267 [M+Na]$^+$; HRMS (ES$^+$) *m/z* calculated for $C_{14}H_{16}N_2O_2Na$ [M+Na]$^+$: 267.1104; found: 267.1105.

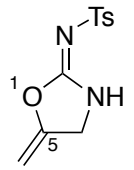
1-Acetyl-4-phenyl-imidazolidin-2-one (210)



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 ºC 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 ºC; 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, N*C*OCH_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

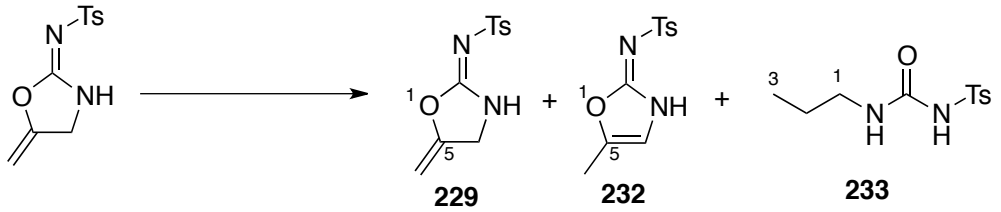
(ES$^+$) *m/z* calculated for $C_{11}H_{12}N_2O_2Na$ [M+Na]$^+$: 227.0791; found: 227.0791.

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



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 silca, 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 ºC, IR (film) 3318 (N-H), 1635 (C=N), 1163 (SO_2), 851 (ArH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 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=*C*H$_2$), 46.0 (1C, C-4), 21.5 (1C, CH_3); (ES$^+$) *m/z* = 275 [M+Na]$^+$; HRMS (ES$^+$) *m/z* calculated for $C_{11}H_{13}N_2O_3S$ [M+H]$^+$: 253.0641; found: 253.0639.

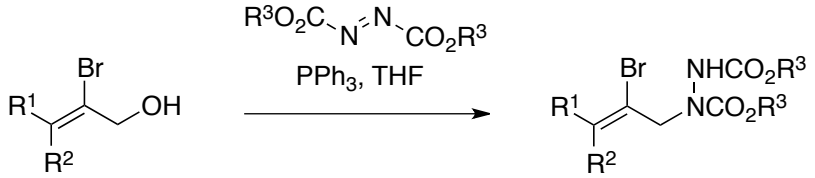
***N*-Tosyl-5-methyl-1,3-oxazolidin-2-imine (231), *N*-Tosyl-5-methyl-1,3-oxazolin-2-imine (232) and *N*-tosyl-*N*'-propylurea (233)**



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 ºC 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 (SO_2), 872 (ArH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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, CH_3), 1.48 (2H, sex, *J* = 7.3 Hz, H-2), 0.85 (3H, t, *J* = 7.3 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 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, CH_3), 11.2 (1C, CH_3); (ES^+) *m/z* = 279 $[M+Na]^+$; HRMS (ES^+) *m/z* calculated for $C_{11}H_{16}N_2O_3SNa$ $[M+Na]^+$: 279.0774; found: 279.0776. Further elucidation afforded **232** (149 mg, 30%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) 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, CH_3), 2.14 (3H, d, *J* = 1.4 Hz, CH_3); (ES^+) *m/z* = 275 $[M+Na]^+$. The data is accordance with the values reported by Padwa for isomer **228**.[128] Further elucidation afforded **229** (185 mg, 26%) as a crystalline white solid. M.p. 138.8-139.3 ºC; IR (film) 3354 (N-H) 1616 (1=N) 1153 (SO_2) cm^{-1};

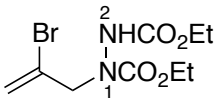
^{1}H NMR (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* =8.2 Hz, ArH), 7.73 (1H, s, H-3), 7.23 (2H, d, *J* = 8.2 Hz, ArH), 4.84 (1H, m, H-5), 3.85 (1H, t, *J* = 9.0 Hz, H-4), 3.33 (1H, dd, *J* = 7.6, 9.1 Hz, H-4), 2.37 (3H, s, Ar-CH_3), 1.40 (3H, s, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 161.5 (1C, C-2), 142.8 (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-*C*H_3), 19.9 (1C, CH*C*H_3); (ES$^+$) *m/z* = 277 [M+Na]$^+$; HRMS (ES$^+$) *m/z* calculated for $C_{11}H_{15}N_2O_3SNa$ [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).

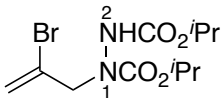
Diethyl 1-(2-bromoallyl)hydrazine-1,2-dicarboxylate (250)



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**

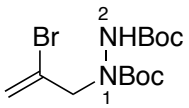
(1.93 g, 90%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 6.72 (1H, m, NH), 5.79 (1H, br s, CBr=C*H*), 5.57 (1H, d, *J* = 1.9 Hz, CBr=C*H*), 4.41-4.23 (2H, m, NCH_2CBr), 4.15 (4H, br q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.23 (6H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); MS (ES+) m/z = 319 [M(^{81}Br)+Na]$^+$, 317 ([M(^{79}Br)+Na]$^+$. Data is in accordance with the values reported by Shipman an co-workers.[100]

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



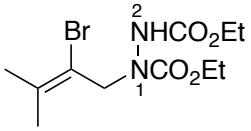
271 was synthesised according to General Procedure 1 with the following: 2-Bromoallyl alcohol (1.56 g, 11.39 mmol), triphenylphosphine (6.16 g, 23.4 mmol), di-isopropylazodicarboxylate (4.60 mL, 23.4 mmol) and THF (120 mL). Purification on silica gel (12.5% ethyl acetate in petroleum ether) afforded **271** (2.75 g, 75%) as a white crystalline solid. M.p. 68.0 – 69.1 ºC; 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=C*H*), 5.61 (1H, s, CBr=C*H*), 4.97 (2H, br m, $CO_2CH(CH_3)_2$) 4.35 (2H, br s, NCH_2CBr), 1.26 (12H, d, *J* = 6.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 155.8 (1C, $CO_2CH(CH_3)_2$), 155.5 (1C, $CO_2CH(CH_3)_2$), 128.2 (1C, -*C*Br=CH_2), 119.9 and 119.4 (1C, -CBr=*C*H_2), 70.6 (1C, $CO_2CH(CH_3)_2$), 70.0 (1C, $CO_2CH(CH_3)_2$), 58.0 and 57.3 (1C, NCH_2CBr), 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 $C_{11}H_{19}{}^{79}BrN_2O_4Na$ [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 ºC; IR (film) 3315 (N-H), 1708 (C=O), 1146 (C-O) cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) 6.10-6.39 (1H, br m, H-2), 5.80 (1H, br d, *J* = 18.2 Hz, CBr=C*H*), 5.59 (1H, s, CBr=C*H*), 4.30 (2H, br s, NCH_2CBr), 1.47 (18H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 154.7 (2C, *C*O_2C(CH_3)$_3$), 128.8 (1C, -*C*Br=CH_2), 119.4 (1C, -CBr=*C*H_2), 81.8 (2C, CO_2*C*(CH_3)$_3$), 58.3 (1C, N*C*H_2CBr), 28.2 (3C, -C(*C*H_3)$_3$), 28.1 (3C, -C(*C*H_3)$_3$); MS (ES^+) *m/z* = 373 [M(^{79}Br)+Na]$^+$, 375 [M(^{81}Br)+Na]$^+$; HRMS (ES^+) *m/z* calculated for $C_{13}H_{23}{}^{79}BrN_2O_4Na$ [M+Na]$^+$: 373.0733; found: 373.0731.

