The Generation and Reactivity of Functionalised Organozinc Carbenoids for Cyclopropane Synthesis

A Thesis Presented by

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Declaration

I, Laure Jerome, confirm that the work presented in this thesis is, to the best of my knowledge, my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

This thesis describes the generation and reactivity of functionalised organozinc carbenoids for cyclopropane synthesis with alkenes.

In the introductory chapter, a brief overview of the different methods for preparation of heteroatom-functionalised cyclopropanes is presented, including [2+1] cycloaddition reactions using a carbene or carbenoid as a cyclopropanating agent with an alkene, ionic stepwise methods, and chemical modifications from existing cyclopropanes. The remainder of this chapter then focuses on previous work within our own group in this area.

The second chapter presents the results obtained from different areas of research in the present study, the first of these being a deeper understanding and extension of the research work undertaken by my predecessor for the development of the cyclopropanation reaction using an "amidoorganozinc" carbenoid derived from *N*,*N* diethoxymethyloxazolidinones derivatives in the presence of a source of zinc and chlorotrimethylsilane. Thus, the chemoselectivity and stereoselectivtity of the reaction were fully studied, and a quadrant model was constructed to rationalise the stereochemistry of the products obtained. The second part of this section outlines the generation of new enantiopure organozinc carbenoids precursors derived from substituted chiral precursors followed by the synthesis of novel enantiopure highly functionalised *N*-cyclopropyl oxazolidinones. The intramolecular version of this cyclopropanation reaction was then successfully studied using diethoxylactam derivatives as organozinc carbenoid precursors. The methodology was then applied to the preparation of novel aminocyclopropyl functionalised compounds selected as interesting building blocks which can lead to the synthesis of natural and biologically active compounds. The fifth part of this chapter describes subsequent studies towards the design of new carbenoid precursors containing additional functional groups of interest. Finally, a brief study on the potential of an organozinc carbenoid to participate in a novel [2,3] sigmatropic rearrangement was investigated.

The thesis concludes with a summary of the results obtained, a detailed description of the experimental procedures used and the characterization and analysis of the compounds prepared, together with a full bibliography.

Contents

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Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
^{t}Bu	*tert*-butyl
c	cyclo
cap	caprolactam
cat.	catalytic
CFA	cyclopropane fatty acid
CI	chemical ionisation
Cp	cyclopentadienyl
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DMAP	dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
eq.	molar equivalents
EI	electron impact
Et	ethyl
ESI	electronspray ionisation
EWG	electron withdrawing group
FAB	fast atom bombardment

Fmoc	fluorenylmethyloxycarbonyl
FT	Fourier transform
g	gram(s)
G.C.	gas chromatography
h	hours
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infra red
J	coupling constant
L	unspecified ligand
L.A.	Lewis acid
lit.	literature value
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet
M	metal
Me	methyl
min	minutes
ml	millilitre(s)
mg	milligram(s)
m.p.	melting point
NADPH	nicotinamide adenine dinucleotide phosphate
NaHMDS	sodium bis(trimethylsilyl)amide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
OPP	pyrophosphate
p	*para*
PMB	*para* methoxybenzyl
PMP	*para* methoxyphenyl
Ph	phenyl
ppm	parts per million
^{i}Pr	*iso* propyl
Py	pyridine
R	unspecified carbon substituent
r.t.	room temperature

s	singlet
t	triplet
T	temperature
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
q	quartet
qn	quintet

Chapter 1: Introduction

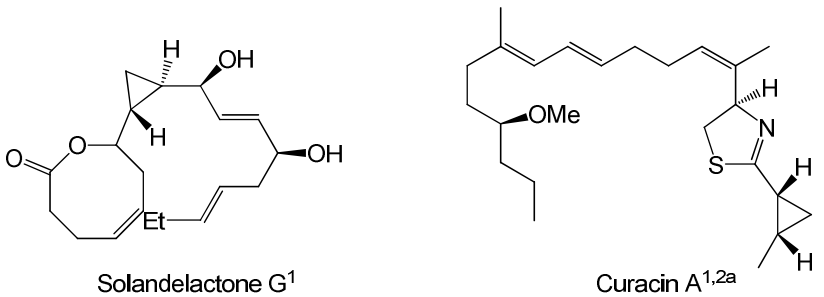
1.0. Introduction

1.0.1. Background

The present thesis is concerned with the synthesis of heteroatom functionalised cyclopropanes and, in particular, aminocyclopropanes. For this reason, in the following introductory chapter, it is appropriate to provide a brief review of the synthetic methods which have been used in their construction. In a second section a concise overview of the chemistry which has been developed within our own group on the properties and reactivity of organozinc carbenoids will also be presented.

1.0.2. Occurrence in nature and biosynthesis

As reported in a review by Donaldson[1], the cyclopropyl unit is present in a large number of biologically active natural products and pharmaceuticals.[1,2] Two examples are illustrated below (Figure 1).



Solandelactone G[1]

1

Curacin A[1,2a]
antimitotic agent

2

Figure 1

Heteroatom-substituted cyclopropanes are also present in a wide range of biologically active natural and unnatural compounds as illustrated below by the natural immunosuppressant and antibacterial belactosin A **3**[3] and the alkoxycyclopropane **4**, a potential inhibitor of PDE4 which is an isozyme present in abundance in inflammatory and immune cells,[4] and **5**, an agonist for group II metabotropic glutamate receptors.[5] The heteroatom-substituted cyclopropanes are used extensively in medicinal chemistry programmes due to their unique steric and electronic properties and their ability to

function as alkene bioisosteres without the associated metabolitic lability. Perhaps the most abundant naturally-occurring cyclopropyl compound is the aminocyclopropane carboxylic acid **6**, a gem-disubstituted cyclic amino acid which is a key intermediate in the production of the plant hormone ethylene (Figure 2).[2]

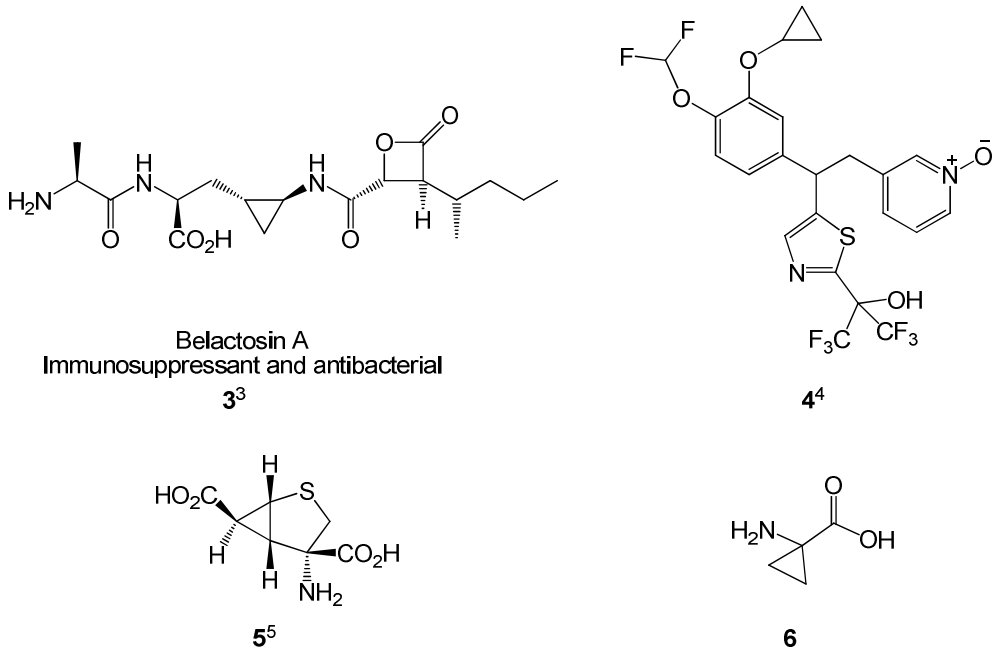
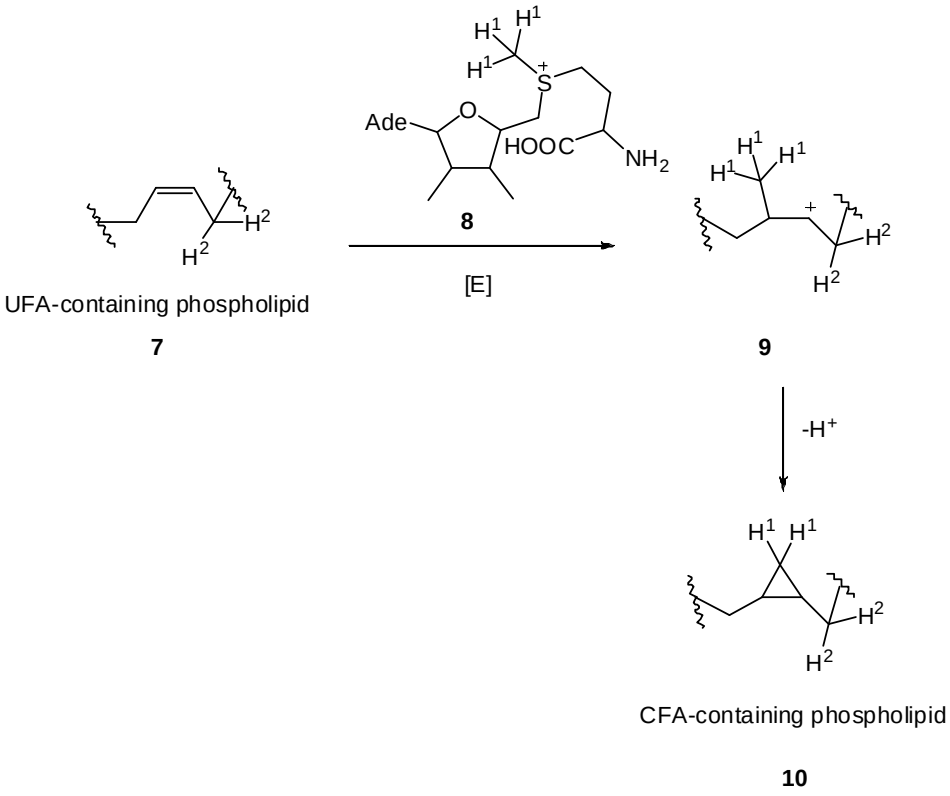


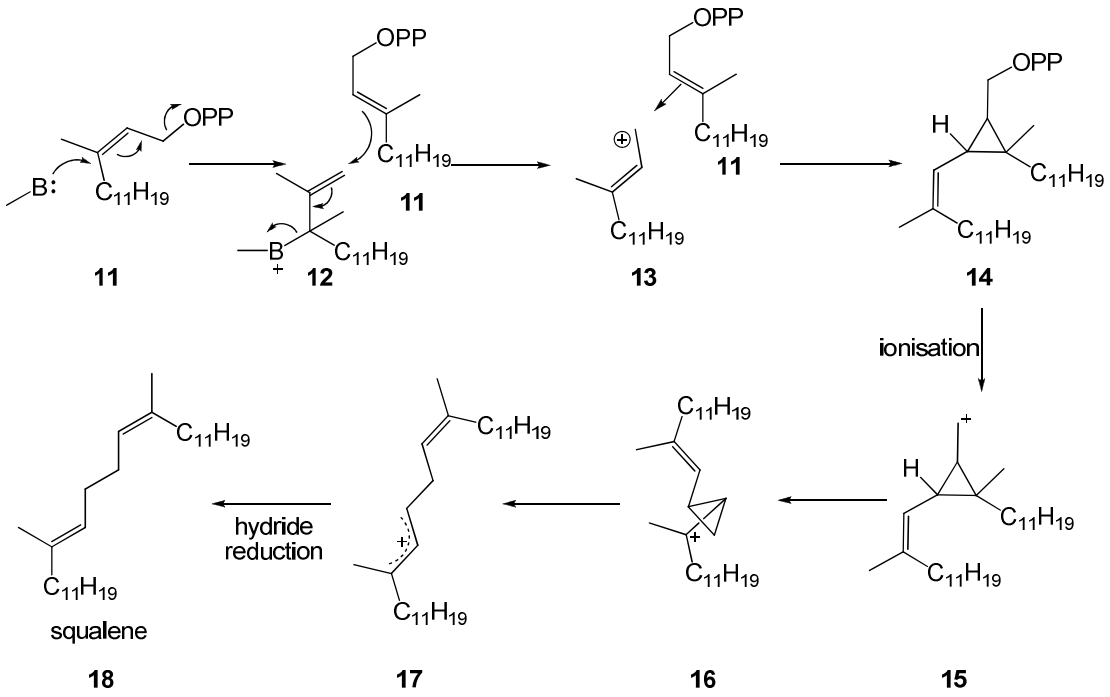
Figure 2

Although the synthetic chemist has yet to rival nature, it is interesting to comment on some studies in this area. Thus a biosynthetic pathway for the synthesis of the cyclopropyl ring has been described by Cronan Junior *et al*. for the conversion of an unsaturated fatty acid (UFA) of the membrane lipid of bacteria into a cyclopropane fatty acid (CFA) in membrane lipids of bacteria by a 1,3 ring closure reaction. This catalytic insertion of a "methylene group" from AdoMet to a double bond enables the *in situ* modification of the bacteria's lipidic membrane (Scheme 1).[6]



Scheme 1

Moreover, it has also been reported that the synthesis of squalene, an intermediate in the biosynthesis of cholesterol, proceeded following a sequence of reactions including the formation of a cyclopropane ring as a key intermediate. The mechanism of this transformation involved farnesyl pyrophosphate as the starting material (Scheme 2).[7]



Scheme 2

An enzyme containing a thiol group attacks **11** by nucleophilic substitution to form **12** which reacts with another molecule of **11** to form the "Π complex **13**". The loss of a proton from **13** leads to **14** which undergoes ionisation to give the primary carbocation **15**. Rearrangement leads to the formation of the tertiary carbocation **16** which can undergo ring opening to **17**, which after reduction affords squalene **18**. In the absence of the reducing agent NADPH, squalene is not formed and the cyclopropane can be isolated.[8]

1.0.3. Synthetic studies

The cyclopropyl unit has a wide appeal due to its occurrence in natural products as well as its use in synthetic and medicinal chemistry. As such, there have been numerous synthetic studies in the literature. They can be formed by photochemical reactions and enzymatic approaches, but in order to aid clarity in the discussion, we will focus in this section on the formation of heteroatom-substituted cyclopropanes. Three distinct approaches can be taken for the construction of heteroatom-functionalised cyclopropanes: by carbene and carbenoid [2+1] cycloaddition with an alkene, by ionic stepwise methods, or by functional group manipulation of existing cyclopropanes.

1.1. Carbenes and carbenoids

A cyclopropane can be obtained by [2+1] cycloaddition between a carbene or carbenoid and an alkene. In this section, carbenes and carbenoids will be discussed as a function of the method used to generate them, followed by an overview of the methods available for the synthesis of heteroatom-substituted cyclopropanes using a carbene or a carbenoid.

1.1.1. Carbenes as cyclopropanating agents

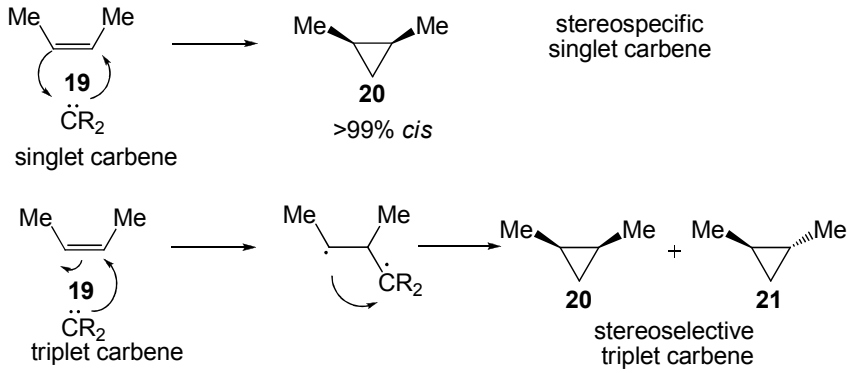
Carbenes are neutral species containing a carbon atom with 6 valence electrons: with two pairs involved in the two σ bonds and two further nonbonding electrons. Carbenes are electron-poor entities which require another pair of electrons to complete their valence shell of electrons. Like carbocations, they are electrophilic but they are, of course, uncharged. This has consequences for the type of nucleophiles with which carbenes choose to react. Carbenes may therefore react with compounds that would not normally be considered as nucleophiles, such as simple alkenes, by taking electrons from the available HOMO.[8]

Carbenes may be subdivided into two classes due to the two possible arrangements of electrons in the empty shells (spin states) which are termed triplet and singlet. The orbitals are the same in both cases but triplet carbenes have two unpaired electrons, one in each of the sp^2 and p orbitals, whilst singlet carbenes have a pair of electrons in the nonbonding sp^2 orbital and also possess a vacant p orbital (Figure 3).[8]

triplet carbene singlet carbene

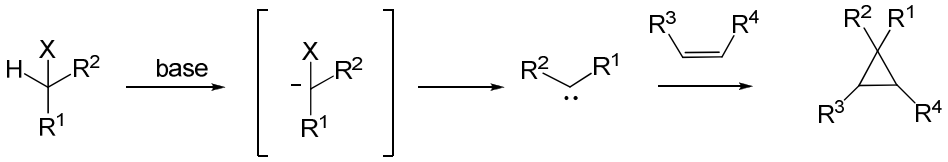
Figure 3

Carbene species react with alkenes to give a cyclopropane in two distinct ways depending on the electronic character of the carbene. Singlet carbenes add stereospecifically to alkenes and triplet carbenes react as diradicals and hence can give rise to nonstereospecific additions to alkenes (Scheme 3).



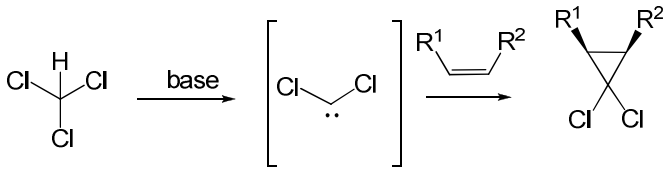
Scheme 3

A singlet carbene can readily be obtained by treatment of an appropriate substrate *via* deprotonation with a base and α-elimination of the leaving group X from the same carbon. The resulting species can cyclopropanate an alkene by a [2+1] cycloaddition reaction as shown below (Scheme 4).



Scheme 4

In 1862 Geuther reported on the use of haloforms as dihalocarbene precursors.[9] The mechanism involving the α-elimination of chloroform by treatment with a base to give dichlorocarbene was described in 1950.[10] The α-elimination process is more facile if the substituents are capable of delocalising the negative charge. The reaction of a dichlorocarbene, formed *in situ* with an olefin leads stereospecifically to a dichlorocyclopropane (Scheme 5).[11,12,13]

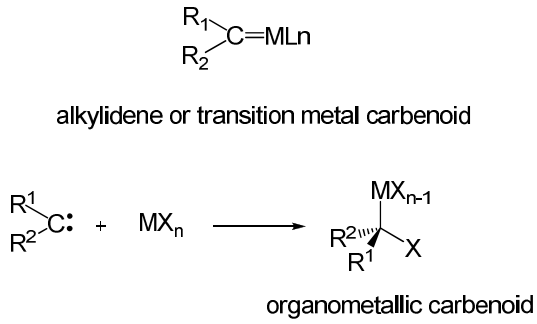


Scheme 5

Carbene reactivity increases as a function of the number of substituents and their increasing electronegativity, confirming their proposed electrophilic character and decreases with simple alkenes following the order tetra>tri>unsym-di>sym- di>mono alkyl substituted.[10] In general *syn* (*anti*) addition occurs in most cases, except where a carbene is substituted with a heavy halogen atom. The reaction of cyclic strained alkenes may induce rearrangements and the cyclopropane product is often not isolable.[14]

1.1.2. Carbenoids as cyclopropanating agents

Free carbenes are typically highly reactive and are hence short-lived species. However, they can be stabilised by a metal making them more suitable for synthetic purposes as outlined below. In contrast to carbenes, carbenoids are defined as carbon species bonded to a metal and a leaving group. There are three principal sources of metallocarbenoid precursors: geminal haloalkanes used in the presence of metals, diazo compounds used in conjunction with transition metals such as rhodium, copper or palladium and Fisher carbenes as metal carbenoids. Those carbenoids formed from transition metals with available vacant d orbitals are often called alkylidenes (Scheme 6).[8]

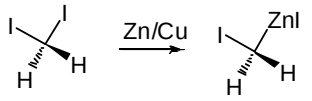


Scheme 6

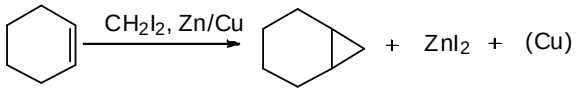
1.1.2.1. Simmons-Smith reaction

The most famous method for the stereospecific cyclopropanation of unsaturated compounds using a metallocarbenoid precursor such as a geminal dihaloalkane in the presence of a metal is the Simmons-Smith reaction discovered in 1958 using an organozinc carbenoid.