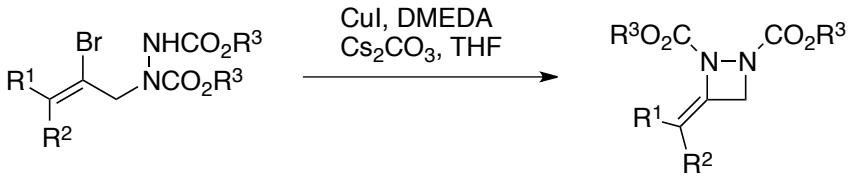
Di-ethyl 1-(2-bromo-3-methylbut-2-enyl)hydrazine-1,2-dicarboxylate (272)



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); ^{1}H NMR (400 MHz,

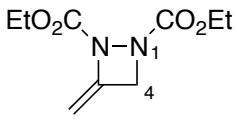
$CDCl_3$) 6.31-6.58 (1H, m, NH), 4.51 (2H, br s, NCH_2CBr), 4.23 (4H, q, J = 7.1 Hz, $CO_2CH_2CH_3$), 1.91 (3H, s, CH_3), 1.83 (3H, s, CH_3), 1.27, (6H, t, J = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}CNMR (100 MHz, $CDCl_3$) 156.0 (1C, $CO_2C(CH_3)_3$), 155.4 (1C, $CO_2C(CH_3)_3$), 137.0 and 136.6 (1C, -CBr=C$(CH_3)_2$), 115.3 (1C, -CBr=$C(CH_3)_2$), 62.5 (1C, $CO_2CH_2CH_3$), 61.9 (1C, $CO_2CH_2CH_3$), 53.9 and 53.3 (1C, NCH_2CBr), 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(^{79}Br)+Na]$^+$, 347 [M(^{81}Br)+Na]$^+$; HRMS (ES^+) m/z calculated for $C_{11}H_{19}{}^{79}BrN_2O_4Na$ [M+Na]$^+$: 345.0420; found: 345.0225.

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



To a mixture of hydrazodicarboxylate (1.0 molar equiv.), CuI (0.2 molar equiv) and Cs_2CO_3 (2.0 molar equiv.) in THF was added dropwise *N*,*N*'-dimethylethylenediamine (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).

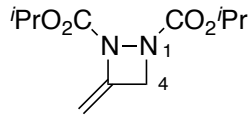
Diethyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (251)



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,

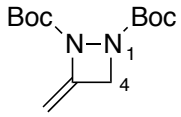
2.55 mmol), Cs_2CO_3 (4.16 g, 12.75 mmol) and THF (50 mL). Purification on silica gel (20% ethyl acetate in petroleum ether) afforded **251** (1.31 g, 96%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 4.94 (1H, dt, *J* = 3.3, 2.3 Hz, C=C*H*), 4.65 (2H, t, *J* = 2.3 Hz, H-4), 4.40 (1H, dt, *J* = 3.3, 2.3 Hz, C=C*H*), 4.28 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.22 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.31 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.28 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); 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)



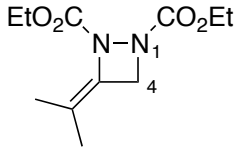
273 was synthesised according to General Procedure 2 with the following: **271** (821 mg, 2.55 mmol), copper iodide (97 mg, 0.51 mmol), DMEDA (108 μL, 1.02 mmol), Cs_2CO_3 (1.66 g, 5.10 mmol) and THF (20 mL). Purification on silica gel (20% ethyl acetate in petroleum ether) afforded **273** (567 mg, 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 COC*H*$(CH_3)_2$), 4.63–4.65 (2H, m, H-4), 4.39–4.41 (1H, m, C=C*H*), 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, $CO_2CH(CH_3)_2$), 154.9 (1C, $CO_2CH(CH_3)_2$) 142.4 (1C, C-3), 90.1 (1C, $C=CH_2$) 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 $C_{11}H_{19}N_2O_4Na$ $[M+Na]^+$: 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), Cs_2CO_3 (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. ^{1}H NMR (400 MHz, $CDCl_3$) 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(CH_3)$_3$), 1.50 (9H, s, C(CH_3)$_3$); MS (ES$^+$) m/z = 293 [M+Na]$^+$. Data is in accordance with the values reported by Shipman and co-workers.[100]

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



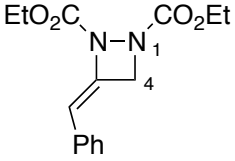
274 was synthesised according to General Procedure 2 with the following: **272** (870 mg, 2.70 mmol), copper iodide (118 mg, 0.62 mmol), DMEDA (132 μL, 1.24 mmol), Cs_2CO_3 (2.03 g, 6.22 mmol) and THF (20 mL). Purification on silica gel (20% ethyl acetate in petroleum ether) afforded **274** (610 mg, 93%) as a colourless oil. IR (film) 2985 (-CH_3), 1710 (C=O), 1269 (C-O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 4.68 (2H, br s, H-4), 4.23 (2H, 2H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.23 (2H, 2H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.78 (3H, m, C=C(CH_3)$_2$), 1.49 (3H, br s, C=C(CH_3)$_2$), 1.29 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.27 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 160.5 (1C,

$CO_2CH_2CH_3$), 157.8 (1C, $CO_2CH_2CH_3$), 129.3 (1C, C-3), 113.5 (1C, C=$C(CH_3)_2$), 62.9 (1C, $CO_2CH_2CH_3$), 62.8 (1C, $CO_2CH_2CH_3$), 58.4 (1C, C-4), 18.6 (1C, C=C($CH_3)_2$), 18.4 (1C, C=C($CH_3)_2$), 14.4 (1C, $CO_2CH_2CH_3$), 14.3 (1C, $CO_2CH_2CH_3$); MS (ES^+) *m/z* = 265 $[M+Na]^+$, HRMS (ES^+) *m/z* calculated for $C_{11}H_{19}N_2O_4Na$ $[M+Na]^+$: 265.1159; found: 265.1155.

General Procedure 3

To a stirred mixture of diethyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (1 molar equiv.), phenyl iodide (1.5 molar equiv.), Bu_4NCl (1 molar equiv) and $Pd(OAc)_2$ (0.04 molar equiv.), in dimethylacetamide was added Cy_2NMe (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_2O and water. The phases were separated and the aqueous layer extracted with Et_2O. The combined extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified on silica gel (ethyl acetate in hexane).

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



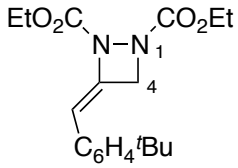
258 was synthesised according to General Procedure 3 with the following: **251** (500 mg, 2.34 mmol), phenyl iodide (0.391 mL, 3.51 mmol), Bu_4NCl (651 mg,

2.34 mmol), palladium (II) acetate (21 mg, 0.09 mmol), Cy_2NMe (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, $CDCl_3$) 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=C*H*Ph), 5.00 (2H, d, *J* = 2.5 Hz, H-4), 4.35 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.29 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 1.38 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 1.33 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); MS (ES^+) *m/z* = 313 $[M+Na]^+$. Data is in accordance with that reported by Shipman and co-workers.[100]

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

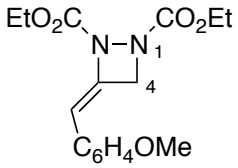
To a stirred solution of **277** (40 mg, 0.14 mmol) in 1,4-dioxane (1 mL) was added $PhB(OH)_2$ (50 mg, 0.41 mmol), XPhos (4 mg, 0.008 mmol), Pd_2dba_3 (3 mg, 0.003 mmol) and Cs_2CO_3 (98 mg, 0.30 mmol). The reaction was stirred at 110 ºC for 1 h. Upon cooling, the reaction mixture was filtered over Celite®, washed through with CH_2Cl_2 (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 (3*E*)-3-(4-*tert*-butyl-benzylidene)-1,2-diazetidine-1,2-dicarboxylate (276)



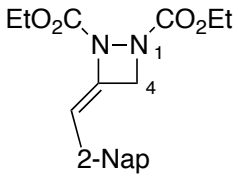
276 was synthesised according to General Procedure 3 with the following: **251** (200 mg, 0.94 mmol), 4-*tert*-butyliodobenzene (0.198 mL, 1.12 mmol), Bu_4NCl (260 mg, 0.94 mmol), palladium (II) acetate (15 mg, 0.07 mmol), Cy_2NMe (238 mg, 1.12 mmol) and DMAc (6 mL). Purification on silica gel (12.5% ethyl acetate in hexane) afforded **276** (136 mg, 42%) as a colourless oil. IR (neat) 2963 (CH_3), 1720 (C=O), 1316 (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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=C*H*Ar), 5.01 (2H, d, *J* = 2.4 Hz, H-4), 4.36 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.29 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.38 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$) 1.34 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.31 (9H, s, Ar-C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 160.5 ($CO_2CH_2CH_3$), 155.5 ($CO_2CH_2CH_3$), 149.6 (1C, ArC), 136.5 (1C, C-3), 131.8 (1C, ArC), 126.4 (2C, ArCH), 125.8 (2C, ArCH), 63.3 (1C, $CO_2CH_2CH_3$), 63.1 (1C, $CO_2CH_2CH_3$), 58.5 (1C, C-4), 34.5 (1C, Ar-*C*(CH_3)$_3$), 31.3 (3C, Ar-C(CH_3)$_3$), 14.5 (1C, $CO_2CH_2CH_3$), 14.4 (1C, $CO_2CH_2CH_3$); MS (ES^+) *m/z* = 369 $[M+Na]^+$, HRMS (ES^+) *m/z* calculated for $C_{19}H_{26}N_2O_4Na$ $[M+Na]^+$: 369.1785; found: 365.1786.

Diethyl (3*E*)-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), Bu_4NCl (260 mg, 0.94 mmol), palladium (II) acetate (15 mg, 0.07 mmol), Cy_2NMe (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. ^{1}H NMR (400 MHz, $CDCl_3$) 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=C*H*Ar), 4.96 (2H, d, *J* = 2.5 Hz, H-4), 4.32 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.26 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 3.77 (3H, s, OCH_3), 1.34 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.30 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); MS (ES^+) *m/z* = 343 $[M+Na]^+$. The data is in accordance with that reported by Shipman and co-workers.[100]

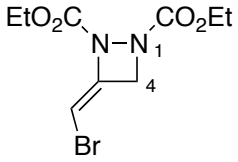
Diethyl (3*E*)-3-(naphthalene-2-ylidene)-1,2-diazetidine-1,2-dicarboxylate (275)



275 was synthesised according to General Procedure 3 with the following: **251** (200 mg, 0.94 mmol), 2-iodonaphthalene (285 mg, 1.12 mmol), Bu_4NCl (260 mg, 0.94 mmol), palladium (II) acetate (15 mg, 0.07 mmol), Cy_2NMe (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 ºC; IR (neat) 2981 (-CH_3), 1713 (C=O), 1284 (C-O), 745 (Ar-H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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=C*H*Ar), 5.11 (2H, d, *J* = 2.4 Hz, H-4), 4.38 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.34 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.41 (3 H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.35 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 160.4 (1C, $CO_2CH_2CH_3$), 155.4 (1C, $CO_2CH_2CH_3$), 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, $CO_2CH_2CH_3$), 63.2 (1C, $CO_2CH_2CH_3$), 58.6 (1C, C-4), 14.5 (1C, $CO_2CH_2CH_3$), 14.4 (1C, $CO_2CH_2CH_3$); MS (ES^+) *m/z* = 363 $[M+Na]^+$, HRMS (ES^+) *m/z* calculated for $C_{19}H_{21}N_2O_4$ $[M+H]^+$: 341.1496; found: 341.1497.

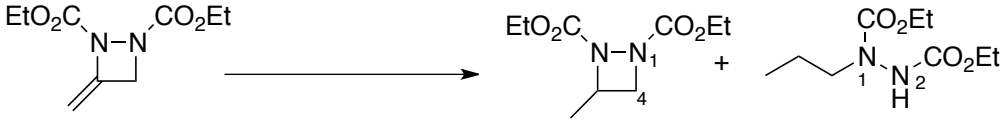
Diethyl (3*E*)-3-(bromomethylene)-1,2-diazetidine-1,2-dicarboxylate (277)



To a stirred solution of **251** (200 mg, 0.94 mmol) in CH_2Cl_2 (4 mL) at -78 ºC was added bromine (0.046 mL) dropwise. After 1 h the solution was allowed to reach -60 ºC, DBU was added dropwise and the reaction mixture was stirred for a further 4 h whilst being allowed to slowly warm to 25 ºC. The reaction

mixture was poured into brine (20 mL) and extracted with CH_2Cl_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}; ^1H NMR (400 MHz, $CDCl_3$) 6.05 (1H, t, *J* = 2.6 Hz, C=C*H*Br), 4.62 (2H, d, *J* = 2.6 Hz, H-4), 4.32 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.27 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.35 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.32 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) 159.2 (1C, $CO_2CH_2CH_3$), 153.7 (1C, $CO_2CH_2CH_3$), 137.8 (1C, C-3), 84.1 (1C, C=CHBr), 62.5 (1C, $CO_2CH_2CH_3$), 62.4 (1C, $CO_2CH_2CH_3$), 57.0 (1C, C-4), 13.3 (1C, $CO_2CH_2CH_3$), 13.3 (1C, $CO_2CH_2CH_3$); MS (ES^+) *m/z* = 315 $[M(^{79}Br)+Na]^+$, 317 $[M(^{81}Br)+Na]^+$, HRMS (ES^+) *m/z* calculated for $C_9H_{13}{}^{79}BrN_2O_4Na$ $[M(^{79}Br)+Na]^+$: 314.9951; found: 314.9952.

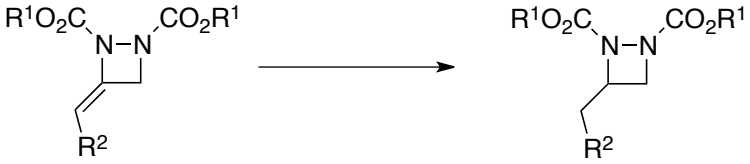
Diethyl 3-methyl-1,2-diazetidine-1,2-dicarboxylate (280) and diethyl 1-(propyl)hydrazine-1,2-dicarboxylate (281)



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 ºC 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}; ^1H NMR (400 MHz, $CDCl_3$) 6.31-6.64 (1H, m, H-2), 4.14-4.22

(4H, m, $CO_2CH_2CH_3$), 3.46 (2H, m, $NCH_2CH_2CH_3$), 1.59 (2H, quin, J = 7.3 Hz, $NCH_2CH_2CH_3$), 1.24-1.28 (6H, m, $CO_2CH_2CH_3$), 0.90 (3H, t, J = 7.3 Hz, $NCH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 156.3 (2C, $CO_2CH_2CH_3$), 62.4 (1C, $CO_2CH_2CH_3$), 62.0 (1C, $CO_2CH_2CH_3$), 42.7 (1C, $NCH_2CH_2CH_3$) 20.7 (1C, $NCH_2CH_2CH_3$), 14.6 (1C, $CO_2CH_2CH_3$), 14.5 (1C, $CO_2CH_2CH_3$), 11.1 (1C, $NCH_2CH_2CH_3$); MS (ES^+) m/z = 241 $[M+Na]^+$, HRMS (ES^+) m/z calculated for $C_9H_{18}N_2O_4Na$ $[M+Na]^+$: 241.1159; found: 241.1160. Further elucidation afforded **280** (108 mg, 54%) as a colourless oil. IR (film) 2977 (CH_3), 1702 (C=O), 1273 (C-O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 4.39-4.47 (1H, m, H-3), 4.32 (1H, t, J = 8.0 Hz, H-4), 4.15-4.27 (4H, m, $CO_2CH_2CH_3$), 3.74 (1H, dd, J = 6.2, 8.0 Hz, H-4), 1.48 (3H, d, J = 6.3 Hz, $>CHCH_3$), 1.28 (6H, t, J = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 161.1 (1C, $CO_2CH_2CH_3$), 160.9 (1C, $CO_2CH_2CH_3$), 62.6 (1C, $CO_2CH_2CH_3$), 62.4 (1C, $CO_2CH_2CH_3$), 58.1 (1C, C-3), 56.1 (1C, C-4), 20.7 (1C, $>CHCH_3$), 14.4 (2C, $CO_2CH_2CH_3$); MS (ES^+) m/z = 239 $[M+Na]^+$, HRMS (ES^+) m/z calculated for $C_9H_{16}N_2O_4Na$ $[M+Na]^+$: 239.1002; found: 239.1004.