The reagent is derived from the reaction between diiodomethane and a source of zinc. (Scheme 7).[15]



the Simmons-Smith reagent

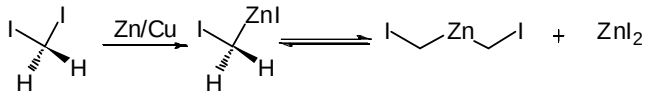


22 **23**

the Simmons-Smith reaction

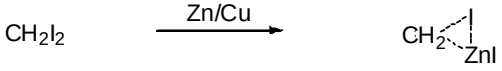
Scheme 7

The key intermediate may be involved in a Schlenk type equilibrium (Scheme 8).



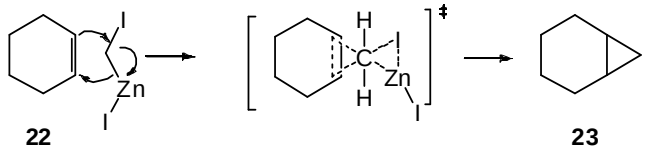
Scheme 8: Structure of the Simmons-Smith reagents

The reaction is stereospecific, with respect to the geometry of the alkene. Studies indicated that diiodomethane forms a 1:1 complex with zinc (from a zinc-copper couple) which is capable of forming cyclopropanes with alkenes. A representation of the complex was proposed as shown below (Scheme 9).[8]



Scheme 9

The mechanism of this reaction has often been represented as proceeding *via* a "butterfly-type" transition state (Scheme 10).[8]

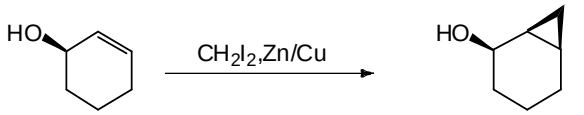


22 **23**

Scheme 10

The zinc carbenoid reagent will behave as a weak electrophile and react more readily with electron-rich olefins.

The cyclopropanation of a chiral allyl alcohol using the Simmons-Smith reaction is highly stereoselective with the new methylene group adding to the same face of the double bond as the alcohol group (Scheme 11).[8]



24 **25**

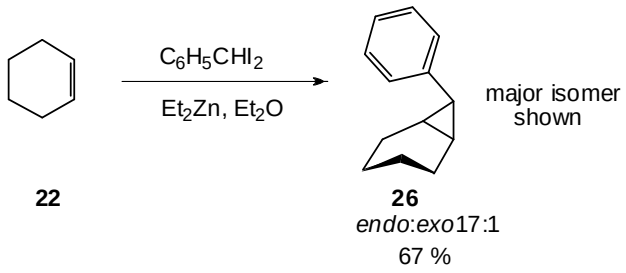
63%
d.r. >99%

Scheme 11

Numerous variants of the original Simmons-Smith method have been reported in the literature, including the use of $Zn/CuCl/CH_2I_2$,[16] Zn(Ag) couple/CH_2I_2,[17] $Zn/TiCl_4/CH_2Br_2$,[18] $Zn/AcCl/CuCl/CH_2Br_2$[19] and Zn/CH_2Br_2 under sonication[20] in order to improve the reaction time and yields.

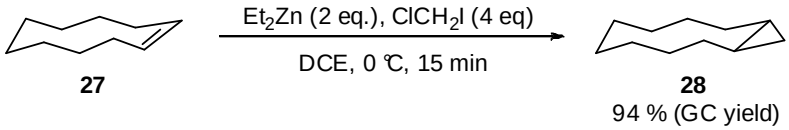
To avoid use of heterogeneous conditions, Furukawa demonstrated that a cyclopropanating agent could be generated by an alkyl exchange reaction between diethyl zinc and a 1,1-dihaloalkane.[21] The additional major advantages of Furukawa's homogeneous system are that reagent formation is rapid under mild conditions, the reaction is suitable for the cyclopropanation of vinyl ethers and similar substrates that often undergo polymerisation under classic Simmons-Smith conditions, and finally that the reaction is not restricted to the formation of a non-functionalised cyclopropane and

thus can be applied to a wider range of reagents.[21] For example, the reaction between cyclohexene and 1,1-diiodomethylbenzene gives a mixture of *endo* and *exo* isomers of a functionalised cyclopropane (Scheme 12).



Scheme 12

In a detailed study, Denmark and Edwards found that the (chloromethyl)zinc reagent, prepared from $ClCH_2I/Et_2Zn$, was even more reactive that the (iodomethyl)zinc analogue (Scheme 13).[22]

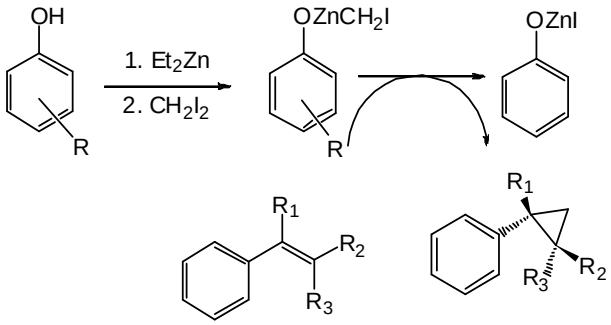


Scheme 13

Compound **28** was obtained in 94% yield (according to GC analysis) compared to the 12% obtained using CH_2I_2 as the dihalo compound under the same conditions.[22]

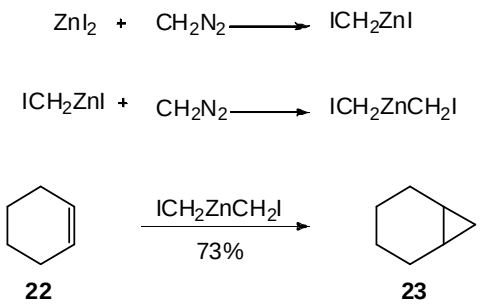
Different studies were carried out on the organozinc reagents by Shi *et al.* who demonstrated that when the acidity of RXH increased, the reactivity of the novel organozinc species increased. Thus $CF_3CO_2ZnCH_2I$ as a cyclopropanating agent is generally very effective.[23]

In a similar manner Charette *et al.* studied the reactivity of new reagents with $ArOZnCH_2I$ (RX = ArO) and found that carbenoids possessing electron-withdrawing groups on the aromatic ring (F, Cl or Br in position 2, 4 and 6) also gave cyclopropanes in higher yields (Scheme 14).[24]



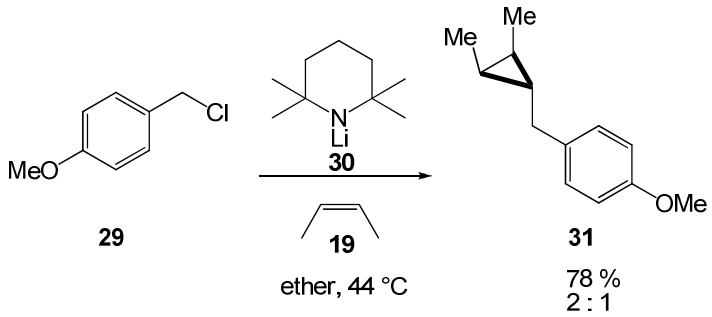
Scheme 14

Finally, it is interesting to note that Wittig reported a method for the generation of Simmons-Smith like reagents using diazoalkanes and zinc iodide. The cyclopropanating agent is formed by the addition of diazomethane to a suspension of zinc(II) halide (Scheme 15).[25]



Scheme 15

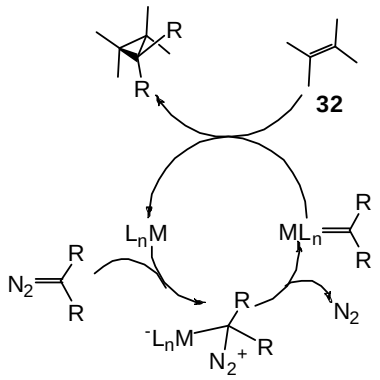
Other metals than zinc can also be used to generate metallocarbenoids for cyclopropanation reactions. Organolithium carbenoid can probably be formed *in situ* by an α-elimination of a primary alkyl halide such as **29** with a lithium base to induce a cyclopropanation reaction. The intermediate can trap an alkene to form a cyclopropane. Thus, cyclopropane **31** was obtained in 78% in a 2:1 *syn*/*anti* ratio, by reaction of *p*-methoxybenzylchloride **29** with *cis*-butene **19** in the presence of LiTMP **30** at reflux (Scheme 16).[26]



Scheme 16

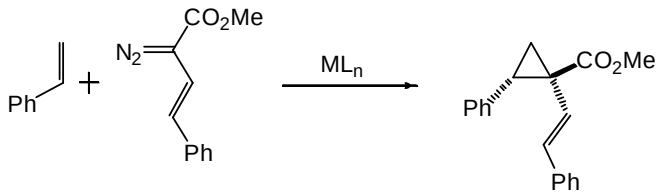
1.1.2.2. Diazoalkanes as cyclopropanating agents

Diazoalkanes can be used as carbenoid precursors and more specifically, diazomethane can transfer a methylene group to an alkene double bond *via* a metal catalysed reaction to form a cyclopropane. The process can be applied to a wide range of alkenes. Different metal catalysts, either chiral or achiral, such as copper, palladium, or rhodium have all been used for cyclopropanation using diazomethane. The transition metal catalyst reacts initially with the diazo compound liberating N_2, thus generating a transient electrophilic carbenoid which is most often represented in the alkylidene form (Scheme 17).[27,28]



Scheme 17

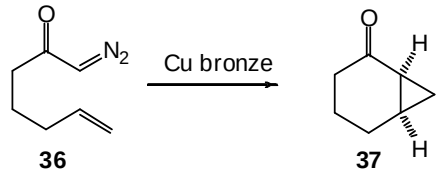
In general, α-diazoketones or α-diazoesters are more commonly employed as diazoalkanes to carry out cyclopropanation reactions, as they are sufficiently reactive, but much less dangerous to handle. The reaction is mediated by a wide range of chiral or non-chiral catalysts containing metals such as copper, palladium, rhodium, cobalt, ruthenium or osmium (Scheme 18).[29]



33 **34** **35**

Scheme 18

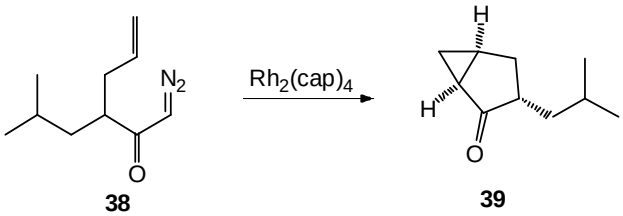
The first intramolecular version of a cyclopropanation reaction using a diazoketone was published by Stork in 1961 using copper to obtain compound **37** (Scheme 19).[30]



36 **37**

Scheme 19

Different examples using copper catalysts for the intramolecular reactions were initially reported that required high temperatures and demonstrated low selectivity.[31] However dirhodium tetracarboxylate catalysts now appear to be the most active for cyclopropanation under mild reaction conditions and have hence become the reagents of choice for these transformations (Scheme 20).[32]

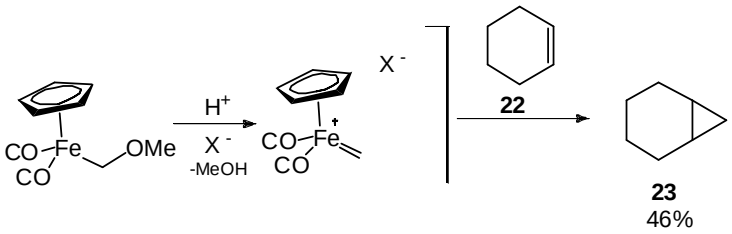


38 **39**
100%

Scheme 20

1.1.2.3. Fischer carbenes as cyclopropanating agents

Pettit and Jolly were the first to suggest that transition metal carbenoid complexes might serve as carbene transfer reagents.[33] Thus, the treatment of $CpFe(CO)_2CH_2OMe$ with acid in the presence of cyclohexene produced norcarane **23** in 46% yield (Scheme 21).[33]

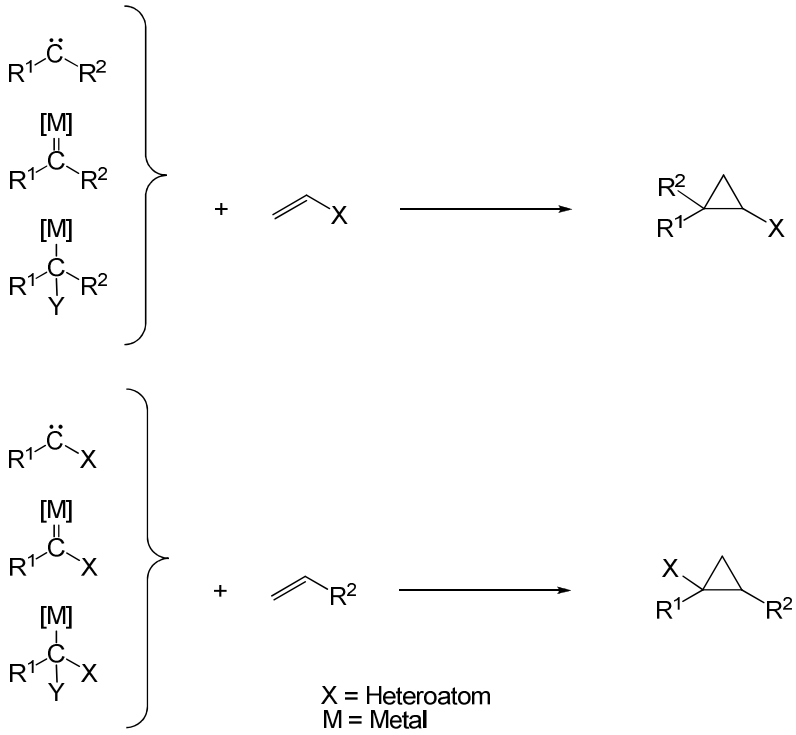


Scheme 21

In general terms, the carbenoid intermediate is similar to that formed during a cyclopropanation with diazo compounds. Fischer improved this reaction and found that the complexes $(CO)_5M=C(OMe)Ph$, where M was chromium, molybdenum or tungsten (Fischer carbenes), also reacted with activated alkenes to give cyclopropanes.[34,35,36]
In the final analysis however, such atom inefficient stoichiometric reagents often required high temperatures and pressures and competing metathesis reactions also proved problematic. In consequence, they have not been adopted within the synthetic community.

1.1.3. Heteroatom-functionalised cyclopropane synthesis

There are two strategically different methods used to obtain a heteroatom substituted cyclopropane *via* a [2+1] cycloaddition reaction with a carbene or carbenoid and an alkene. The first employs a heteroatom-functionalised alkene and a simple carbene or carbenoid species whilst the second uses a heteroatom-functionalised carbene or carbenoid and an alkene. The carbenoids are derived from either halo compounds, diazo compounds or Fisher carbenes (Scheme 22).

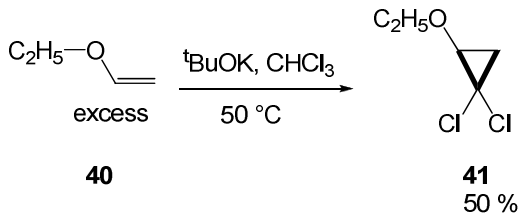


Scheme 22

1.1.3.1. Reactions with heteroatom-functionalised alkenes

1.1.3.1.1. Alkoxycyclopropanes

The simplest example of this approach can be found in the the cyclopropanation of vinyl ether **40** in the presence of chloroform and potassium *tert*-butoxide which affords the dichloroalkoxycyclopropane **41** in 50% yield (Scheme 23).[37]

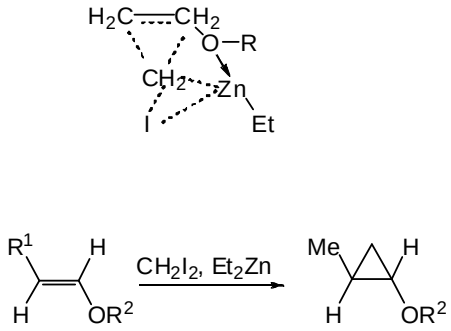


Scheme 23

The dihalocarbene intermediate was formed *in situ* by reaction of the base with chloroform and subsequent trapping of the vinylether to give the corresponding cyclopropane.