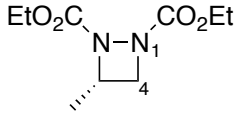
General Procedure 4



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,

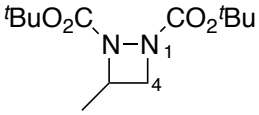
purged with hydrogen three times and then charged with hydrogen to 50 Bar. The reaction was stirred at 50 ºC for the required amount of time, allowed to cool and concentrated *in vacuo*. Purification on silica gel (ethyl acetate in hexane) afforded the desired compound.

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



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.

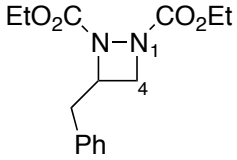
Diethyl 3-methyl-1,2-diazetidine-1,2-dicarboxylate (284)



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. $[\alpha]^{30}_D$ = +24.5 (EtOAc); IR (neat) 2979 (CH_3), 1700 (C=O), 1158 (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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, $CO_2C(CH_3)_3$), 1.48 (9H, s, $CO_2C(CH_3)_3$), 1.45 (3H, d, *J* = 6.4 Hz, >C-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 160.1 (1C, $CO_2C(CH_3)_3$), 160.0 (1C, $CO_2C(CH_3)_3$), 81.8 (1C, $CO_2C(CH_3)_3$), 81.7 (1C, $CO_2C(CH_3)_3$), 57.4 (1C, C-3), 55.6 (1C, C-4), 28.1 (6C, $CO_2C(CH_3)_3$), 20.7 (1C, >C-CH_3); MS (ES^+) *m/z* = 295 $[M+Na]^+$, HRMS (ES^+) *m/z* calculated for $C_{13}H_{24}N_2O_4Na$ $[M+Na]^+$: 295.1652; found: 295.1652.

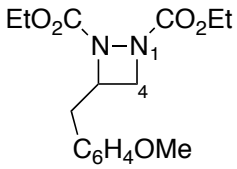
Diethyl 3-benzyl-1,2-diazetidine-1,2-dicarboxylate (282)



282 was synthesised according to General Procedure 4 with the following: **258** (50 mg, 0.17 mmol), $[Rh(NBD)_2]BF_4$ (1 mg, 0.01 mmol), (*R*)-1-[(S_P)-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. $[\alpha]^{30}_D$ = +36.0 (EtOAc); IR (film) 2984 (CH_3), 1705 (C=O), 1270 (C-O), 702 (Ar-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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 $CO_2CH_2CH_3$), 3.82 (1H, dd, *J* = 6.0, 8.4 Hz, H-4), 3.11 (1H, dd, J = 5.0, 14.0 Hz, -C*H*Ph), 3.04 (1H, dd, *J* = 7.7, 14.0 Hz, -C*H*Ph), 1.25 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.22 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 160.8 (2C, $CO_2CH_2CH_3$), 135.4 (1C, ArC), 129.5 (2C, ArCH), 128.4 (2C, ArCH), 126.4 (1C, ArCH), 62.5 (2C, $CO_2CH_2CH_3$), 62.1 (1C, C-3), 53.8 (1C, C-4), 40.2 (1C, -CH_2Ph), 14.4 (2C, $CO_2CH_2CH_3$); MS (ES^+) *m/z* =

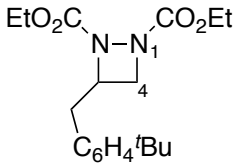
315 $[M+Na]^+$, HRMS (ES^+) *m/z* calculated for $C_{15}H_{20}N_2O_4Na$ $[M+Na]^+$: 315.1315; found: 315.1311.

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



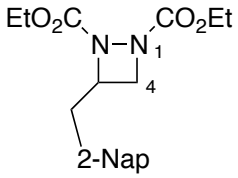
287 was synthesised according to General Procedure 4 with the following: **260** (50 mg, 0.16 mmol), $[Rh(NBD)_2]BF_4$ (1 mg, 0.01 mmol), (*R*)-1-[(S_P)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (2 mg, 0.01 mmol), and ethyl acetate (2 mL). Purification on silica gel (20% ethyl acetate in hexane) afforded **287** (17 mg, 34%, 18% ee) as a colourless oil. $[\alpha]^{30}_D$ = +12.3 (EtOAc); IR (neat) 2980 (CH_3), 1705 (C=O), 1244 (C-O), 769 (ArH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), 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 $CO_2CH_2CH_3$), 3.83 (1H, dd, *J* = 6.1, 8.4 Hz, H-4), 3.79 (3H, s, -OCH_3), 3.07 (1H, dd, J = 4.9, 14.1 Hz, -C*H*Ar), 3.00 (1H, dd, *J* = 7.6, 14.1 Hz, -C*H*Ar), 1.28 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 1.24 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) 160.8 (2C, $CO_2CH_2CH_3$), 158.7 (1C, Ar*C*-OCH_3), 130.5 (2C, ArCH), 127.3 (1C, ArC), 114.0 (2C, ArCH), 62.5 (2C, $CO_2CH_2CH_3$), 62.3 (1C, C-3), 55.2 (Ar-OCH_3), 53.7 (1C, C-4), 39.2 (1C, -CH_2Ar), 14.4 (2C, $CO_2CH_2CH_3$); MS (ES^+) *m/z* = 345 $[M+Na]^+$, HRMS (ES^+) *m/z* calculated for $C_{16}H_{22}N_2O_5Na$ $[M+Na]^+$: 345.1421; found: 345.1419.

Diethyl 3-(4-tert-butlylbenzyl)-1,2-diazetidine-1,2-dicarboxylate (285)



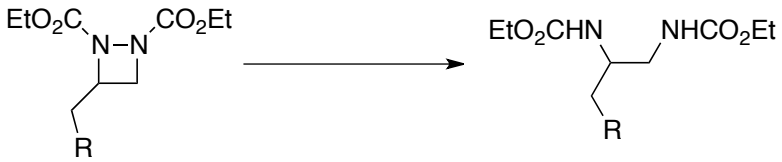
285 was synthesised according to General Procedure 4 with the following: **276** (80 mg, 0.23 mmol), $[Rh(NBD)_2]BF_4$ (1 mg, 0.01 mmol), (*R*)-1-[(S_P)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (3 mg, 0.01 mmol), and ethyl acetate (2 mL). Purification on silica gel (10% ethyl acetate in hexane) afforded **285** (46 mg, 58%, 19% ee) as a colourless oil. $[\alpha]^{30}_D$ = +14.6 (EtOAc); IR (film) 2959 (CH_3), 1707 (C=O), 1270 (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.32 (2H, d, *J* = 8.5 Hz, ArH), 7.14 (2H, d, *J* = 8.5 Hz, ArH), 4.53-4.59 (1H, m, H-3), 4.07-4.29 (5H, H-4, 2 x $CO_2CH_2CH_3$), 3.85 (1H, dd, *J* = 6.0, 8.3 Hz, H-4), 3.11 (1H, dd, *J* = 4.8, 14.1 Hz, -C*H*Ar), 3.03 (1H, dd, *J* = 8.0, 14.1 Hz, -C*H*Ar), 1.30 (9H, s, -C(CH_3)$_3$), 1.27 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.24 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 160.9 (2C, $CO_2CH_2CH_3$), 149.9 (1C, Ar*C*-C(CH_3)$_3$), 132.3 (1C, ArC), 129.2 (2C, ArCH), 125.5 (2C, ArCH), 62.5 (2C, $CO_2CH_2CH_3$), 62.2 (1C, C-3), 53.9 (1C, C-4), 39.7 1C, -CH_2Ar), 34.5 (1C, Ar-*C*(CH_3)$_3$), 31.4 (3C, Ar-C(*C*H_3)$_3$), 14.4 (2C, $CO_2CH_2CH_3$); MS (ES^+) *m/z* = 371 $[M+Na]^+$, HRMS (ES^+) *m/z* calculated for $C_{19}H_{28}N_2O_4Na$ $[M+Na]^+$: 371.1941; found: 371.1933.

Diethyl 3-(naphthalene-2-ylmethyl)-1,2-diazetidine-1,2-dicarboxylate (286)



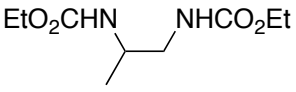
286 was synthesised according to General Procedure 4 with the following: **275** (40 mg, 0.118 mmol), $[Rh(NBD)_2]BF_4$ (1 mg, 0.003 mmol), (*R*)-1-[(S_P)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (3 mg, 0.003 mmol), and ethyl acetate (2 mL). Purification on silica gel (12.5% ethyl acetate in hexane) afforded **286** (22 mg, 55%, <30% ee) as a colourless oil. $[\alpha]^{30}_D$ = +22.1 (EtOAc); IR (film) 2981 (CH_3), 1749 (C=O), 1296 (C-O), 750 (ArH) cm^{-1}; ^{1}H 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 $CO_2CH_2CH_3$), 3.90 (1H, dd, *J* = 6.0, 8.4 Hz, H-4), 3.30 (1H, dd, *J* = 4.9, 14.0 Hz, -C*H*Ar), 3.23 (1H, dd, *J* = 7.6, 14.0 Hz, C*H*Ar), 1.24 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.15 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz,$CDCl_3$) 160.9 (1C, $CO_2CH_2CH_3$), 160.8 (1C, $CO_2CH_2CH_3$), 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, $CO_2CH_2CH_3$), 62.5 (1C, $CO_2CH_2CH_3$), 62.2 (1C, C-3), 53.9 (1C, C-4), 40.4 (1C, -CH_2Ar), 14.4 (1C, $CO_2CH_2CH_3$), 14.3 (1C, $CO_2CH_2CH_3$); 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-diazetidine (1 molar equiv.) in THF at -78 ºC 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 NH_4Cl (1 mL). After warming to room temperature, Et_2O (2 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification on silica gel (ethyl acetate in hexane) afforded the desired product.

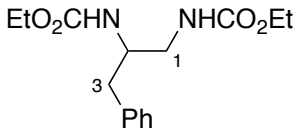
(*S*)-Diethyl propane-1,2-diylbiscarbamate ((*S*)-290



(*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 ºC; IR (neat) 3308 (N-H), 2980 (CH_3), 1681 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), 5.28 (1H, br s, NH), 5.02-5.11 (1H, br m, NH), 4.02-4.10 (4H, m, $CO_2CH_2CH_3$), 3.77 (1H, br m, H-2), 3.15-3.29 (2H, m, H-1), 1.19 (6H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 1.12 (3H, d, J = 6.7 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 157.4 (1C, $CO_2CH_2CH_3$), 156.6 (1C, $CO_2CH_2CH_3$), 60.9 (1C, $CO_2CH_2CH_3$), 60.7 (1C, $CO_2CH_2CH_3$), 47.6 (1C, C-2), 46.4 (1C, C-1), 18.4 (1C, C-3), 14.6 (2C, $CO_2CH_2CH_3$); MS (ES^+) m/z = 241 $[M+Na]^+$, HRMS (ES^+) m/z calculated for $C_9H_{18}N_2O_4Na$ $[M+Na]^+$: 241.1159; found: 241.1157.

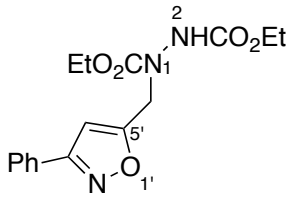
Diethyl (3-phenylpropane-1,2-diyl)biscarbamate (291)



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. $[\alpha]^{30}_D$ = +24.0 (EtOAc); M.p 87.1-87.9 ºC; IR (neat) 3322 (N-H), 2980 (CH_3), 1684 (C=O), 1262 (C-O), 751 (ArH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.18 (5H, m, ArH), 4.94 (2H, br s, NH), 4.05-4.13 (4H, m, $CO_2CH_2CH_3$), 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, $CO_2CH_2CH_3$), 1.21 (3H, t, J = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) 157.4 (1C, $CO_2CH_2CH_3$), 156.6 (1C, $CO_2CH_2CH_3$), 137.3 (1C, ArC), 129.2 (2C, ArCH), 128.7 (1C, ArCH), 126.7 (2C, ArCH), 61.1 (1C, $CO_2CH_2CH_3$), 60.9 (1C, $CO_2CH_2CH_3$), 53.1 (1C, C-2), 44.2 (1C, C-1), 38.9 (1C, C-3), 14.6 (2C,

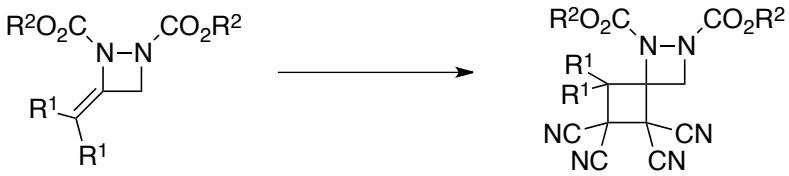
$CO_2CH_2CH_3$); MS (ES^+) *m/z* = 295 $[M+H]^+$, HRMS (ES^+) *m/z* calculated for $C_{15}H_{23}N_2O_4$ $[M+H]^+$: 295.1652; found: 295.1647.

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



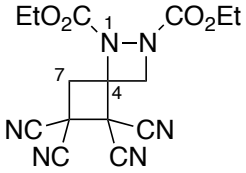
To a stirred solution of **251** (100 mg, 0.47 mmol), in CH_2Cl_2 (3 mL) was added phenyl hydroximoyl chloride (87 mg, 0.56 mmol) in CH_2Cl_2 (2 mL). The reaction was allowed to reach room temperature, stirred for 24 h then concentrated *in vacuo*. Purification on silica gel (20% ethyl acetate in hexane) afforded **300** (87 mg, 56%) as a white crystalline solid. M.p 57.1-58.1 ºC; IR (neat) 3286 (N-H), 2978 (CH_3), 1681 (C=O), 1208 (N-O), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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, NCH_2Ar), 4.15-4.25 (4H, br m, $CO_2CH_2CH_3$), 1.25 (6H, br m, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 168.2 (1C, C-5'), 162.6 (2C, $CO_2CH_2CH_3$), 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, $CO_2CH_2CH_3$), 62.3 (1C, $CO_2CH_2CH_3$), 45.5 (1C, NCH_2Ar), 14.4 (2C, $CO_2CH_2CH_3$); MS (ES^+) *m/z* = 356 $[M+Na]^+$, HRMS (ES^+) *m/z* calculated for $C_{16}H_{19}N_3O_5Na$ $[M+Na]^+$: 356.1217; found: 356.1221.

General Procedure 6



To a solution of 3-methylene-1,2-diazetidine (1 molar equiv.) in CH_2Cl_2 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)

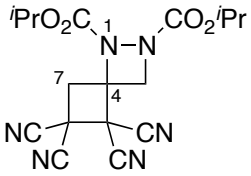


303 was synthesised according to General Procedure 6 with the following: **251** (0.05 g, 0.23 mmol), tetracyanoethylene (0.03 g, 0.23 mmol) and CH_2Cl_2 (3 mL). Recrystallisation from ethyl acetate afforded **303** (0.067 g, 98%) as a white crystalline solid. M.p. 184.3-185.1 °C; IR (neat) 2985 (CH_3), 1718 (C=O), 1269 (C-O) cm^{-1}; ^1H NMR (400 MHz, CD_3CN), 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 $CO_2CH_2CH_3$), 3.71 (1H, d, J = 15.9 Hz, H-7), 1.35 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 1.31 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR[i] (100 MHz, CD_3CN) 159.1 (1C, $CO_2CH_2CH_3$), 155.2 (1C, $CO_2CH_2CH_3$), 111.2 (1C, CN), 110.7 (1C, CN), 108.4 (1C, CN),