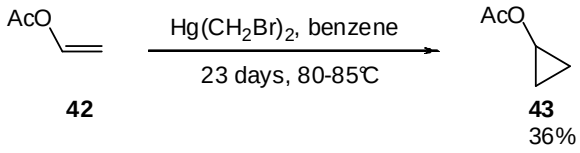
Other reagents can be used to form the dichlorocarbene *in situ* such as ethyl trichloroacetate and sodium methoxide. The choice of method used for the generation of the carbene depends on the nature of the vinyl ether. Ethyl trichloroacetate with sodium methoxide is preferred in the case of the cyclopropanation of an aryl vinyl ether. [37]

More recently, the Furukawa group has studied their variant of the Simmons-Smith reaction and demonstrated that the reactivity of vinyl ether towards zinc carbenoids was better than dichlorocarbene.[38] Coordination of the oxygen atom of the vinyl ether to the zinc may stabilise the transition state and enhance the reactivity (Scheme 24).[39]



Scheme 24

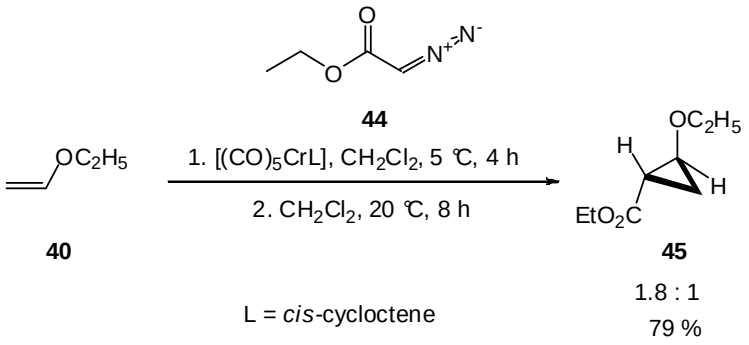
Other metals such as mercury can also be used to generate metallocarbenoids and hence alkoxycyclopropanes (Scheme 25)[40]



42 **43** 36%

Scheme 25

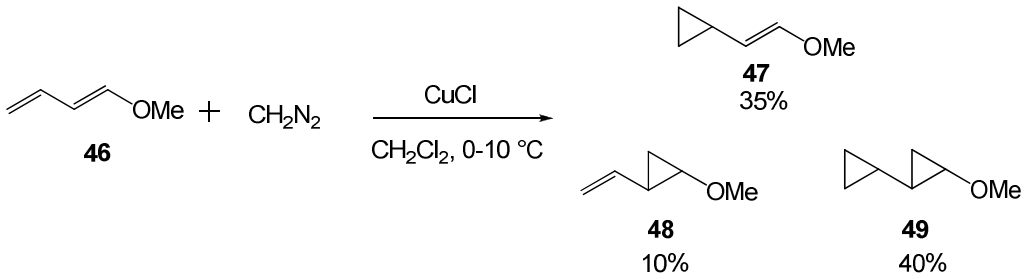
The carbenoid can also be generated from a diazo compound for the cyclopropanation of vinyl ethers using metals such as copper[41] and chromium.[42] Thus, alkoxycyclopropane **45** was obtained in 79% yield, (but with with low selectivity), from vinyl ether **37** and the diazocyclopropanating agent **44** using a chromium based catalyst (Scheme 26).[42]



Scheme 26

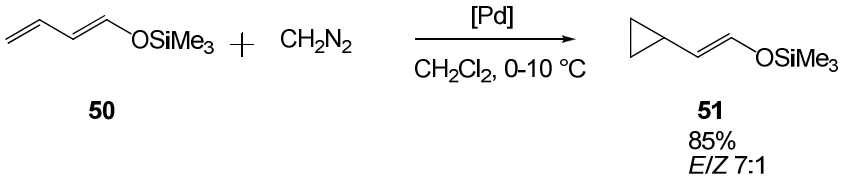
Examples with rhodium catalysts have also been reported.[43] Electron-rich double bonds are preferred which demonstrates the electrophilic nature of the metal carbenoid formed during the reaction.[42]

Non-regioselective cyclopropanation of alkoxy- and acetoxybuta-1,3-dienes in the presence of diazo compounds and a copper catalyst has also been reported (Scheme 27).[44,45]



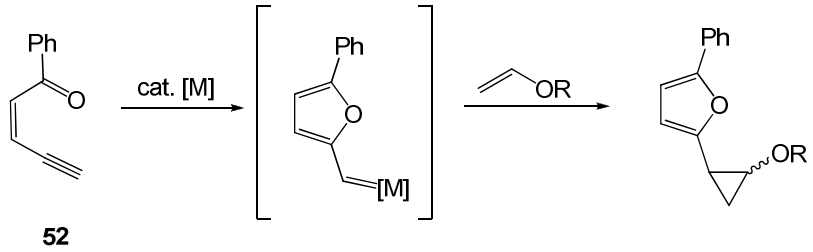
Scheme 27

The double bond which undergoes cyclopropanation in such reactions depends critically on the nature of the catalyst. For example, the less polar terminal double bond is cyclopropanated when a palladium catalyst was used (Scheme 28).[44]



Scheme 28

An elegant tandem sequence involving the use of a Fisher carbene to afford an alkoxycyclopropane in a reaction with a vinyl ether is that shown by Ohe and Uemura *et al*. The reaction can be catalysed by different metal such as chromium, platinum, or rhodium (Scheme 29).[46]

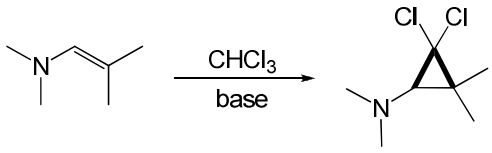


52

Scheme 29

1.1.3.1.2. Aminocyclopropanes

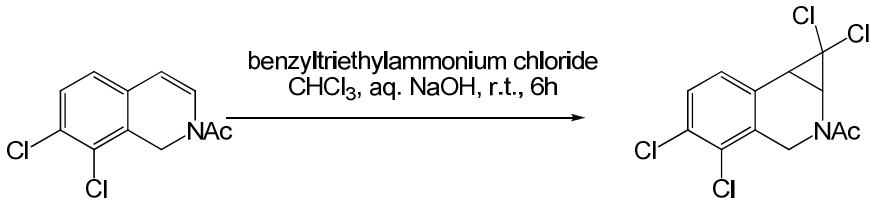
The reaction of an enamine with chloroform in presence of a base afforded a dihaloaminocyclopropane *via in situ* formation of a carbene (Scheme 30).[47,48]



53 **54**

Scheme 30

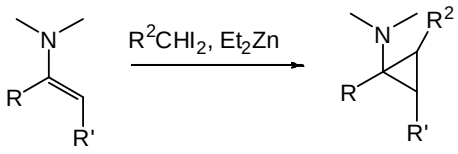
Another example is the treatment of the bicyclic enamide **55** with a phase transfer catalyst and an aqueous solution of sodium hydroxide to give the dihaloaminocyclopropane **56** in 85% yield (Scheme 31).[47]



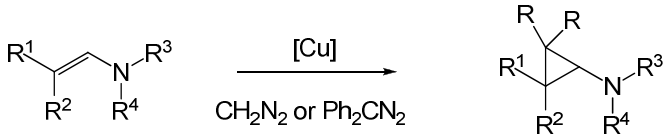
55 **56**
85 %

Scheme 31

The [2+1] cycloaddition between an enamine and a carbenoid such as an organozinc carbenoid using Simmons-Smith-Furukawa type conditions[49,50] or derived from a diazo precursor[49a,50,51] can also afford the corresponding aminocyclopropane (Schemes 32 and 33).

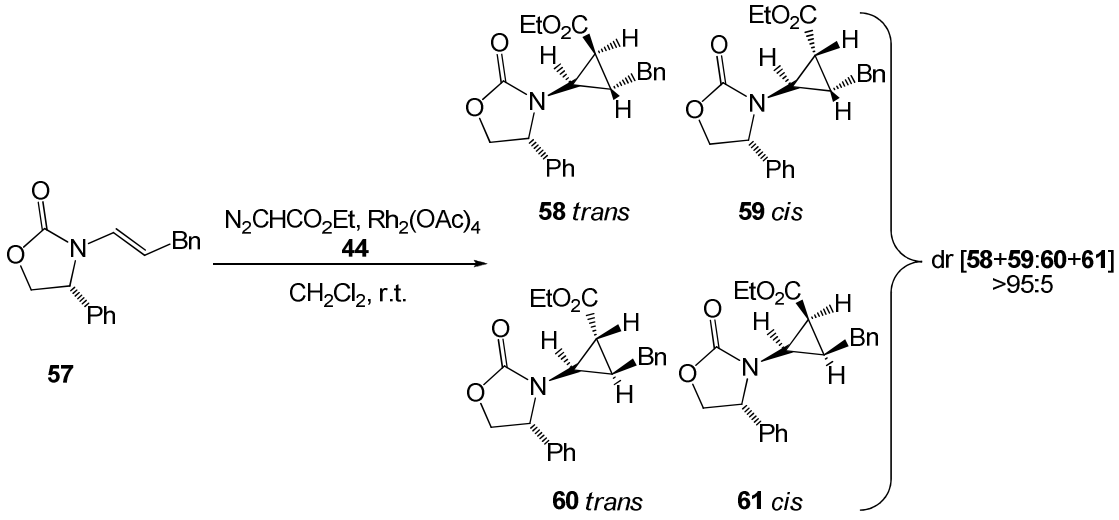


Scheme 32



Scheme 33

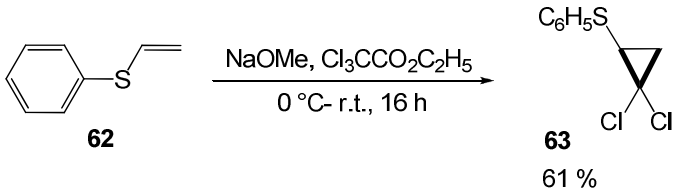
A different catalyst such as a palladium salt can also be used. Hsung *et al*. have described the cyclopropanation of chiral oxazolidinones using dirhodium carbenoids formed *in situ* from a diazoester leading to the *trans N*-cyclopropyl oxazolidinone **58** as the major product. The mixture of cyclopropanes **58** and **59** was obtained in 66% in a 4:1 (*trans*/*cis*) ratio (Scheme 34).[52]



Scheme 34

1.1.3.1.3. Thiocyclopropanes

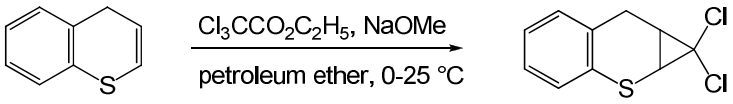
Thiocyclopropanes are less common in the literature than their respective alkoxy and aminocyclopropane counterparts. This stems from their relative reactivity and the fact that the lone pairs of the sulfur atom can react with the carbene to give an ylide which then leads to alternative products. However, the reaction of unsaturated sulfides in the presence of a dichlorocarbene generated *in situ* to give thiocyclopropane has been reported. The thiocyclopropane **63** was synthesised in 61% yield *via in situ* formation of dihalocarbene by reaction of sodium methoxide and ethyl trichloroacetate (Scheme 35).[53,54,55]



62 **63** 61 %

Scheme 35

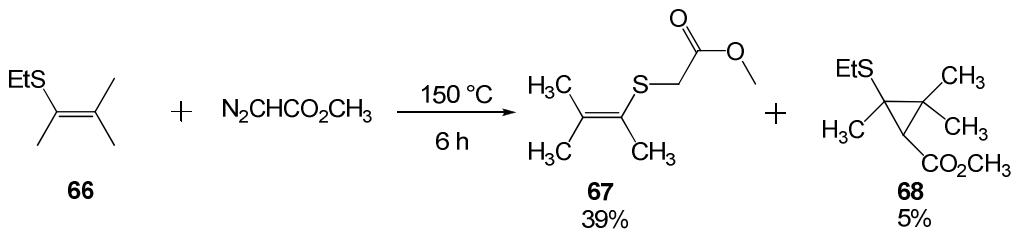
Cyclopropanation of 4*H*-1-benzothiopyran **64** was achieved as well, leading to the corresponding dichlorocyclopropane **65** (Scheme 36).[54]



64 **65** 85 %

Scheme 36

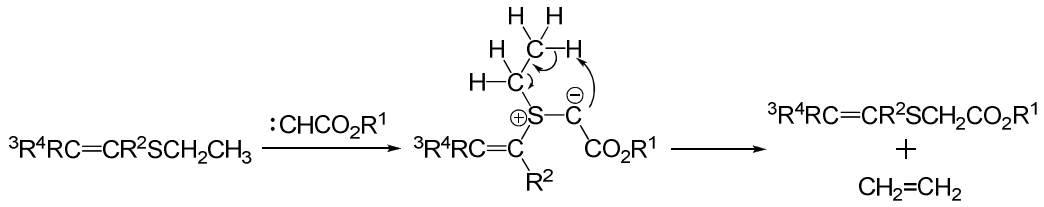
In contrast, the cyclopropanation of vinyl sulfides using metallocarbenoids derived from diazo derivatives as cyclopropanating agents is not as effective as the related reactions with vinyl ethers and enamines. Under the usual cyclopropanation reaction conditions, the reaction can give two products, which are formed in competition: viz., the product of addition (cyclopropane) and a major product formed by insertion (Scheme 37).[56,57]



66 **67** 39% **68** 5%

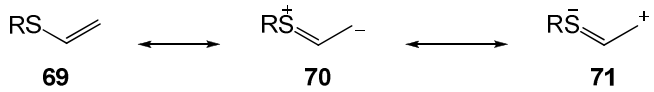
Scheme 37

The insertion product **67** is obtained *via* the intermediate ylide formed by attack of the carbenoid on one of the lone pair electrons of the sulfur, followed by rearrangement. This reaction is favoured with the vinyl sulfide in comparison to the vinyl ether (Scheme 38).[56,57,58,]



Scheme 38

Moreover, the resonance form **70** reveals that vinyl sulfides are considered to be electron-rich. The structure **71** is also possible because of the ability of a sulfur atom to expand its valence shell and this contribution may enhance reactivity of sulfur atom toward a electrophilic carbene (Scheme 39).[56,57]

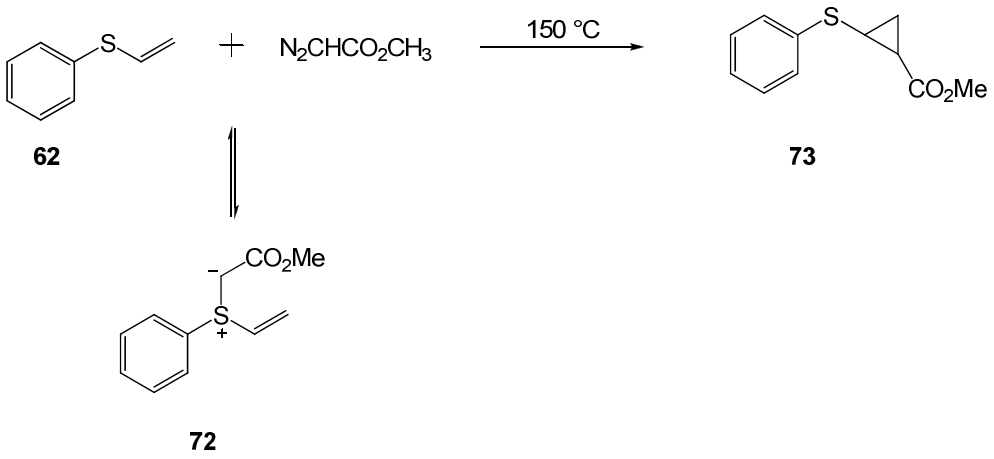


69 **70** **71**

Scheme 39

This character may have an influence on the reactivity of the sulfur atom with the carbene. Moreover, it has been demonstrated that the carbene attacks the sulfur 2.5-5 times quicker than the double bond.[56]

Finally Ando *et al.* have reported the reaction of ethyl diazoacetate with phenyl vinyl sulfide to afford the corresponding cyclopropane exclusively.[57] In this instance, as formation of the ylide is reversible and a subsequent intramolecular rearrangement is not possible, only the cyclopropane is formed (Scheme 40).



Scheme 40

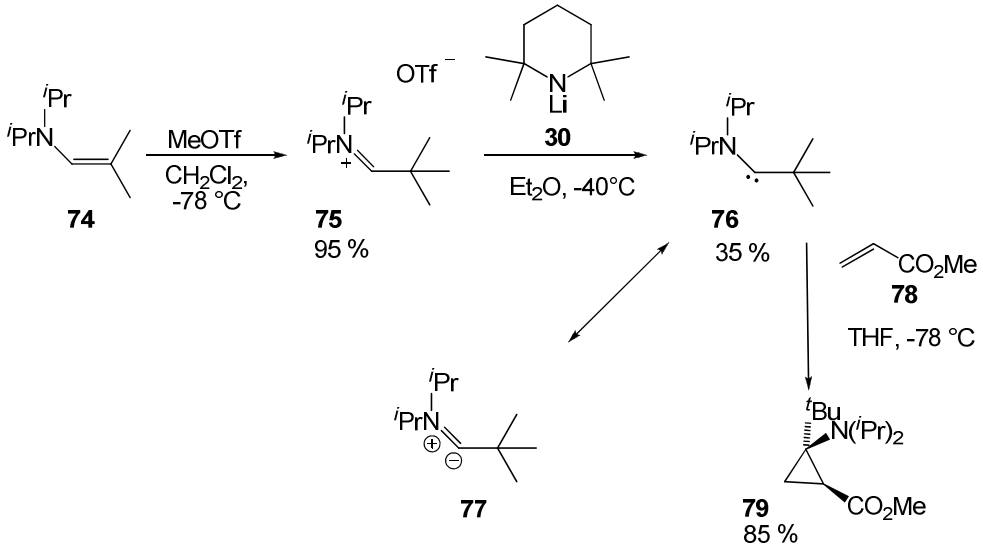
As outlined earlier, by using the Furukawa modification it is possible to use the organozinc carbenoid to cyclopropanate systems such as enamines or vinyl ethers. At present however, to the best of our knowledge, no sulfur atom-substituted cyclopropane has been synthesised by a Simmons-Smith or modified Simmons-Smith protocol.

1.1.3.2. Cyclopropanation using heteroatom-functionalised carbenes or carbenoids

Whilst addition to a heteroatom-substituted alkene is the classical approach, there are also a variety of methods in the literature for the formation of heteroatom-functionalised carbenes and carbenoids and, in particular, for the formation of amino-, alkoxy- and sulfur-substituted cyclopropanes. This has the advantage that there are a plethora of substituted alkenes that are commercially available or readily prepared. In contrast, their vinylic heteroatom substituted counterparts are few. In consequence, there has been considerable interest in the formation and reactivity of heteroatom-functionalised carbenes or carbenoids which can trap an olefin to form a heteroatom-substituted cyclopropane.

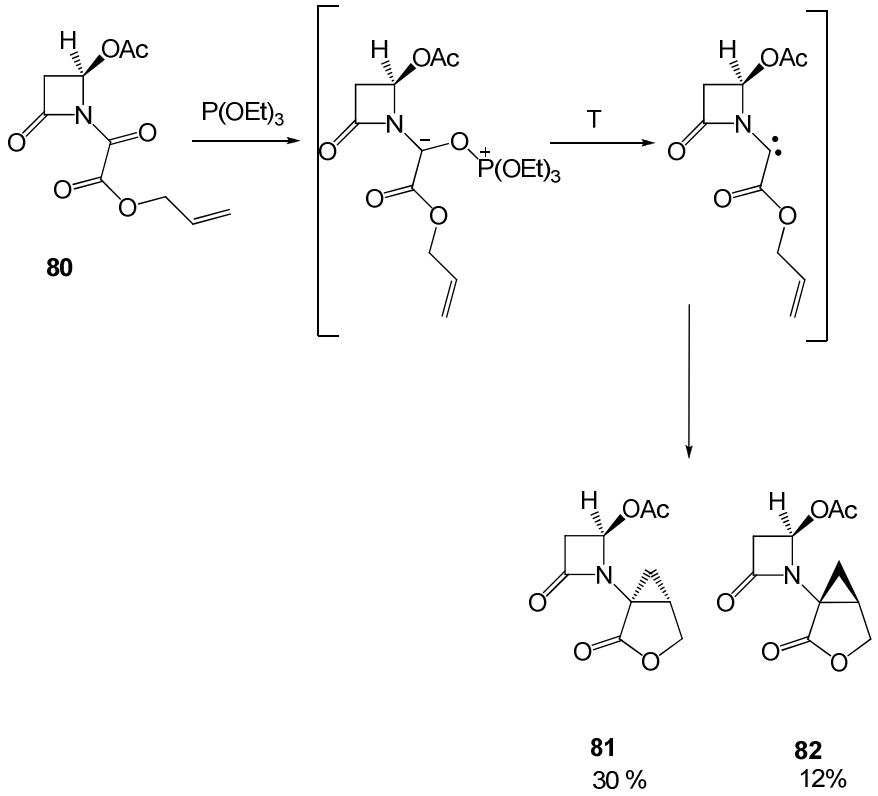
1.1.3.2.1. Aminocarbenes and carbenoids

The first alkylaminocarbene was synthesised and isolated by Bertrand *et al*. in 2004. In this case, only tertiary alkyl aminocarbenes are stable due to potential 1,2 *H*-migration which occurres readily for singlet carbenes. The iminium salt carbene precursor **75** was synthesised by methylation of **74** despite the steric constrains and the reaction of **75** with LiTMP **30** afforded the carbene **76** in 30% yield over 2 steps which could be recrystallised and stored indefinitely. Subsequent reaction of "nucleophilic" carbene **76** with methyl acrylate **78** led stereoselectively to the *syn*-cyclopropane **79** in 85% yield (Scheme 41).[59]



Scheme 41

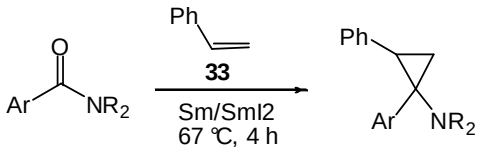
Another example of an aminocarbene, described by Afonso *et al.*, was formed *in situ* from **80** and used in the intramolecular mode to furnish amidocyclopropanes **81** and **82** (Scheme 42).[60]



Scheme 42

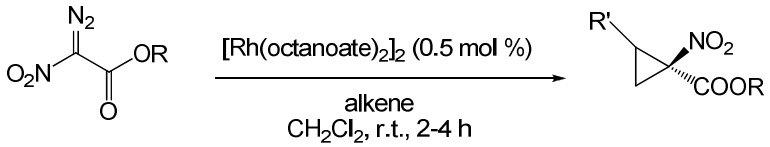
Compound **80** was obtained by reaction of 4-acetoxyazetidinone with allyloxalyl chloride. The carbene was obtained by two-electron transfer from the phosphorus atom to the imide carbonyl oxygen.

Aminocyclopropanes can also be synthesised in an unusual reaction involving an organosamarium aminocarbenoid generated from an amide as reported by Ogawa.[61] This reaction was successful however only in the presence of an excess of styrene (Scheme 43). In the presence of electron-deficient olefins like ethyl acrylate, reduction of the olefins by the couple Sm/SmI_2 was preferred over the reduction of the amide. Electron-rich olefins like butyl vinyl ethers were likewise unsuccessful and only the deoxygenative coupling of amides was observed.



Scheme 43

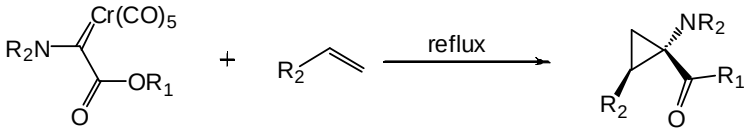
The diazo compound prepared from an α-nitro ester is a useful rhodium carbenoid precursor for trapping electron rich alkenes to afford nitrocyclopropanes (Scheme 44)[62,63,64]



Scheme 44

This method of course gives access to nitrocyclopropanes and, in order to obtain the aminocyclopropanes, a further reduction step is necessary.

To the best of our knowledge, the only direct addition of an α-amino functionalised carbenoid to an alkene was recently reported by Barluenga, who developed the first intermolecular cyclopropanation of Fischer dialkylaminocarbene complexes for the synthesis of 1-aminocyclopropanecarboxylic acid derivatives (Scheme 45).[65]



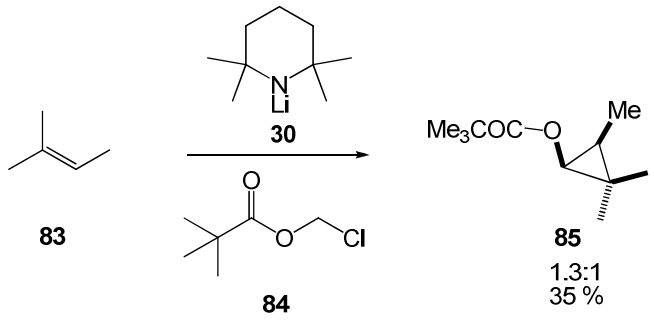
Scheme 45

The reaction was applicable to a wide range of alkenes and generally proceeded with high diastereoselectivity.

In summary, with the exception of the particular case of the Barluenga Fischer carbenoid and the isolated example of the generation of the organosamarium carbenoid from an amide there is no general method for the addition of aminocarbenes or carbenoids to alkenes.

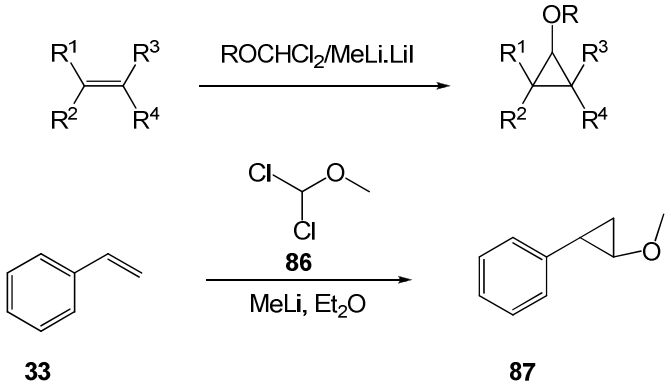
1.1.3.2.2. Alkoxycarbenes and carbenoids

Alkoxycarbenes can be generated in situ by the classical approach involving treatment of an α-halo ether such as **84** with a strong non-nucleophilic base such as LiTMP **30** to give an organolithium carbenoid. This intermediate can subsequently be trapped by an alkene as shown for **83** to afford the alkoxycyclopropane **85** in 35% yield with low stereoselectivity (Scheme 46).[66,67]



Scheme 46

A dihalo ether can also be used for *in situ* formation of an alkoxy carbenoid by lithium halogen exchange as illustrated below (Scheme 47).[14,66,67]

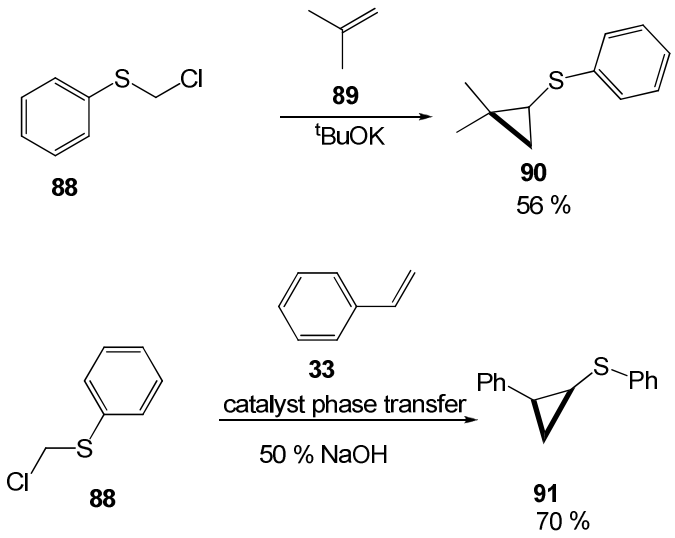


Scheme 47

However due to the high toxicity of these ethers, these methods are not commonly used, but clearly demonstrate the possibility of this route.

1.1.3.2.3. Thiocarbenes

In similar fashion, α-chloromethyl sulfides can be used as carbene precursors for preparation of thiocyclopropanes (Scheme 48).[10, 68,69]



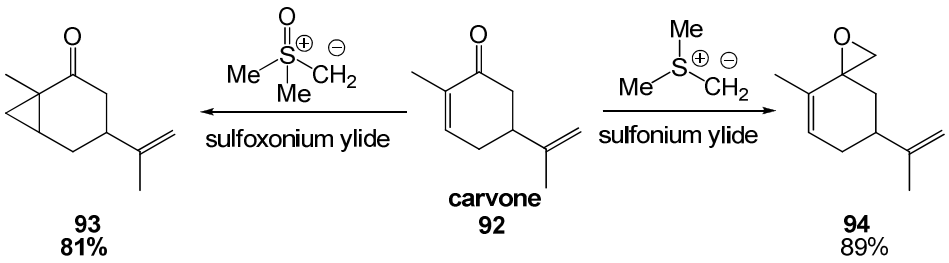
Scheme 48

1.2. Ionic stepwise methods

1.2.1. Ylide chemistry

1.2.1.1. Definition

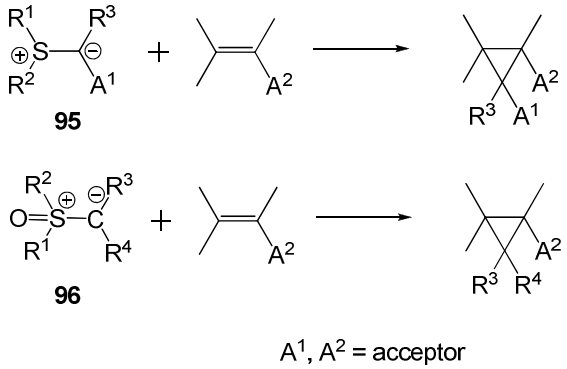
Ylides react with electron-deficient double bonds which are susceptible to Michael additions such as α,β-unsaturated ketones, esters, amides and related systems, including nitriles, sulfones, sulfonamides and nitro compounds, to form cyclopropanes.[8,70] The reaction of a sulfur ylide with a double bond can lead either to the formation of an epoxide or to a cyclopropane depending on the nature of the ylide (Scheme 49).[8]



Scheme 49

"Stabilised" ylides such as **95** and sulfoxonium ylide prefer to react with the double bond to give the cyclopropane. Although the faster reaction will still be addition to the carbonyl group, this is reversible, hence preventing the formation of the epoxide. The 1,4-addition which leads to formation of the cyclopropane is kinetically slower but thermodynamically more favorable and irreversible in the case of "stabilised" ylides.[8] Moreover the ylide can react selectively with the less hindered face of the alkene to give one cyclopropane.

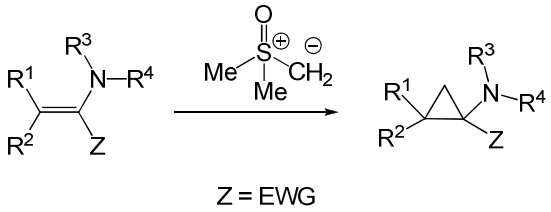
Thus, cyclopropane rings can be obtained by the stepwise reaction of a "stabilised" sulfur ylide or a sulfoxonium ylide with an electron deficient double bond (Scheme 50).



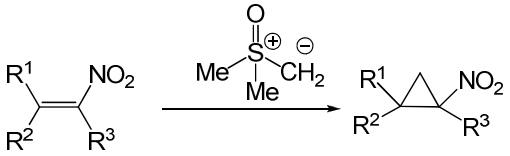
Scheme 50

1.2.1.2. Synthesis of heteroatom substituted cyclopropanes

This section focuses on the cyclopropanation reaction of α,β-unsaturated systems which leads to heteroatom substituted cyclopropanes. Thus, aminocyclopropanes or nitrocyclopropanes can be obtained *via* 1,4 Michael addition of suitably constituted α-amino unsaturated Michael acceptors (Scheme 51) or α,β-unsaturated nitroalkenes (Scheme 52).[50,71,72,73]



Scheme 51

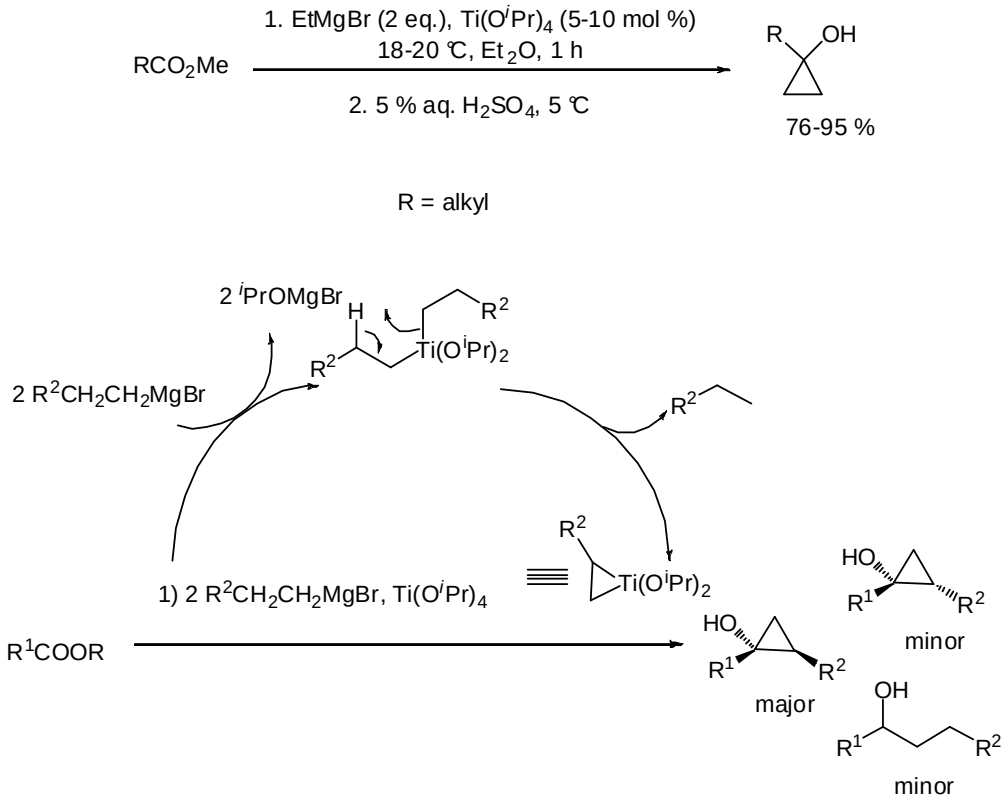


Scheme 52

To the best of our knowledge no example of the synthesis of alkoxycyclopropanes or thiocyclopropanes using ionic, stepwise ylide chemistry have been reported in the literature.

1.2.2. Titanium-mediated cyclopropanation

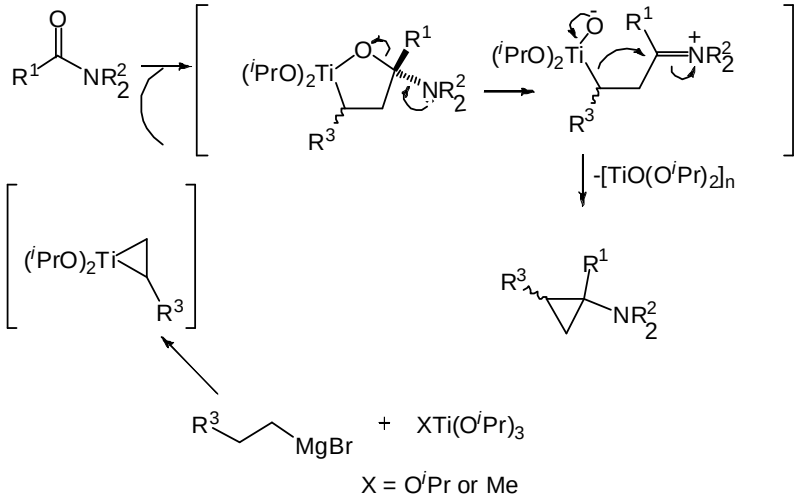
A new method has recently been developed for the synthesis of aminocyclopropanes using a titanium-mediated reaction whose origin stems from the elegant work of Kulinkovich, who developed the reaction of carboxylic esters with Grignard reagents in the presence of titanium(IV) alkoxides leading to cyclopropanol derivatives. The original reaction was carried out by addition of a solution of ethylmagnesium bromide to an ester in the presence of a catalytic amount of titanium(IV) isopropoxide. The mechanism proposed is shown in Scheme 53 along with the catalytic cycle (Scheme 53).[74,75]



Scheme 53

The key step of the reaction is the formation of the organotitanium species which reacts with the ester to give the alkoxycyclopropane as the major product.

Recently, de Meijere applied the original Kulinkovich hydroxycyclopropanation protocol to *N*,*N*-dialkylamides and thus developed a facile preparation of *N*,*N*-dialkycyclopropylamines (Scheme 54).[76]

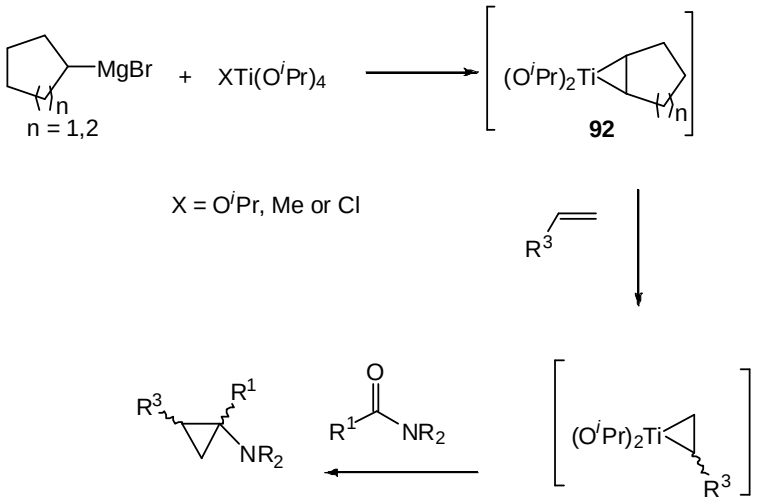


Scheme 54

The de Meijere variant of the Kulinkovich reaction can be applied to a wide range of carboxamide and Grignard compounds. In principle, primary cyclopropylamines can be easily synthesised by hydrogenolysis of *N*,*N*-dibenzylcyclopropylamines. However, since cyclopropyl rings are also hydrogenated with ring opening, this method cannot be applied to all substrates, especially cyclopropanes substituted with an aromatic group

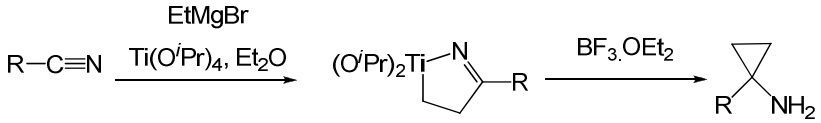
A recent improvement of the protocol lies in the use of methyltriisopropyloxytitanium instead of tetraisopropyloxytitanium for cyclopropanation of an ester or a dialkylamide and is preferable in terms of yield.[76c,76e]

A further development is the generation of a titanacyclopropane intermediates by alkene-ligand exchange which provides access to more highly substituted cyclopropylamines from cyclic and acyclic alkenes, alkadienes and even trienes. This method enables the formation of functionalised organotitanium species that cannot be obtained directly from a Grignard compound. This improvement was initially demonstrated by Kulinkovich for the cyclopropanation of esters.[77,78,76e] The titanacyclopropanes derived from cyclopentyl- and cyclohexylmagnesium halides appear to be the best for alkene ligand exchange (Scheme 55).[76e,78]



Scheme 55

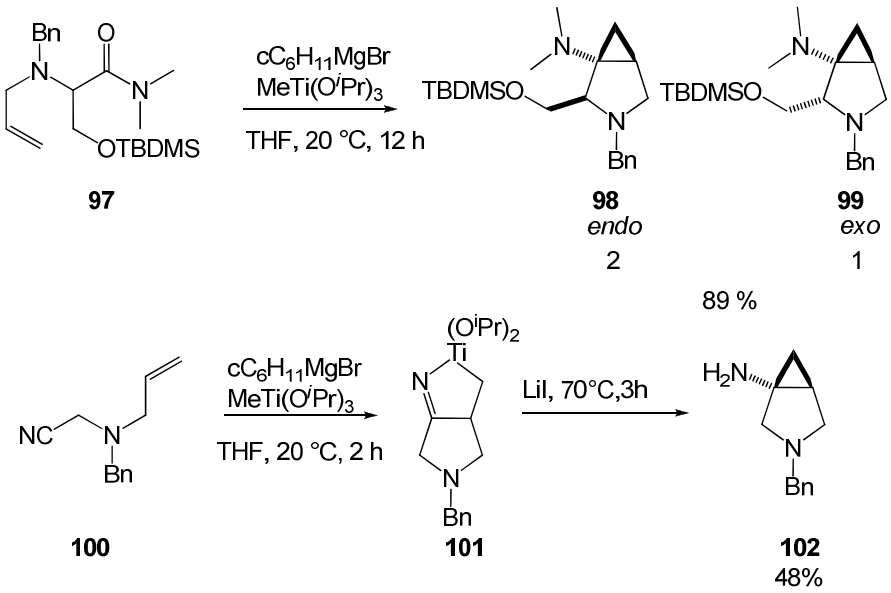
The titanium mediated approach can be also applied to nitriles giving, in the same fashion, the corresponding cyclopropylamines (Scheme 56).[79]



Scheme 56

In contrast with the reaction developed by De Meijere, the use of a Lewis acid is crucial for the ring-contraction giving the cyclopropane. [79a] The reaction can be applied to a wide range of functionalised nitriles.[79b,79c]

The intramolecular variants of this cyclopropanation reaction have also been applied to prepare polycyclic aminocyclopropanes from suitably tethered *N*,*N*-dialkylcarboxamides and carbonitriles (Scheme 57).[76a,76c,80]

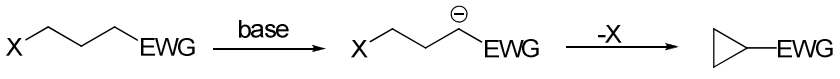


Scheme 57

Although this method seems to be a most simple and direct route to access aminocyclopropanes, the process is limited to a relatively small number of substrates due to the incompatibility of Grignard reagents with other functional groups such as carbonyl groups and halides.

1.2.3. 1,3-Ring-closure Reactions

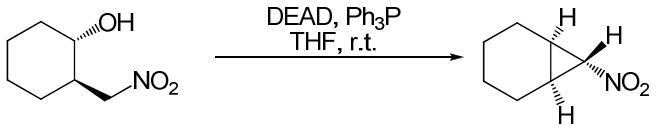
The construction of cyclopropanes by a 1,3-ring-closure reaction is a kinetically favoured process in spite of the strain generated. An approach which has often been used features a starting material containing an electron-withdrawing group and a leaving group in a 1,3-relationship. In the presence of a base the cyclopropane is then obtained by intramolecular displacement (Scheme 58).