[i] Only one carbon observed for C-5/C-6

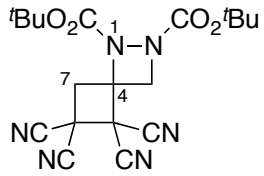
107.8 (1C, CN), 68.3 (1C, C-4), 63.3 (1C, $CO_2CH_2CH_3$), 62.7 (1C, $CO_2CH_2CH_3$), 57.7 (1C, C-3) 40.6 (1C, C-7), 31.4 (1C, C-5 or C-6), 13.3 (1C, $CO_2CH_2CH_3$), 13.3 (1C, $CO_2CH_2CH_3$); MS (ES^+) *m/z* = 365 $[M+Na]^+$, HRMS (ES^+) *m/z* calculated for $C_{15}H_{14}N_6O_4Na$ $[M+Na]^+$: 365.0969; 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 CH_2Cl_2 (3 mL). Recrystallisation from ethyl acetate afforded **305** (59 mg, 80%) as a white crystalline solid. M.p. 172.1-172.9 ºC; IR (neat) 2986 (CH_3), 1704 (C=O), 2365 (-CN) 1285 (C-O) cm^{-1}; ^1H NMR (400 MHz, CD_3CN) 5.12 (1H, sept, *J* = 6.4 Hz, $CO_2CH(CH_3)_2$), 4.99 (1H, sept, *J* = 6.3 Hz, $CO_2CH(CH_3)_2$), 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, $CO_2CH(CH_3)_2$), 1.31 (6H, t, *J* = 6.3 Hz, $CO_2CH(CH_3)_2$); ^{13}C NMR[i] (400 MHz, CD_3CN) 158.8 (1C, $CO_2CH(CH_3)_2$), 154.4 (1C, $CO_2CH(CH_3)_2$), 111.2 (1C, CN), 110.8 (1C, CN), 108.5 (1C, CN), 107.3 (1C, CN), 72.1 (1C, $CO_2CH(CH_3)_2$), 71.0 (1C, $CO_2CH(CH_3)_2$), 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, $CO_2CH(CH_3)_2$), 20.6 (2C, $CO_2CH(CH_3)_2$); MS (ES^+) *m/z* = 393 $[M+Na]^+$, HRMS (ES^+) *m/z* calculated for $C_{17}H_{18}N_6O_4Na$ $[M+Na]^+$: 393.1282; found: 393.1284.

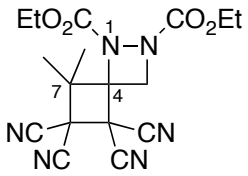
Di-*tert*-butyl-5,5,6,6-tetracyano-1,2-diazaspiro[3.3]heptane-1,2-dicarboxylate (304)



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_2Cl_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}; ^1H 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[i] (100 MHz, $CO(CD_3)_2$) 159.9 (1C, $CO_2C(CH_3)_3$), 154.7 (1C, $CO_2C(CH_3)_3$), 112.6 (1C, CN), 112.1 (1C, CN), 110.3 (1C, CN), 109.3 (1C, CN), 84.9 (1C, $CO_2C(CH_3)_3$), 83.5 (1C, $CO_2C(CH_3)_3$), 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, $CO_2C(CH_3)_3$), 28.1 (3C, $CO_2C(CH_3)_3$); MS (ES^+) m/z = 421 $[M+Na]^+$, HRMS (ES^+) m/z calculated for $C_{19}H_{22}N_6O_4Na$ $[M+Na]^+$: 421.1595; found: 421.1593.

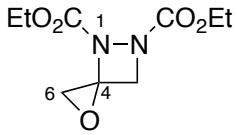
[i] Only one carbon observed for C-5/C-6

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 CH_2Cl_2 (3 mL). Recrystallisation from ethyl acetate afforded **306** (30 mg, 39%) as a white crystalline solid. M.p. 137.7-138 ºC; IR (neat) 2989 (CH_3), 2333 (-CN), 1756 (C=O), 1270 (C-O) cm^{-1}; ^1H NMR (400 MHz, CD_3CN) 4.38-4.50 (3H, m, $CO_2CH_2CH_3$, H-3), 4.22-4.31 (3H, m, $CO_2CH_2CH_3$, H-3), 1.72 (3H, s, $>C(CH_3)_2$), 1.63 (3H, s, $>C(CH_3)_2$), 1.35 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 1.31 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, CD_3CN) 159.2 (1C, $CO_2CH_2CH_3$), 153.8 (1C, $CO_2CH_2CH_3$), 109.8 (1C, CN), 109.5 (1C, CN), 109.1 (1C, CN), 107.3 (1C, CN), 76.3 (1C, C-4), 63.0 (1C, $CO_2CH_2CH_3$), 62.9 (1C, $CO_2CH_2CH_3$), 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, $>C(CH_3)_2$), 20.9 (1C, $>C(CH_3)_2$), 13.3 (1C, $CO_2CH_2CH_3$), 13.2 (1C, $CO_2CH_2CH_3$); MS (ES^+) m/z = 393 $[M+Na]^+$, HRMS (ES^+) m/z calculated for $C_{17}H_{19}N_6O_4$ $[M+Na]^+$: 371.1462; found: 371.1465.

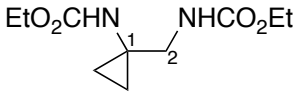
Diethyl 5-oxa-4,5-diazaspiro[2.3]-1,2-dicarboxylate (310)



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 ºC. $NaHCO_3$ (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 ºC. 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_2Cl_2 (1 mL) at 0 ºC. 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}; ^1H 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, $CO_2CH_2CH_3$), 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, $CO_2CH_2CH_3$), 1.29 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 160.8 (1C, $CO_2CH_2CH_3$), 156.8 (1C, $CO_2CH_2CH_3$), 71.2 (1C, C-4), 63.2 (1C, $CO_2CH_2CH_3$), 62.9 (1C, $CO_2CH_2CH_3$), 56.4 (1C, C-3), 47.5 (1C, C-6), 14.3 (1C, $CO_2CH_2CH_3$), 14.3 (1C, $CO_2CH_2CH_3$); MS (ES^+) *m/z*

= 253 $[M+Na]^+$, HRMS (ES^+) *m/z* calculated for $C_9H_{14}N_2O_5Na$ $[M+Na]^+$: 253.0795; found: 253.0795.

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



To a stirred solution of **251** (150 mg, 0.70 mmol) in CH_2Cl_2 (4 mL), was added CH_2CI_2 (282 μL, 3.5 mmol) followed by $ZnEt_2$ (3.5 mL, 3.5 mmol, 1M in hexanes) and the reaction was stirred at 25 ºC for 24 h. The reaction was quenched with $NH_4Cl_{(aq)}$ (2 mL) and extracted with CH_2Cl_2 (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 ºC 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, $CDCl_3$) 5.61 (1H, br s, NH), 5.10 (1H, br s, NH), 4.07-4.13 (4H, m, $CO_2C\underline{H_2}CH_3$), 3.28 (2H, br m, H-2), 1.24 (6H, t, *J* = 7.0 Hz, $CO_2CH_2C\mathit{H_3}$), 0.83 (4H, br s, 4H, $C\mathit{H_2}C\mathit{H_2}$); MS ($ES^+$) *m/z* = 253 $[M+Na]^+$, HRMS (ES^+) *m/z* calculated for $C_{10}H_{19}N_2O_4$ $[M+H]^+$: 231.1339; found: 231.1430.

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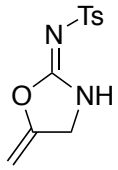
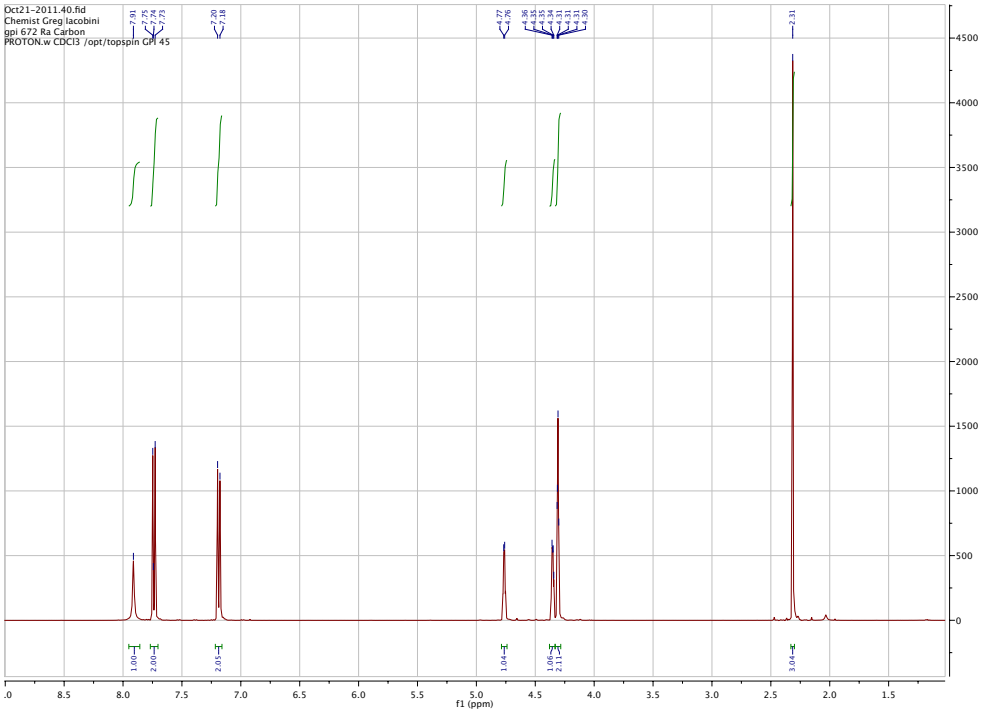
Appendix

Appendix 1

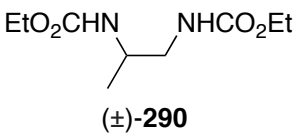
^{1}H NMR spectra (400 MHz) of **235**



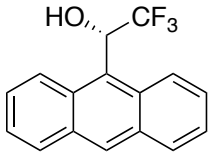


Appendix 2

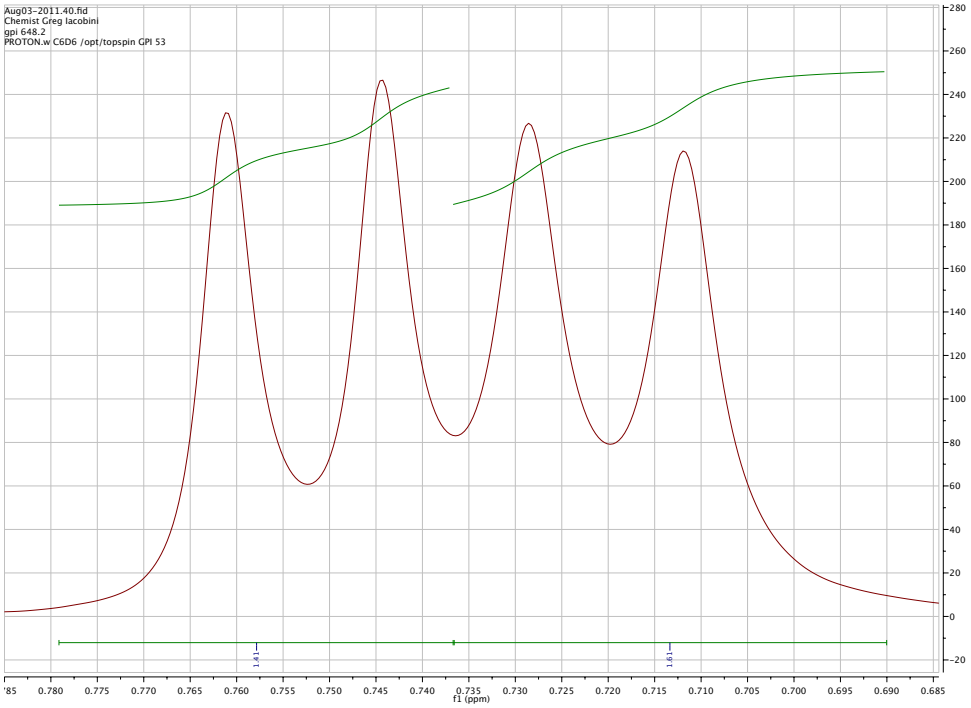
^{1}H NMR Spectra (400 MHz) of (±)-**290** in the presence (*S*)-(+)-1-(9-Anthryl)-2,2,2-trifluoroethanol (focused on methyl group splitting).



(±)-**290**

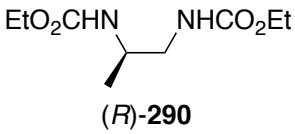


Pirkle's alcohol
(*S*)- (+)-1-(9-Anthryl)-2,2,2-trifluoroethanol

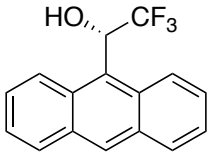


Appendix 2

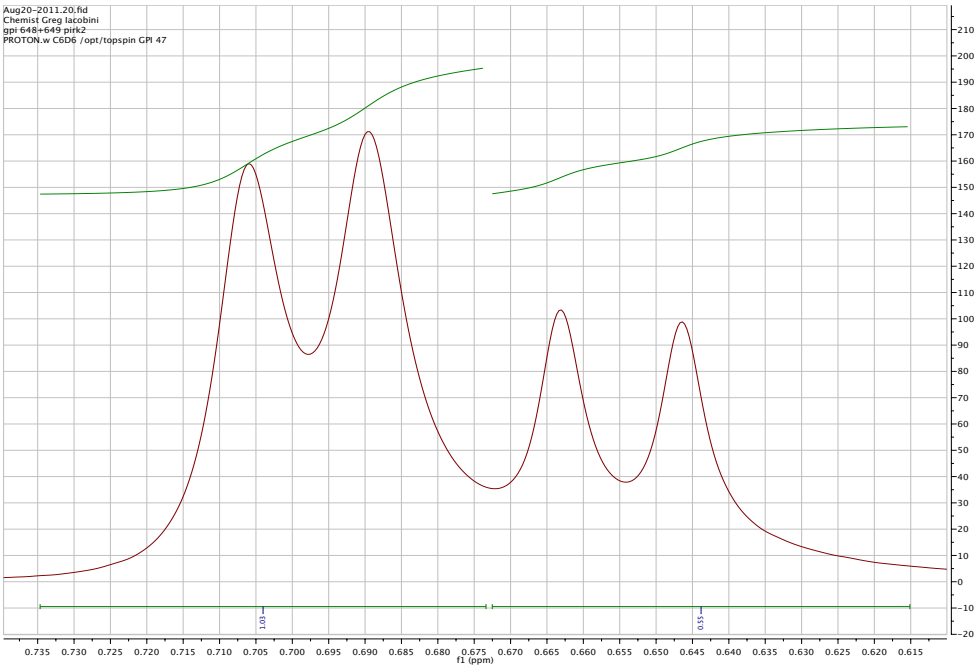
^{1}H NMR Spectra (400 MHz) of (*R*)-**290** in the presence (*S*)-(+)-1-(9-Anthryl)-2,2,2-trifluoroethanol spiked with (±)-**290** (focused on methyl group splitting).