Scheme 58

1.2.3.1. Cyclopropanes bearing nitrogen functionality

The formation of nitrocyclopropanes by intramolecular 1,3-ring-closure under Mitsonobu conditions using diethyl azodicarboxylate and triphenylphosphine has been reported, and when applied to the γ-nitroalkanol **103** led to inversion of configuration (Scheme 59). [81]

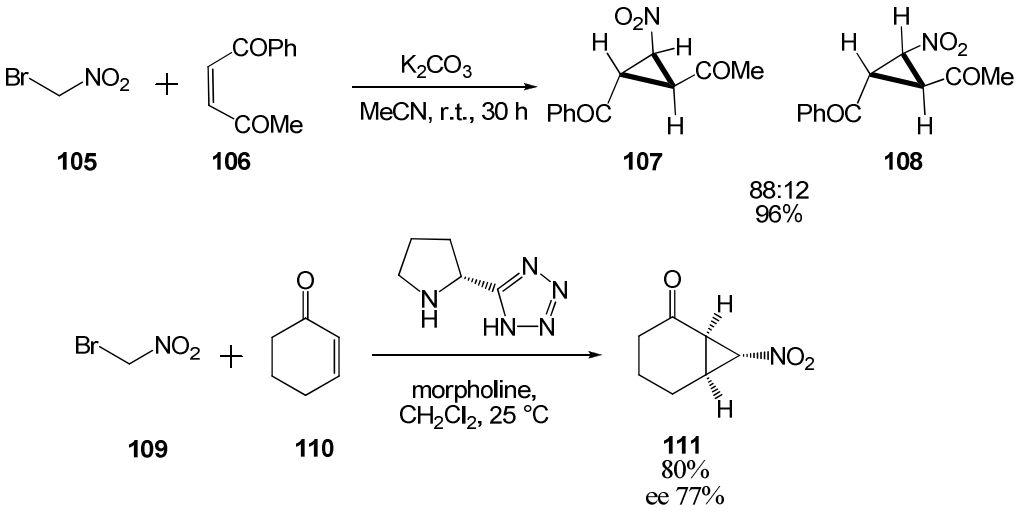


103 **104** 92 %

Scheme 59

A major disadvantage of this method is that the synthesis of the nitroalkanols requires several steps.

Other methods for the formation of nitrocyclopropanes by 1,3-ring-closure feature the use of bromonitromethane as a starting material (Scheme 60). The first of these reactions requires an electrophilic alkene bearing two electron withdrawing groups in the α- and β-positions, [82] whilst the second, developed by the Ley group, provides an elegant demonstration of organocatalysis leading to an enantiopure nitrocyclopropane (Scheme 60).[83]

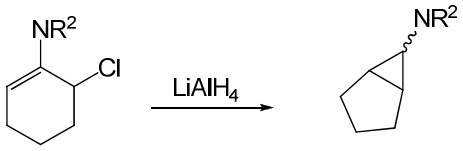


105 **106** **107** **108**

109 **110** **111** 80% ee 77%

Scheme 60

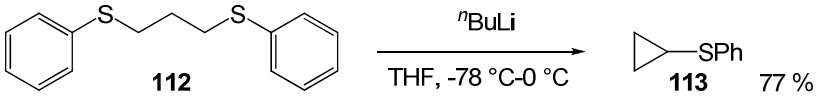
Aminocyclopropanes can also be obtained directly in a similar fashion by treatment of chloro enamines with $LiAlH_4$ (Scheme 61).[50]



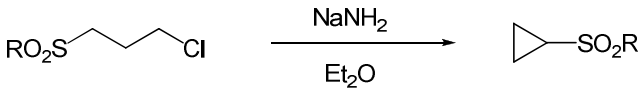
Scheme 61

1.2.3.2. Thiocyclopropanes

Both cyclopropyl sulfides and sulfones can be readily synthesised following classical methodology involving 1,3-ring-closure (Schemes 62 and 63).[84,85]



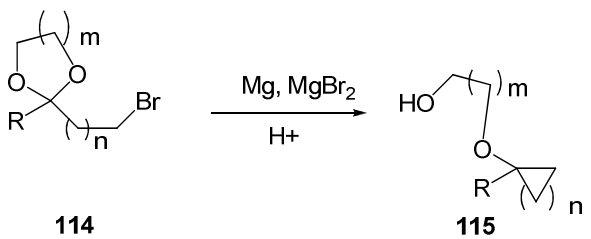
Scheme 62



Scheme 63

1.2.3.3. Alkoxycyclopropanes

In a similar fashion, an example of a 1,3-ring-closure is the treatment of **114** with magnesium in the presence of magnesium bromide as Lewis acid which affords the alkoxycyclopropane **115** (Scheme 64). [86]



Scheme 64

1.3. Functional group modifications leading to heteroatom substituted cyclopropanes from existing cyclopropanes

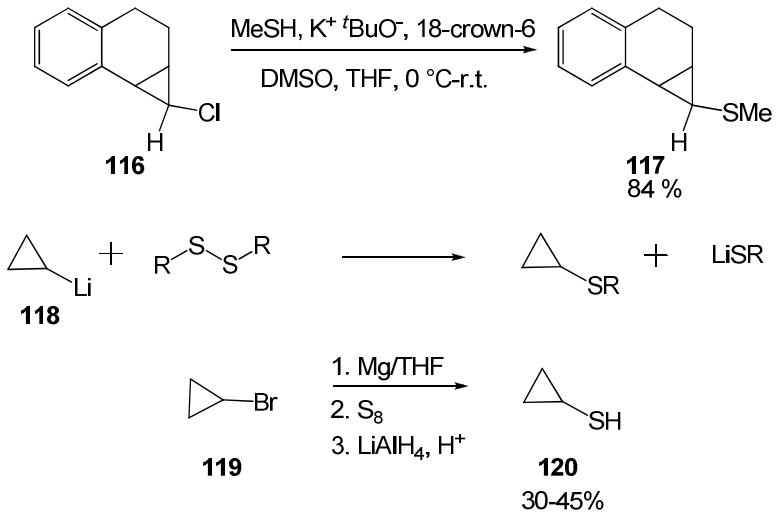
Cyclopropanes bearing a heteroatom can also be synthesised by subsequent functional group manipulation from an existing cyclopropane, either by heteroatom nucleophilic displacement or by a functional group interchange.

1.3.1. Direct displacement

The direct displacement of an existing functionalised cyclopropane affording a heteroatom substituted cyclopropane is possible from a cyclopropane substituted by an appropriate leaving group.

1.3.1.1. Cyclopropanes bearing a sulfur atom

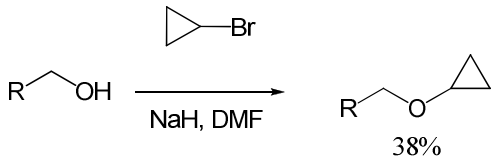
A cyclopropyl sulfide can be obtained by direct displacement of a substituted cyclopropane halide by a thiolate anion,[87,14] *via* reaction of a metallated cyclopropyl anion with diorganyl disulfides,[87] or elemental sulfur[88,89] as illustrated by the following three examples (Scheme 65).



Scheme 65

1.3.1.2. Cyclopropanes bearing an oxygen atom

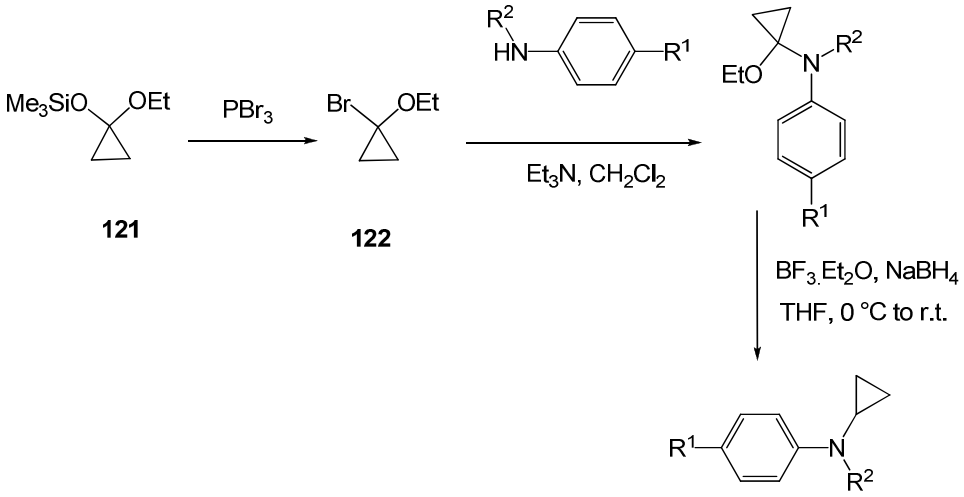
By using a similar concept to the sulfur substituted cyclopropanes, an alkoxy cyclopropane can also be obtained by classical Williamson ether synthesis (Scheme 66).[90]



Scheme 66

1.3.1.3. Aminocyclopropanes

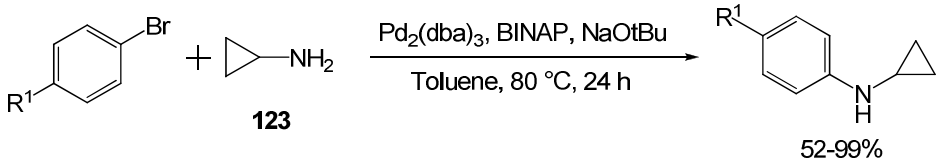
A synthesis of aminocyclopropanes by direct displacement is described below and involves reaction of an aryl amine with a bromo-ethoxycyclopropane (Scheme 67).[91]



Scheme 67

The synthesis starts with the conversion of readily available **121** to the bromide **122** which, after reaction with an aromatic amine to give the *N*-arylcyclopropylamine and reduction affords the aminocyclopropane. Unfortunately, intermediate **122** is not stable at room temperature and difficult to synthesise.

We note parenthetically that a better approach to *N*-arylcyclopropylamines is *via* palladium-catalysed C-N bond formation using aryl bromides and coupling them to commercially available cyclopropylamine, wherein the desired products are formed in moderate to excellent yield (Scheme 68).[92]



Scheme 68

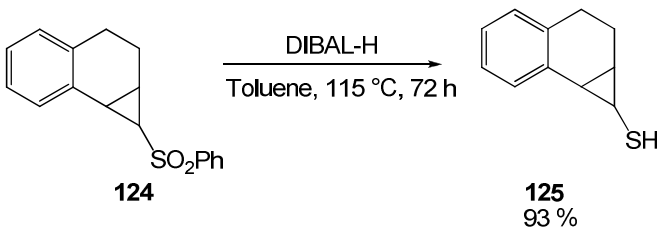
This method requires the use of the commercially available cyclopropylamine and cannot afford aminocyclopropanes with other substituents on the cyclopropane ring.

1.3.2. Functional group interchange

Although trivial, standard chemical transformations have certainly been used to synthesise heteroatom substituted cyclopropanes.

1.3.2.1. Sulfur substituted cyclopropanes

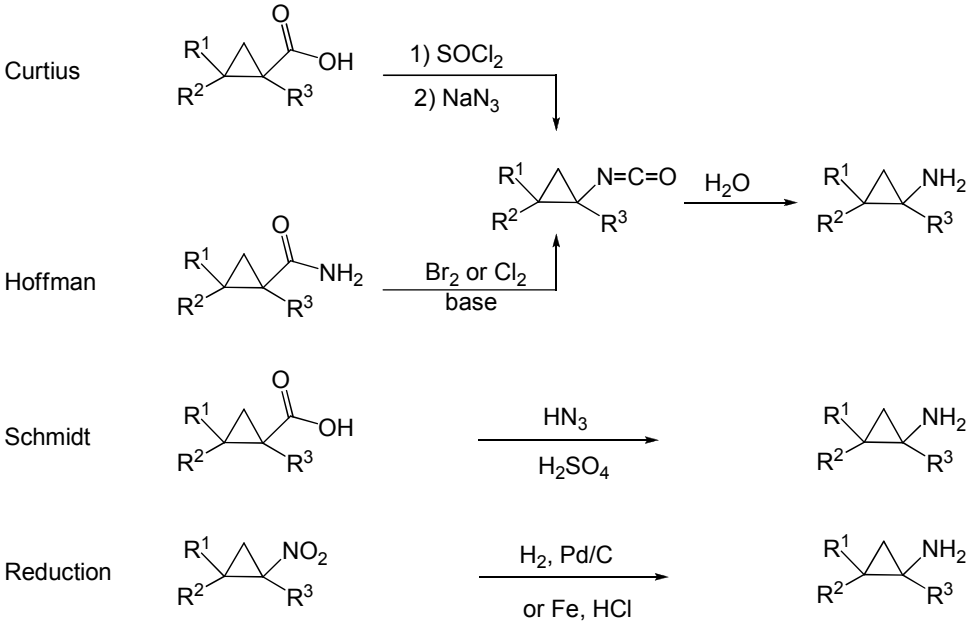
Thus, vigorous reduction of a sulfone group with DIBAL-H has enabled preparation of the parent thiocyclopropane derivative **125** (Scheme 69).[14,87b]



Scheme 69

1.3.2.2. Aminocyclopropanes

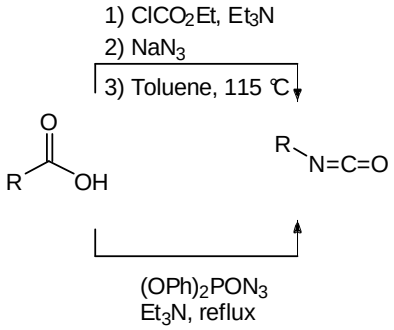
The formation of aminocyclopropanes by functional group interconversion is by far the most commonly employed method in the literature, due in part to the variety of reactions that can be used to access the amino group either from carboxylic acid derivatives as in the Curtius,[93] Hoffmann,[94] or Schmidt reactions,[95] as well as the reduction of a nitro group (Scheme 70).[8]



Scheme 70

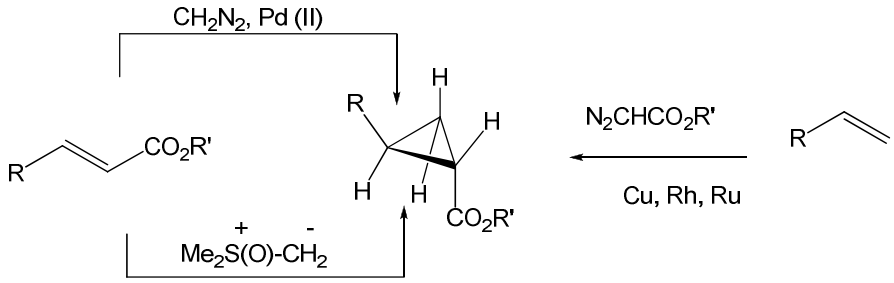
The Curtius and Hoffmann rearrangements are based on conversion of the carboxylic acid derivatives into isocyanates. Treatment of the intermediate isocyanate with water generates the required amine derivative.[93,94] The Schmidt reaction has also been employed whereby a primary amine is obtained by treatment of a carboxylic acid derivative with ammonia and sulfuric acid.[95]

Weinstock[96] developed an alternative method for the conversion of a carboxylic acid to an isocyanate using mixed anhydrides to replace thionyl chloride under milder conditions. To overcome the dangerous properties of sodium azide, Yamada *et al.* developed a modified Curtius reaction using diphenylphosphoryl azide (Scheme 71).[97]



Scheme 71

The required cyclopropyl carboxylic acid used as the starting material for these reactions can readily be obtained by saponification of the corresponding cyclopropyl ester commonly obtained by classical method such as metal-catalysed decomposition of a diazo compound or the use of sulfur ylide chemistry (Scheme 72).[50,98,99,100,101,102,103,]



Scheme 72

As stated at the outset, the present thesis will focus on the synthesis of aminocyclopropanes, and as outlined in the preceding sections, there are numerous methods which already exist to prepare such compounds. Nevertheless, careful examination of the carbenoid approach reveals several disadvantages, particularly in terms of the use of precursors such as toxic gem dihalo compounds or explosive diazo precursors. Most of all, perhaps, in terms of synthetic disconnection, there appears to be no more general route to functionalised carbenoids possessing a nitrogen substituent on the carbenoid carbon. In consequence, the opportunities for using a wide range of stereochemically pure *E* or *Z* alkenes is lost, especially since this feature is generally translated into the stereochemistry of the product.

In generation of organozinc carbenoids from carbonyl compounds and their congeners in various oxidation states there is therefore an attractive alternative, especially since

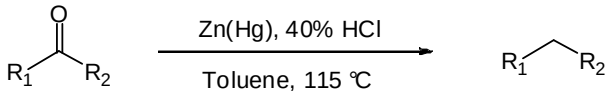
organozinc reagents are generally considered to be non-toxic, mild, and highly chemoselective.

1.4. Previous research within our group

Before addressing the previous work carried out in our own group, it is important to recognise the mechanistic parallel which exists with the classical Clemmensen reduction.

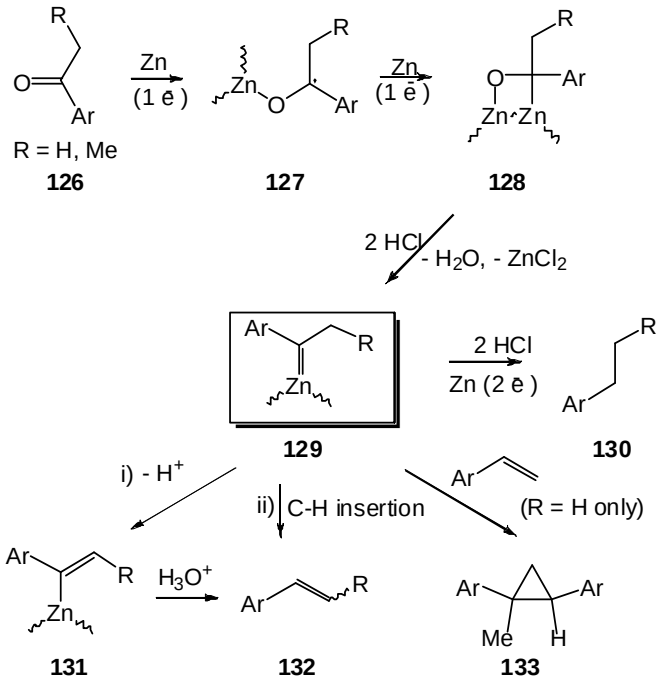
1.4.1. Carbonyl compounds as cyclopropanating agents: The Clemmensen reduction

The Clemmensen reduction using zinc amalgam and hydrochloric acid is one of the simplest methods for the reduction of a carbonyl group of ketones and aldehydes into a methylene group (Scheme 73).[104]



Scheme 73

The mechanism of this reaction has been the subject of ongoing debate and is still not totally understood. The formation of a zinc carbenoid as an intermediate is now commonly accepted[104] following work by Burdon in 1986 who proposed a mechanism involving the zinc carbenoid intermediate (Scheme 74).[105]



i) abstraction of H^+ by base (H_2O, EtOH, ketone); ii) rearrangement (1,2 H-shift). Neither i or ii occur for Ar= 4-$MeOC_6H_4$

Scheme 74

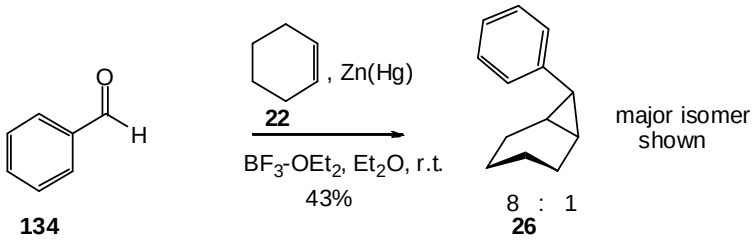
Products analysis and deuterium labelling experiments confirmed the intermediate **129** as a zinc-carbenoid. Protonation of **129,** followed by reduction leads to **130**. The organozinc carbenoid **129** can be deprotonated to give a vinyl-zinc species **131** and converted into **132** by rearrangement, or trapped by an alkene to give a cyclopropane **133**.

1.4.2. Carbonyl compounds as organozinc carbenoid precursors

Whereas attempts by Burdon to capture the zinc-carbenoid intermediate with alkenes other than styrenes failed, possibly due to steric factors, the use of a carbonyl group as a precursor of an organozinc carbenoid in the presence of zinc and a Lewis acid had in fact already been demonstrated by earlier work.

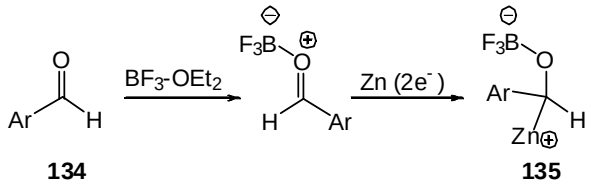
Thus, in 1969, Elphimoff-Felkin and Sarda published the cyclopropanation reaction of an alkene using an aldehyde as a zinc carbenoid precursor in the presence of metallic zinc and boron trifluoride diethyl etherate as a Lewis acid, which could serve as a

possible replacement for the proton source which was responsible for the rapid destruction of the carbenoid (Scheme 75).[106]



Scheme 75

The species **135** was proposed to be the intermediate involved in this reaction (Scheme 76).[106]

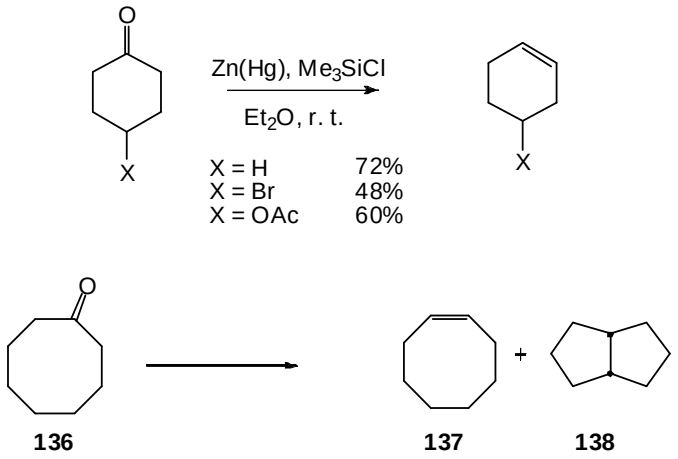


Scheme 76

The formaiton of organozinc carbenoid derived from a carbonyl compound in presence of Lewis Acid was then investigated in details in order to develop new reactions.

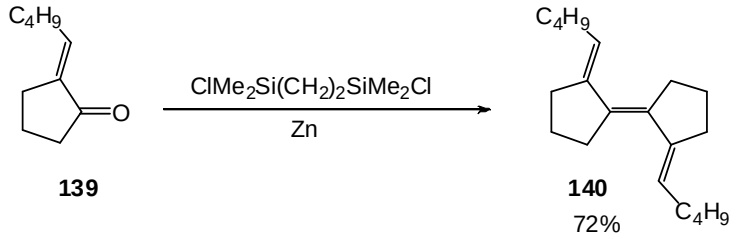
1.4.3. Evolution of organozinc carbenoid chemistry as a cyclopropanating agent within our group

Additionally, in 1973, Motherwell demonstrated the conversion of several cyclohexanone derivatives in the presence of zinc and chlorotrimethylsilane, to the corresponding cyclohexenes. The behaviour of cyclooctanone in particular provided strong presumptive evidence for the intermediacy of an organozinc carbenoid since bicyclo-[3.3.0]-octane is most reasonably derived by transannular C-H insertion (Scheme 77).[107,108]



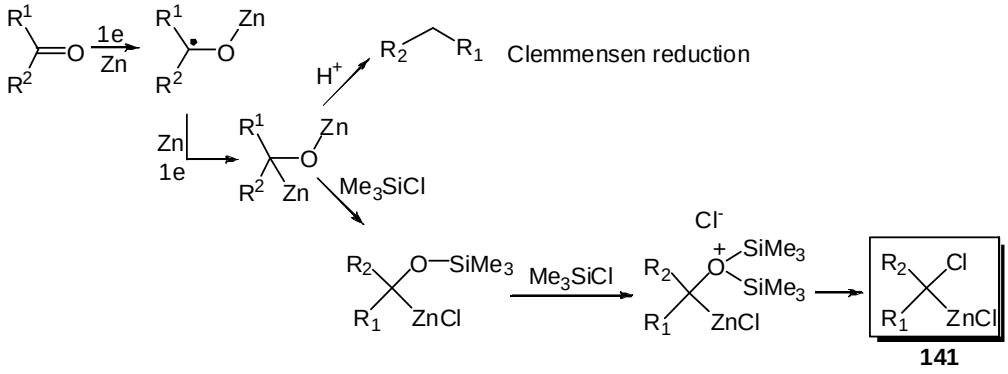
Scheme 77

Further studies within the group demonstrated that reductive McMurry-type dicarbonyl coupling of certain aryl and α,β-unsaturated carbonyl compounds to give alkenes can also be accomplished using chlorotrimethylsilane and zinc at low temperature. The mechanism was proved not to involve pinacolic coupling and diol deoxygenation but to proceed *via* a carbonyl ylide derived by trapping of the organozinc carbenoid with a second molecule of carbonyl compound (Scheme 78).[108,109]



Scheme 78

In both of the above reactions, it was thought that an organozinc carbenoid would be generated directly and efficiently from a carbonyl compound, by treatment with metallic zinc in the presence of a silicon electrophile. A mechanistic pathway involving a series of single electron transfer processes facilitated by the Lewis acidic silicon electrophile as an oxaphilic reagent can be considered as shown below (Scheme 79).[110,111]

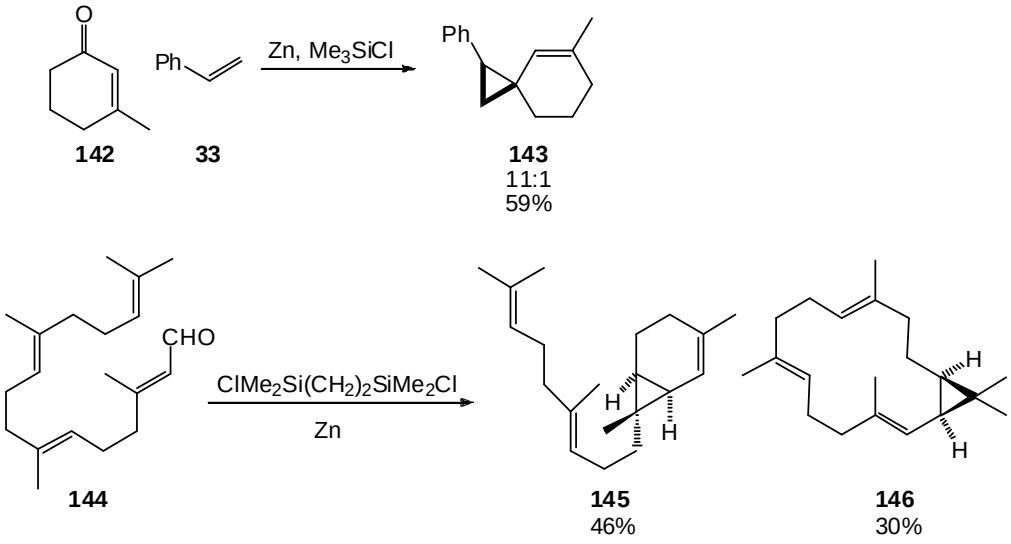


Scheme 79

The organozinc carbenoid intermediate **141** thus generated was also used for a useful range of reactions as described below.

1.4.4. Inter and intramolecular cyclopropanation

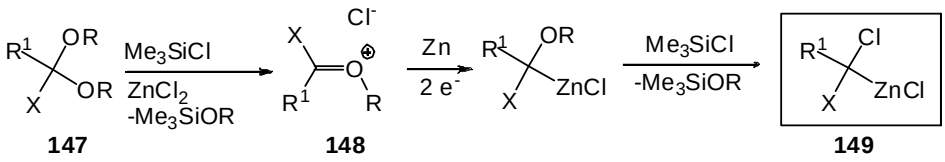
A variety of aryl and α,β-unsaturated carbonyl compounds, on treatment with zinc and a silicon electrophile afford organozinc carbenoids which may be trapped with alkenes to give cyclopropanes both in an *inter*- and *intra*-molecular fashion (Scheme 80).[110,111,112]



Scheme 80

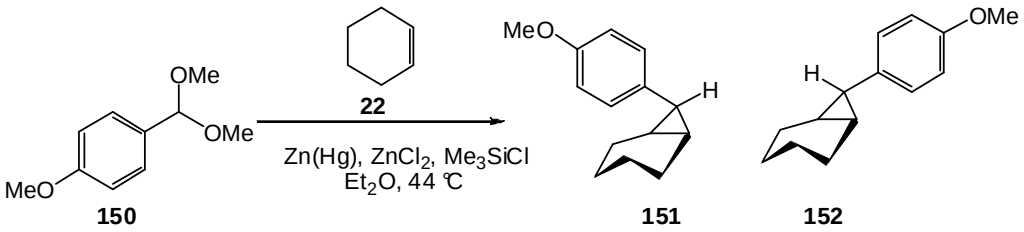
Following on from this concept, it was shown that acetals and ketals can also be used as direct precursors for organozinc carbenoid chemistry and can afford either cyclopropanes or C-H insertion products.[113] In this case, and in contrast to the reactions

of carbonyl compounds, carbenoid formation does not require initial formation of a zinc oxygen bond on the surface, but could involve direct delivery of electrons from zinc to an oxocarbenium ion (**148**) as shown in Scheme 81. A typical cyclopropanation reaction is shown in Scheme 82.[113]



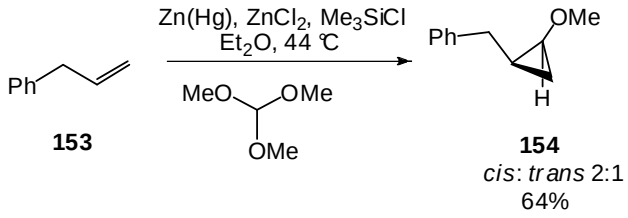
X = H, alkyl, OR_2, NR_3COR_4

Scheme 81



Scheme 82

As a logical consequence of the selection of acetals and ketals, the use of orthoformates as alkoxyorganozinc carbenoid precursors then provided a very simple and practical method for the preparation of alkoxycyclopropanes (Scheme 83).[114]

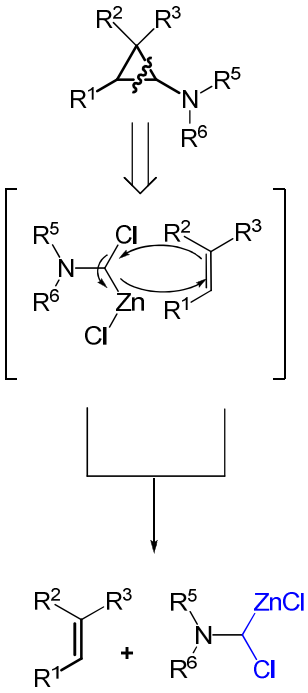


Scheme 83

1.4.5. Synthesis of aminocyclopropanes

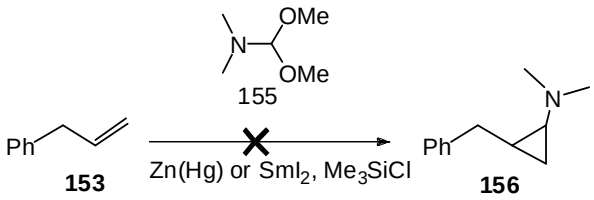
More recent studies in the group have focused on the use of this organometallic chemistry because it is potentially more applicable to a stereocontrolled synthesis of amidocyclopropanes.

The aim was to design an organozinc carbenoid with an amino group attached in order to have access to a wide range of functionalised aminocyclopropanes by a [2+1] cycloaddition from different alkenes and not only a methylene insertion (Scheme 84).



Scheme 84

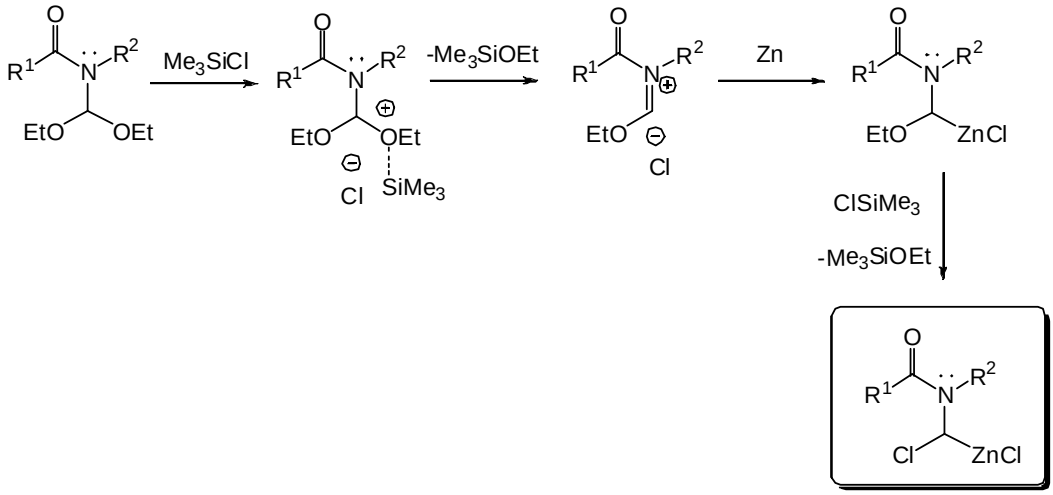
By analogy with the earlier work on orthoformates, Mr. Guillaume Bégis initially worked on a new organozinc precursor containing an amino group such as **155** as the carbenoid precursor. Unfortunately the reaction was not conclusive (Scheme 85).[115,]



Scheme 85

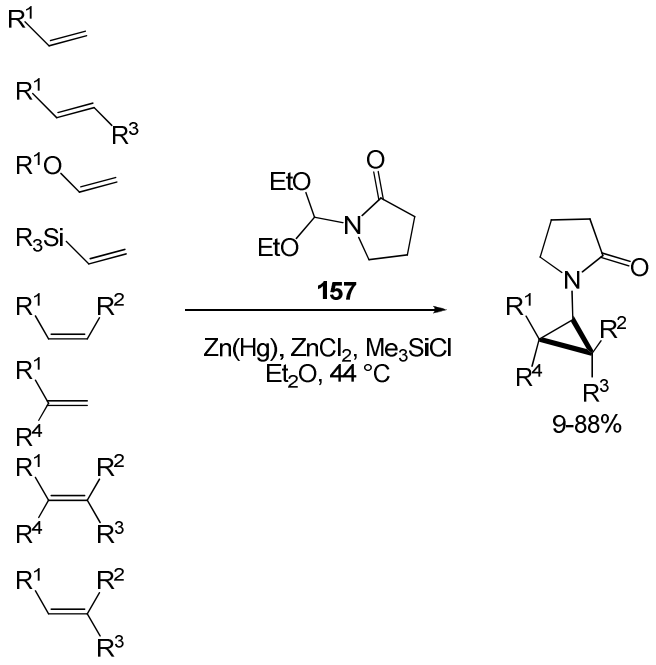
After investigation, Mr. G. Bégis demonstrated that the organozinc carbenoid attached to an amino group capable of trapping an alkene to form a cyclopropane could be obtained from a molecule containing an additional electron-withdrawing group α to the nitrogen atom in order to attenuate the strong electron-donating (nucleophilic) ability of the nitrogen lone pair.

Thus, in an analogous fashion to ketals, acetals and orthoformates, an organozinc carbenoid containing amino functionality was obtained from *N*-diethoxymethylamide derivatives (Scheme 86).



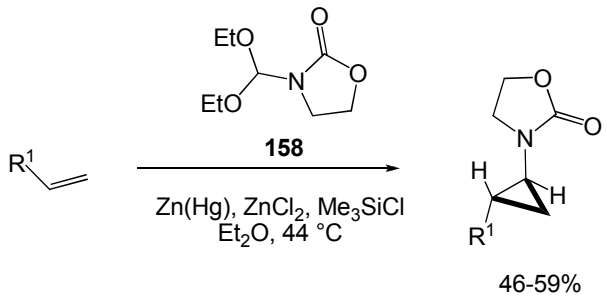
Scheme 86

Careful experimentation by my predecessor, Mr G. Bégis then established that the *N*-diethoxymethyl derivative of pyrrolidinone **157** was preferred over the selection of an acyclic amide and that a useful range of alkenes could then undergo cyclopropanation using this reagent as a carbenoid precursor (Scheme 87).[115, 116]



Scheme 87

Further studies then allowed him to carry out some preliminary work using the closely related but potentially more useful oxazolidinone system **158** (Scheme 88). [115,117]



Scheme 88

These studies paved the way for the present research programme.

Chapter 2: Results and Discussion

2.0. Introduction

The discovery of the amidocyclopropanation and the closely related use of *N*-diethoxymethyl oxazolidinones by my predecessor Mr Guillaume Bégis had laid a very strong foundation which indicated that this simple reaction was of considerable value for organic synthesis.[115,116,117]

Nevertheless, at the outset of the present work, several aspects of the reaction required further study and clarification. Thus, it was necessary to explore the reaction in terms of its chemoselectivity and its tolerance to other functional groups. For these reasons, the following six alkenes (Figure 4) were selected as substrates for cyclopropanation.

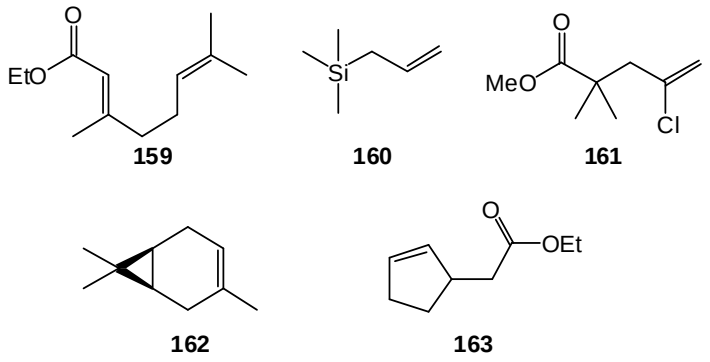


Figure 4

The cyclopropanation of these alkenes was of particular interest to extend the range of chemoselectivity and stereoselectivity, as the alkene **159** contained both an electron-poor and an electron-rich double bond, the alkenes **160** and **161** possess silyl and chloride functionality and the alkenes **162** and **163** a cyclopropyl group, and an ester group which could potentially have a directing influence on the cyclopropane formation.

A particular concern however, as we shall see later, was that it was not possible to predict the stereochemical outcome for any given reaction of an alkene and an amidoorganozinc carbenoid. A selection of the examples prepared by Mr Bégis is shown in Table 1 and illustrates the complexity involved with predicting the stereoselectivity of the cyclopropanation reaction.[115,116]

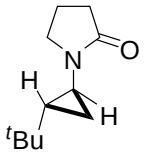
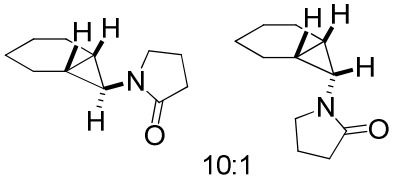
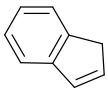
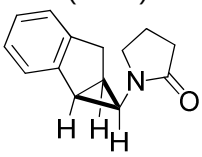
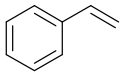
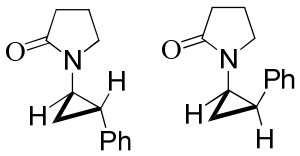
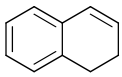
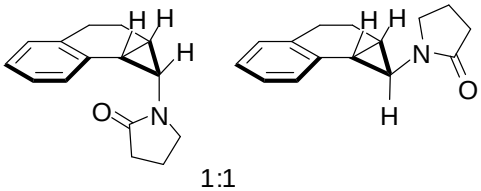
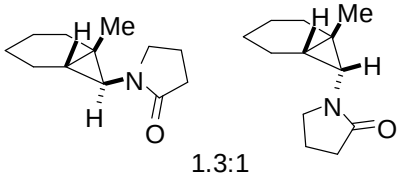
entry	alkene	Products
1		 >95:5
	164	**168** (61%[a])
2		 10:1
	22	**169** **170** (66%[a])
3		 >95:5
	165	**171** (66%[b])
4		 1.1:1
	33	**172** **173** (70%[a,c])
5		 1:1
	166	**174** **175** (28[b])
6		 1.3:1
	167	**175** **177** (63[a])

Table 1

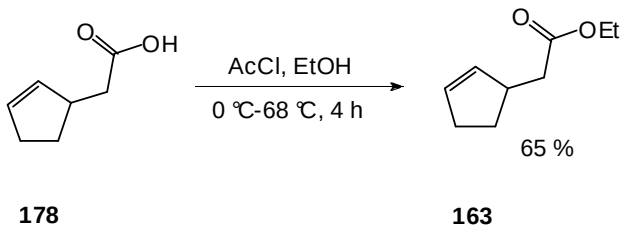
a. Zn(Hg) method. b. Zn/CuCl method. c. The carbenoid precursor was added by syringe pump over 2 h.