(*R*)-**290**

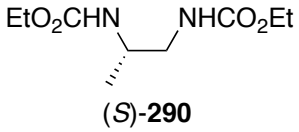


Pirkle's alcohol
(*S*)- (+)-1-(9-Anthryl)-2,2,2-trifluoroethanol

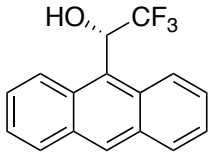


Appendix 2

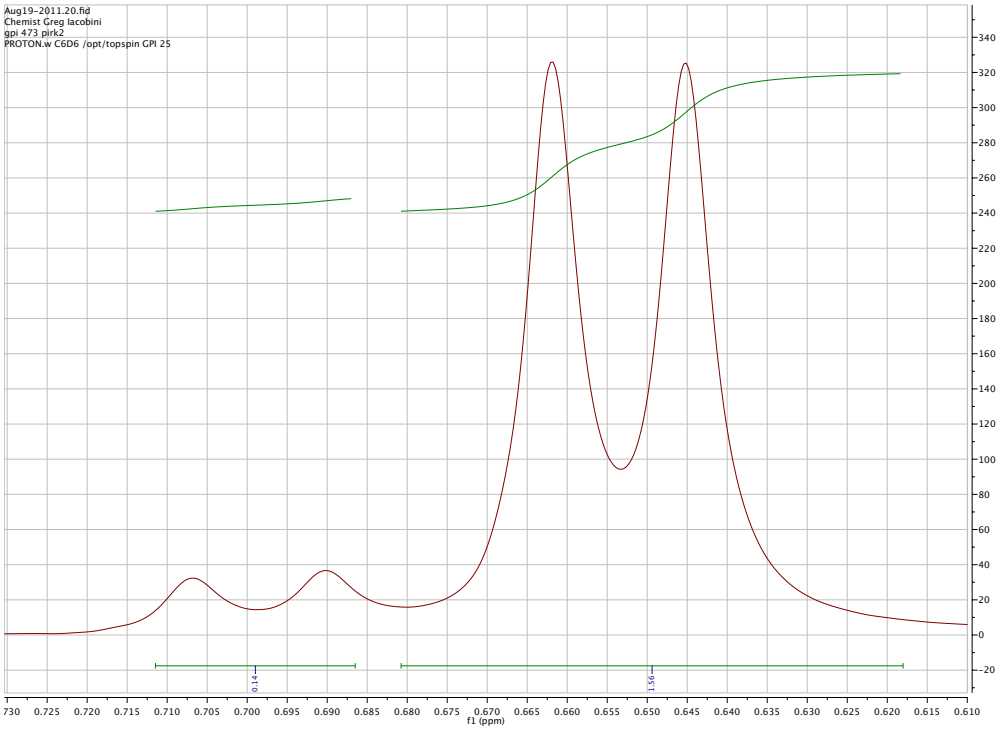
^{1}H NMR Spectra (400 MHz) of (*S*)-**290** in the presence (*S*)-(+)-1-(9-Anthryl)-2,2,2-trifluoroethanol (focused on methyl group splitting).



(*S*)-**290**

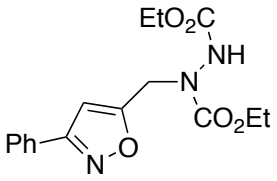


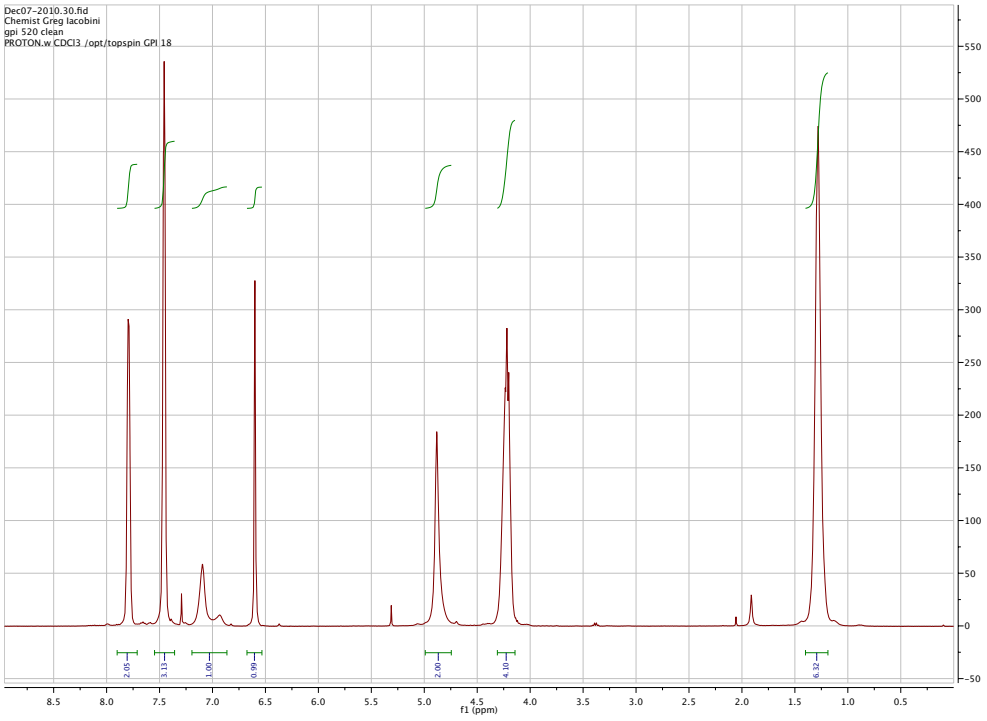
Pirkle's alcohol
(*S*)- (+)-1-(9-Anthryl)-2,2,2-trifluoroethanol



Appendix 3

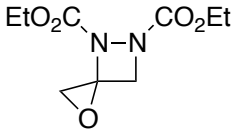
^{1}H NMR (400 MHz) spectra of **300**

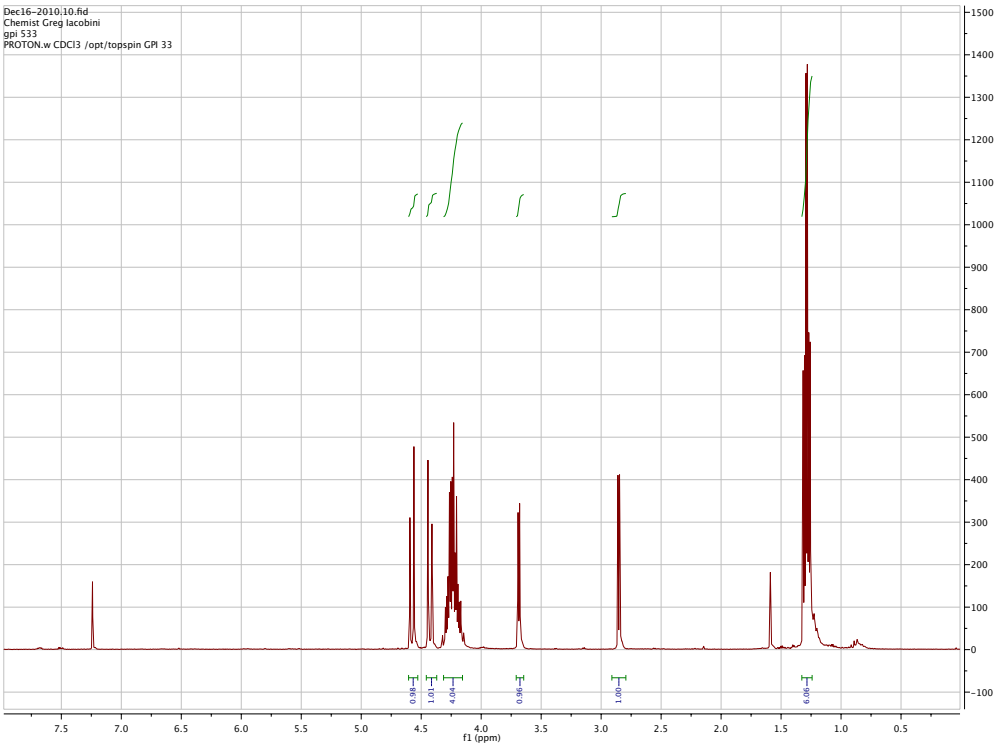




Appendix 4

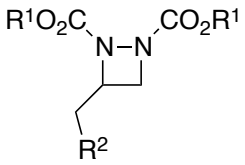
^{1}H NMR Spectrum of **308**





Appendix 5

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



substrate	R^1	R^2	^{i}PrOH (%)	1st peak rt (min)	2nd peak rt (min)
280	Et	H	03	20.96	23.44
284	^{t}Bu	H	01	9.20	9.93
282	Et	Ph	05	17.83	20.74
285	Et	$C_6H_4{}^{t}Bu$	05	14.65	19.58
286	Et	Naphthyl	04	16.02	18.64
287	Et	C_6H_4OMe	02	30.22	32.67