For example, whilst cyclopropanation reactions with **164** and **22** favoured formation of the *trans* or *exo* cyclopropane (Table 1, entry 1 and entry 2), this trend seems to be reversed in the cyclopropanation of **165** (Table 1, entry 3) and is not observed for the closely related cases of styrene **33** (Table 1, entry 4), **166** (Table 1, entry 5) and dihydronaphtalene **167** (Table 1, entry 6).[115,116]

2.1. Oxazolidin-2-one derivatives as carbenoid precursors

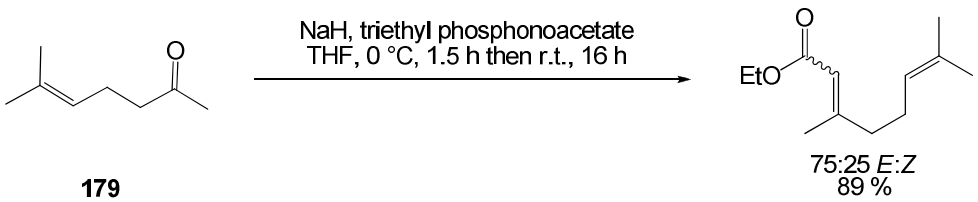
2.1.1. Synthesis of alkenes

Alkenes **160**, **161** and **162** are commercially available, alkene **163** was obtained in 65% yield from the reaction of commercially available (cyclopent-2-enyl)acetic acid **178** with ethanolic HCl (Scheme 89).[118]



Scheme 89

Diene **159** was synthesised from 6-methyl-5-hepten-2-one **179** by reaction with triethyl phosphonoacetate in the presence of sodium hydride in tetrahydrofuran.[119] A mixture of (*E*) and (*Z*) isomers was obtained in 89% overall yield (75:25 *E*:*Z*). The pure *E* isomer was isolated by column chromatography and used for subsequent cyclopropanation reactions (Scheme 90).



Scheme 90

2.1.2. A preamble on the assignment of stereochemistry

The geometry of each cyclopropane synthesised was determined as *trans*, *cis*, *exo* or *endo* by ^{1}H NMR spectroscopy analysis. According to the Karplus equation, the value of the coupling constant of vicinal protons is related to their dihedral angle (Figure 5).[120]

$$^{3}J_{ab} = K\cos^{2} A - 0.28 \text{ for } \quad 0°C < A < 90°C$$

$$^{3}J_{ab} = K'\cos^{2} A - 0.28 \text{ for } \quad 90°C < A < 180°C$$

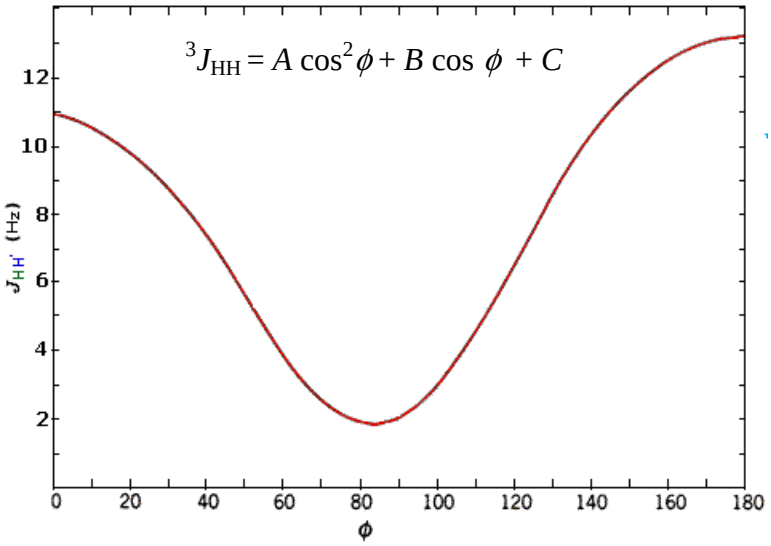


Figure 5

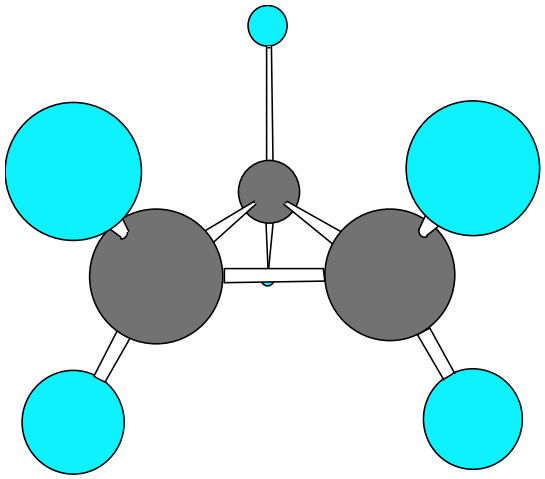


Figure 6

The value of the dihedral angle between two *cis* protons is 0 degrees and between two *trans* protons 145 degrees (Figure 6), thus according to the equation the value of the coupling constant of vicinal protons is larger for *cis* than for *trans* couplings.[120]

$$\mathbf{J}_{\textit{cis}\ \mathbf{(vicinal)}} > \mathbf{J}_{\textit{trans}\ \mathbf{(vicinal)}}$$

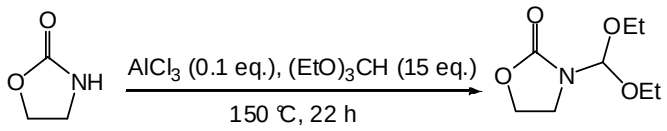
Analysis of the N-C*H* proton of the cyclopropane unit and measurement of its coupling constant allowed easy determination of the geometry of the cyclopropane.

For all the compounds synthesised, the range of values of the coupling constant measured between two *trans* cyclopropyl protons is 1.9 Hz < J_{trans}< 5.5 Hz and the range of values of the coupling constant measured between two *cis* cyclopropyl protons is 6.2 Hz<J_{cis}< 9.0 Hz.

The signal observed for the CHN proton in the *trans* configuration is a doublet of triplets with a *cis* coupling constant and two *trans* coupling constant. The signal observed for the CHN proton in the *cis* configuration is a triplet of doublets with two *cis* coupling constants and one *trans* coupling constant.

2.1.3. Cyclopropanation studies

Diethoxymethyl oxazolidin-2-one **158** had previously been prepared in the laboratory by reaction of oxazolidinone and triethyl orthoformate in the presence of aluminium chloride and was used without further purification (Scheme 91).[115,121]

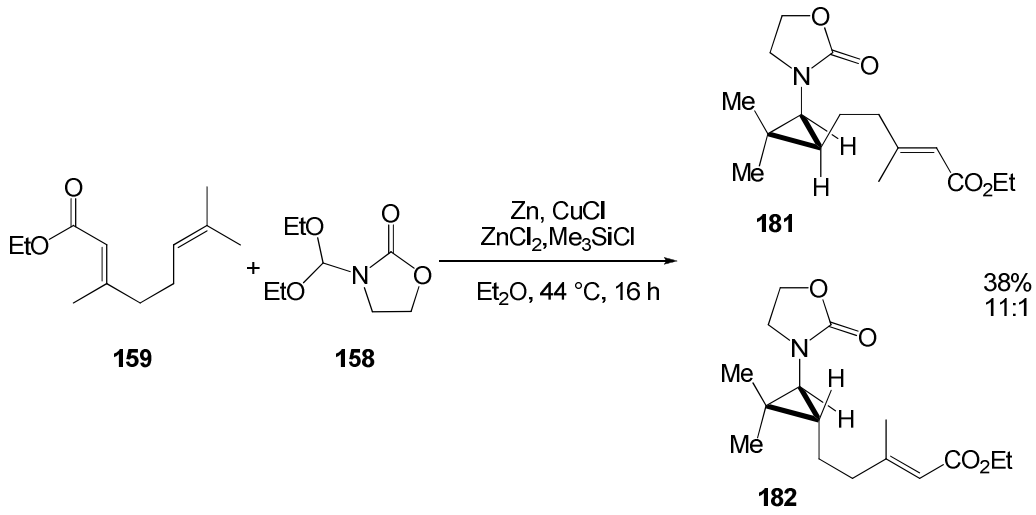


180 **158** 67%

Scheme 91

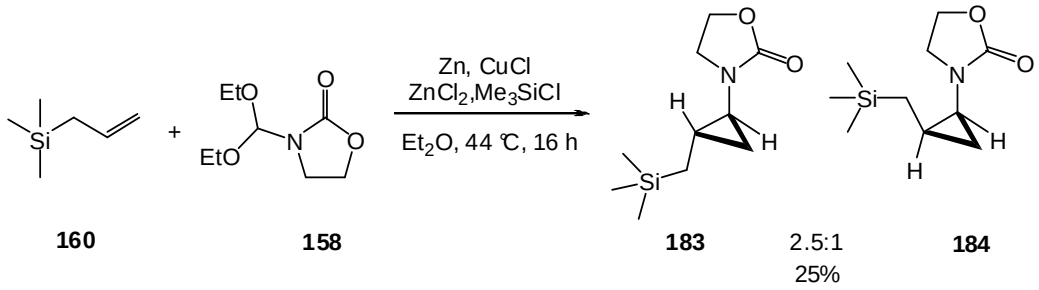
The cyclopropanation reaction was then carried out using zinc, copper chloride, zinc chloride and trimethylsilyl chloride in diethyl ether heated at 44 °C for 16 hours in the presence of the carbenoid precursor **158** and the mono-, di-, and trisubstituted alkenes **159**, **160**, **161**, **162** and **163** to obtain the corresponding *N*-cyclopropyloxazolidinones in stereoselective fashion in moderate to good yields.

Pleasingly, under the reaction conditions used, chemoselective cyclopropanation of the more electron-rich double bond was observed for the cyclopropanation of **159**, confirming our hypothesis on the essentially electrophilic nature of the carbenoid. The *cis* cyclopropane **181** was the major product (38% yield) obtained with a ratio *cis*:*trans* 11:1 based on the crude ^{1}H NMR spectrum. The ester group was tolerated under the reaction conditions (Scheme 92).



Scheme 92

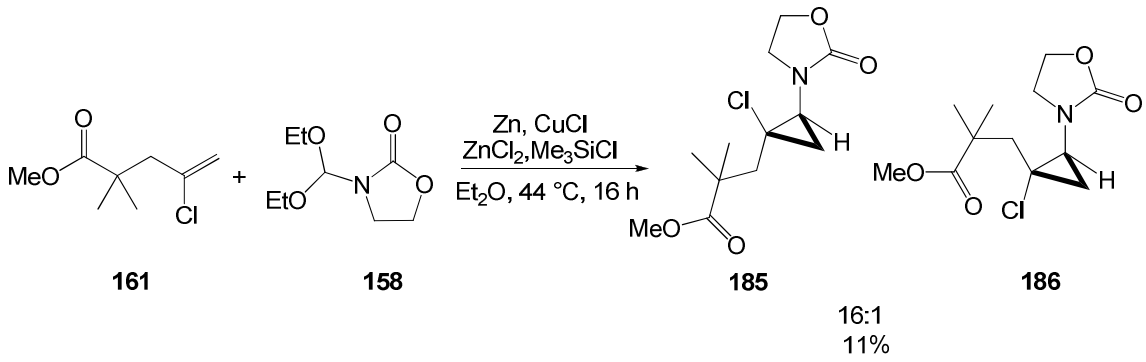
Based on the ^{1}H NMR spectrum of the isolated products resulting from the cyclopropanation reaction of allyltrimethylsilane, **160**, the *trans N*-cyclopropyl oxazolidinone **183** and the *cis* diastereoisomer **184** were obtained in a ratio of 2.5:1. The 25% yield was calculated for the mixture of the two isomers obtained after purification by flash column chromatography (Scheme 93).



Scheme 93

We were pleased to note that, in spite of the electrophilic nature of some of the intermediates involved in carbenoid generation it was possible to use an allylsilane.

The cyclopropanation of alkene **161** led in low yield (11%) to the formation of the cyclopropane **185** (the major isomer) in which the smaller halogen is adjacent to the amido group (Scheme 94).



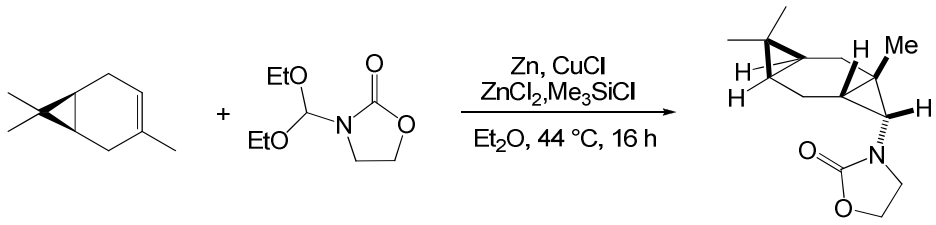
161 **158** **185** **186**

16:1
11%

Scheme 94

Once again, the ester and halogen group were tolerated under the reaction conditions.

The major diastereoisomer resulting from the cyclopropanation of **162** was the *endo* cyclopropane **187** obtained in 58% yield (Scheme 95).

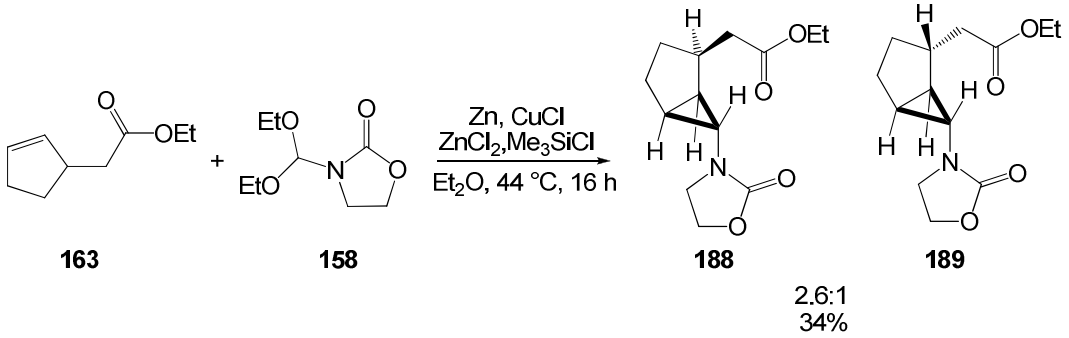


162 **158** **187**
58%

Scheme 95

According to ^{1}H NMR spectroscopy studies, a strong preference for one (**187**) of the four possible diastereoisomers was observed.

The two major diastereoisomers obtained and isolated from the cyclopropanation reaction of **163**, were the two *exo* cyclopropanes (**188** and **189**) obtained in a ratio 2.6:1 (based on the crude ^{1}H NMR spectrum). The yield of the reaction (34%) was calculated from the total yield of isomers obtained after purification by flash column chromatography (Scheme 96).

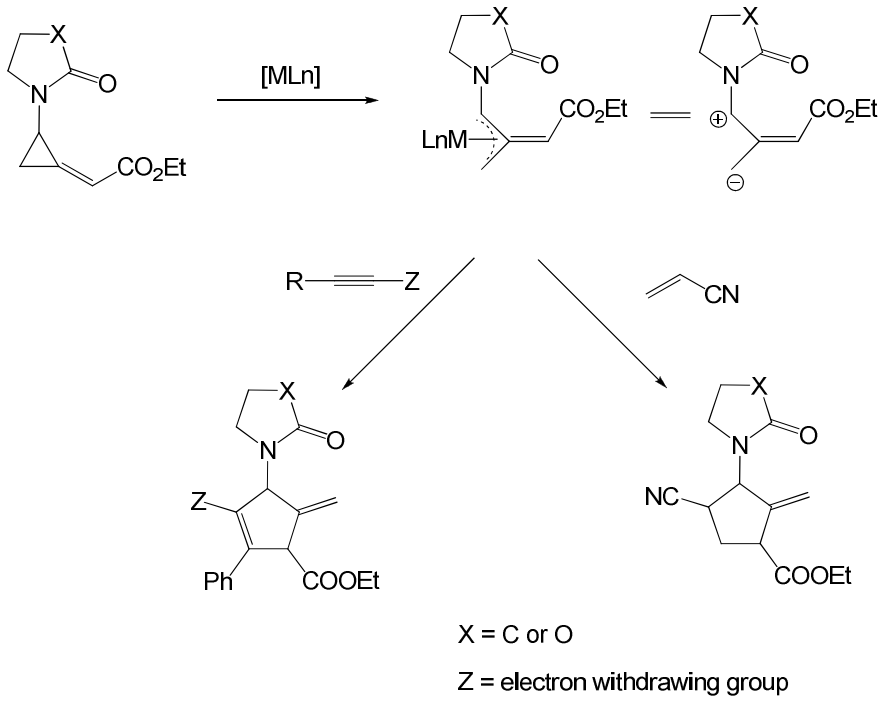


Scheme 96

In this case, although four diastereoisomers could in principle be obtained. ^{1}H NMR spectroscopy indicated a preference for only two of these.
The ability of the ester group to coordinate the organozinc carbenoid and favour delivery to the more hindered face of the alkene in this reaction was noteworthy.

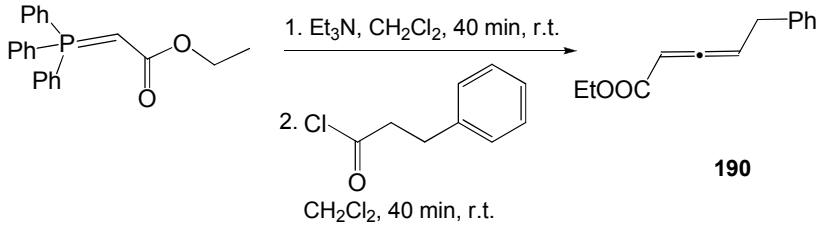
First of all, in terms of the chemoselectivity of the reaction, the above results confirm the electrophilic character of the organozinc carbenoid, and prove that silyl, ester and halogen functionality are all tolerated under the reaction conditions using zinc and trimethylsilyl chloride.[122]
The rationalisation of the stereochemical outcome in such reactions will be discussed later (*vide infra*).

We also wished to investigate the cyclopropanation of allenic substrates since the formation of a methylene cyclopropane by amidocyclopropanation of an electronically differentiated allene could lead to further transition metal mediated cycloaddition reactions as shown below and could be used for the design of more complex molecules (Scheme 97).[14,123]



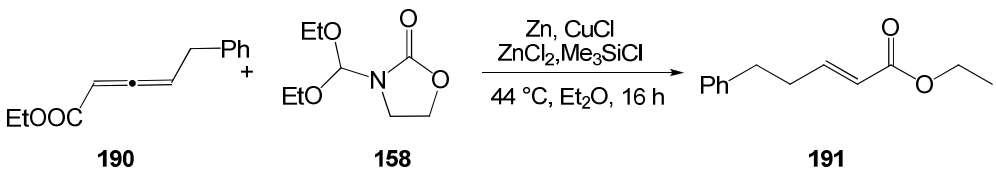
Scheme 97

Allene **190** had been synthesised previously in the laboratory by reaction of 3-phenylpropanoyl chloride with ethoxycarbonylmethylphosphorane in presence of triethylamine in dichloromethane (Scheme 98). [124]



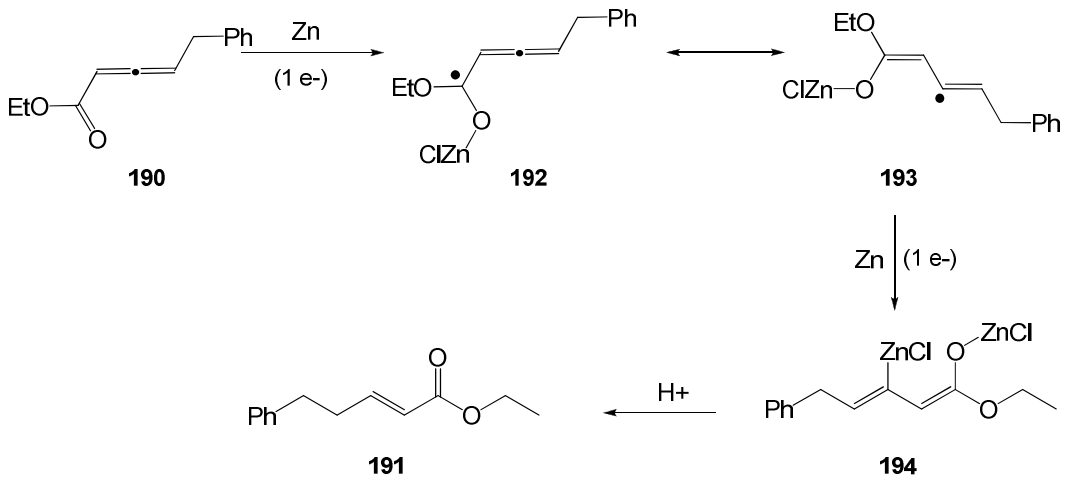
Scheme 98

The cyclopropanation reaction was carried out using our oxazolidin-2-one derivative **158** as a carbenoid precursor. Unfortunately no evidence for cyclopropane formation was observed under the reaction conditions (Scheme 99).



Scheme 99

The only product observed was the alkene **191**, obtained by the reduction of one of the double bonds. The proposed mechanism explaining this result is shown below (Scheme 100).



Scheme 100

The allene **190** was therefore reduced by two single electron transfers from zinc in the presence of a proton source which is encouraged by the formation of a conjugated zinc ester enolate. Unfortunately, reduction of one double bond of the allene was faster and more favourable than trapping by the organozinc carbenoid and led to **191**. This result is different from the chemoselective cyclopropanation of the more electron-rich double bond of the diene **159** which yields a cyclopropane, and in which the unsaturated ester moiety did not react.

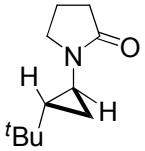
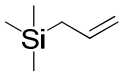
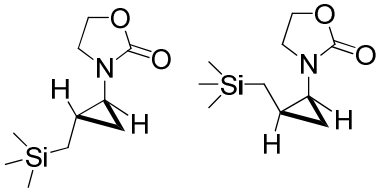
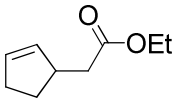
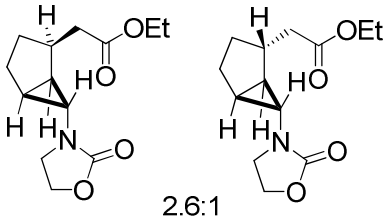
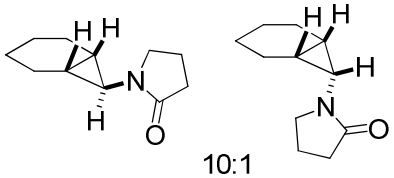
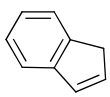
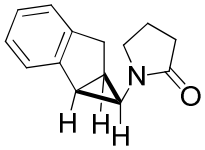
The replacement of trimethylsilyl chloride by Et_2AlCl as a Lewis Acid and proton scavenger would certainly be of interest as well as other allenes which do not contain the α,-β unsaturated ester unit.

2.1.4. Stereochemistry

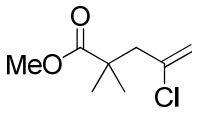
As indicated earlier, our thoughts now focused on the more vexatious problem of rationalising the stereochemical outcome of these reactions.

When taken together with the results obtained from the cyclopropanation of other alkenes which had previously been studied within our group from pyrrolidinone or oxazolidinone precursors, overall comparison of the different results clearly illustrates the complexity in

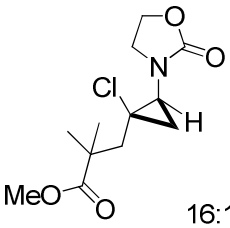
predicting the stereoselectivity of the cyclopropanation reaction which seems to depend on the nature of the alkene (Table 2).[115,116]

Entry	alkene	Products
1[a]		
	164	>95:5 **168** (61%[b])
2		
	160	2.5:1 **183** **184**
3		(25%[c]) 
	163	2.6:1 **188** **189**
4[a]		(34%[c]) 
	22	10:1 **169** **170**
5[a]		(66%[b]) 
	165	>95:5 **171** (66%[c])

6



161

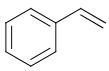


16:1

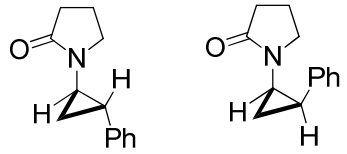
184 **186**

(11%[c])

7[a]



33

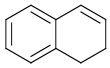


1.1:1

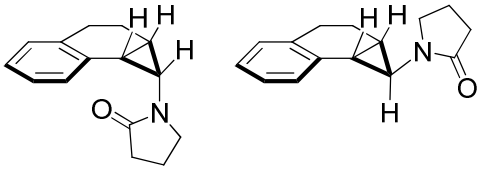
172 **173**

(70%[b,d])

8[a]



166



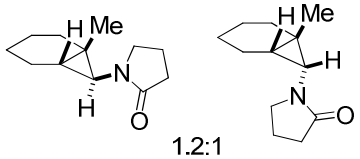
1:1

174 **175**

(28%[c])

9[a]

167

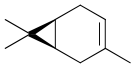


1.2:1

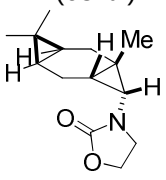
176 **177**

(63%[b])

10



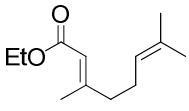
162



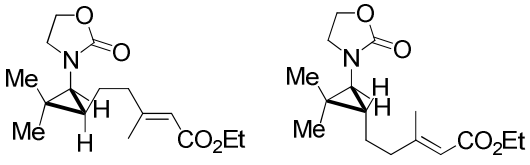
>90:10

187 (58%[c])

11



159



11:1

181 **182**

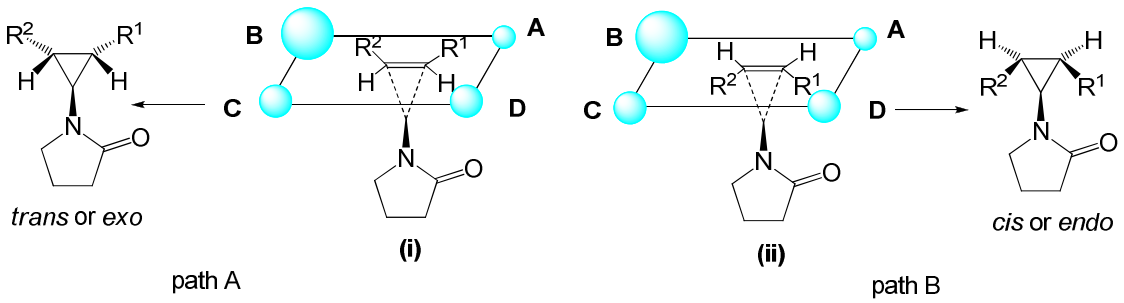
(38%[c])

a. Cyclopropanes synthesised previously in the group by Mr G. Bégis and Dr T. D. Sheppard b. Zn(Hg) method. c. Zn/CuCl method. d. The carbenoid precursor was added by syringe pump over 2 h.

Table 2

In general, reaction with a monosubstituted alkene tends to favour formation of the *trans* product, and increasing bulk reinforces this behaviour (Table 2, entries 1 and 2). The trends for more substituted alkenes were more difficult to rationalise. The *exo*/*trans* cyclopropane was the major isomer observed in the case of the cyclopropanation of disubstituted alkenes **163** and **22** (Table 2, entry 3 and entry 4) and the trisubstituted alkenes **162** (Table 2, entry 10) whereas the *endo* or *cis* cyclopropane was the major isomer in the case of the cyclopropanation of the disubstituted alkenes **165** and **161** (Table 2, entry 5 and entry 6) and the trisubstituted alkene **159** (Table 2, entry 11). Moreover cyclopropanation of other mono-, di- and trisubstituted alkenes showed virtually no stereoselectivity (Table 2, entry 7, entry 8 and entry 9).

At first sight, there appeared to be little pattern in the observed results, so in order to gain insight we tried to explain the stereoselectivity using a quadrant model in which the quadrant A was largely unhindered, B sterically congested, and C and D moderately hindered (Scheme 101). During the cyclopropanation reaction with a monosubstituted alkene, R^2 (which is a proton) fits well in the quadrant B (the most sterically hindered) and R^1 in the quadrant A (the most unhindered) which leads to the formation of a *trans* or *exo* cyclopropane (Scheme 101, path A). Whereas for a *cis* disubstituted alkene, R_2 would not fit well in quadrant B due to steric interactions and the alternative approach of the alkene would be preferred leading to the *cis* or *endo* cyclopropane (Scheme 101, path B).[122]



Scheme 101

Considering the related cyclopropanation using the oxazolidin-2-one **158** as an organozinc carbenoid precursor, two transitions state were proposed using the quadrant model and placing the zinc atom in quadrant D. Coordination of the zinc to the oxygen atom of the carbonyl group would then place the oxazolidinone ring in quadrant C, and the methylene group in quadrant B, leaving quadrant A empty. During the approach of a monosubstituted alkene, the R_1 group would prefer to fit in quadrant A (R^2 is a proton) giving rise to a *trans*

cyclopropane. However if a disubstituted alkene was cyclopropanated, the second transition state (ii) would be preferred to give the *endo* cyclopropane where R^1 and R^2 would fit in the moderately sterically congested quadrants D and C respectively occupied by the zinc atom and the carbonyl group. This pathway would avoid the interaction between R^2 and the methylene group alpha to the nitrogen atom which takes place in the *exo* transition state (i) (Figure 7).

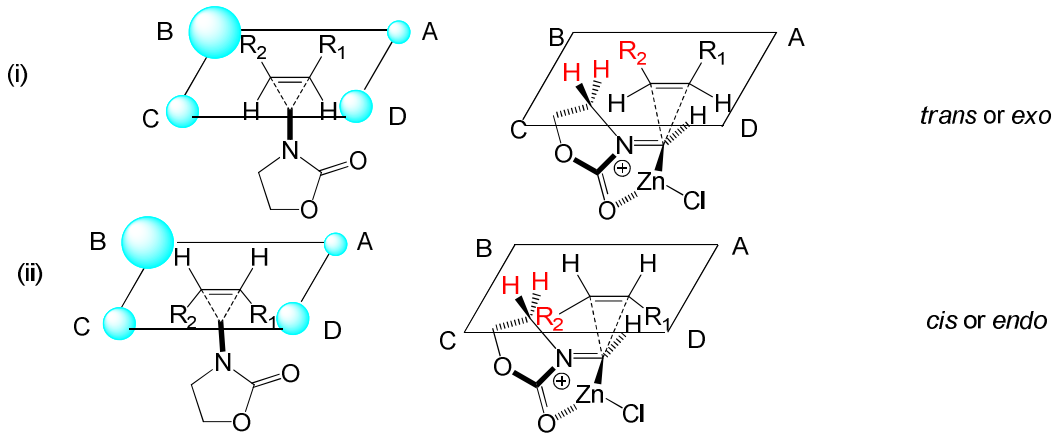
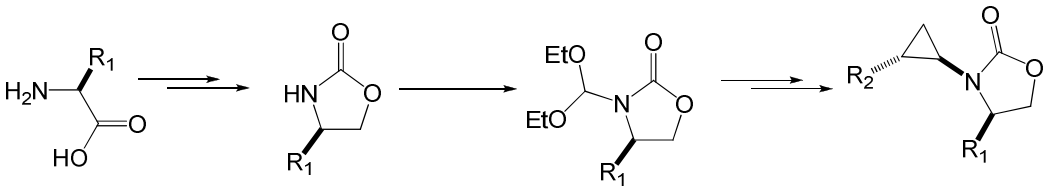


Figure 7

Although semi empirical, this quadrant model manages to explain the different possible approaches of the alkene to the organozinc carbenoid. This model was an *a posteriori* explanation and confirmed most of the results observed.

2.2. Chiral oxazolidin-2-one derivatives as carbenoid precursors

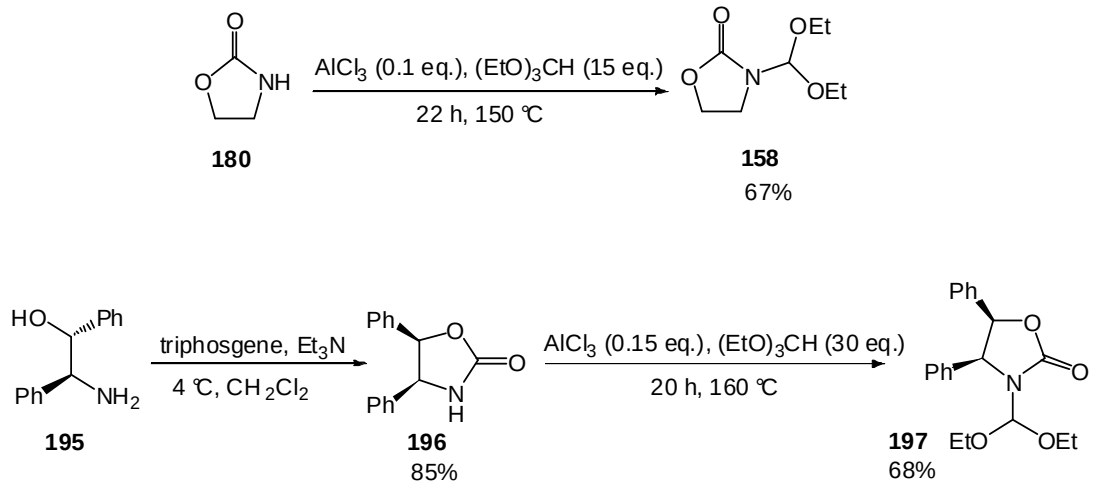
On completion of the fundamental studies described above, we then moved to a second goal of our research programme which involves the design of a wider range of enantiopure functionalised organozinc carbenoid precursors in order to have access to a wider range of highly functionalised *N*-cyclopropyl oxazolidinone (Scheme 102).



Scheme 102

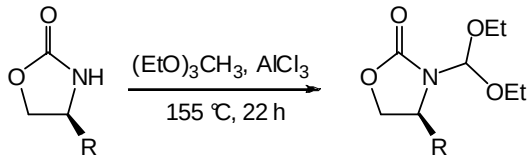
2.2.1. Synthesis of chiral carbenoid precursors

At this stage, the parent enantiopure oxazolidinone carbenoid precursor **197** had also previously been prepared within the group from commercially available (−)-2-amino-1,2-diphenylethanol **195** in two steps by an analogous route to that used for the achiral compound **158** as outlined below (Scheme 103). [115,117,121]



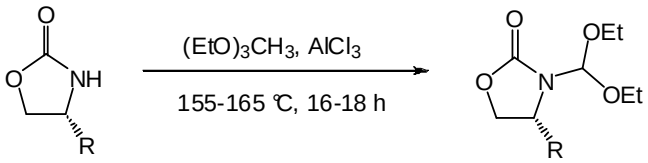
Scheme 103

Whilst the yields of the above reactions were sufficient to allow subsequent synthetic steps, the synthesis of other enantiopure carbenoid precursors carried out by Mr. G. Bégis had led to diminished yields and therefore posed a problem (Tables 3 and 4).[115]



Oxazolidinone	R	Yield	Product
198	CH_2Ph	25%	**200**
199	^{i}Pr	29%	**201**

Table 3

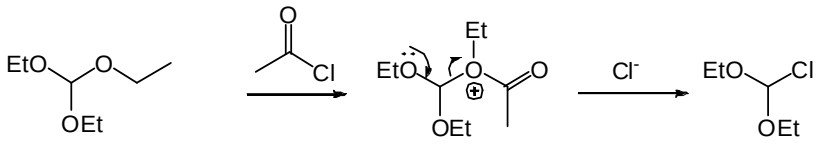


Oxazolidinone	R	Yield	Product
202	PMP	26%	**206**
203	Ph	33%	**207**
204	CO_2Et	55%	**208**
205	$CH_2OTBDMS$	60%	**209**

Table 4

As illustrated above, the conditions developed up to this point were capricious and not convenient. Moreover application on large scale tended to diminish the yield and the high boiling point of triethyl orthoformate made it difficult to remove any excess at the end of the reaction.[115]

Accordingly a range of other methods were investigated in order to find better conditions for the formation of these precursors under milder conditions, with a smaller quantity of triethyl orthoformate and more moderate reaction temperatures. In the first instance, we elected to add acetyl chloride to the reaction mixture with the intention of facilitating the departure of one of the ethoxy groups of triethyl orthoformate as shown in Scheme 104 and thus generating the more reactive halide **212** *in situ*.



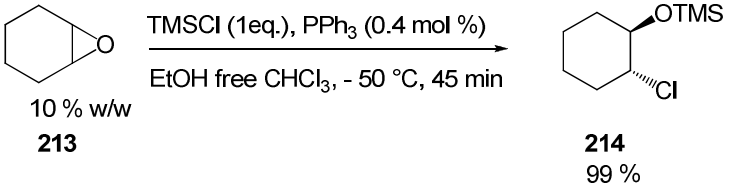
210 **211** **212**

Scheme 104

An initial result demonstrated that *N*-diethoxymethyl oxazolidin-2-one **158** could be obtained on a 10 g scale in good yield using a "catalytic amount" of acetyl chloride, and only 2.6 equivalents of triethyl orthoformate at room temperature (Scheme 105).[122]

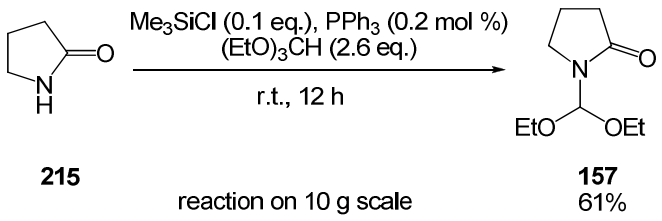
Scheme 105

With a similar objective in mind, we also investigated the addition of chlorotrimethylsilane in the presence of triphenylphosphine as a genuine catalyst. This combination was chosen since it is known that stereoselective epoxide ring opening to vicinal siloxychlorohydrins can be achieved at low temperature in the presence of a catalytic amount of triphenylphosphine in ethanol free chloroform (Scheme 106).[125]



Scheme 106

It was gratifying to note that *N*-diethoxymethyl pyrrolidin-2-one **157** was thus obtained in good yield using a catalytic amount of trimethylsilyl chloride and triphenylphosphine, and triethyl orthoformate in dichloromethane at room temperature (Scheme 107).[122]

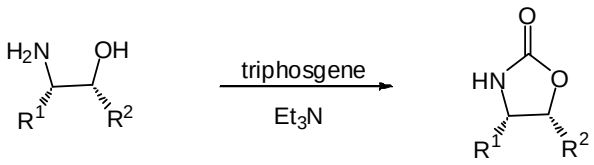


Scheme 107

Following these initial studies on inexpensive systems, we then applied these results to the preparation of new chiral carbenoid precursors, in the hope of obviating the problems outlined above.

The necessary chiral oxazolidin-2-one precursors were readily prepared in good to quantitative yield from natural amino acid derivatives (Table 5 entries 1-3) and from

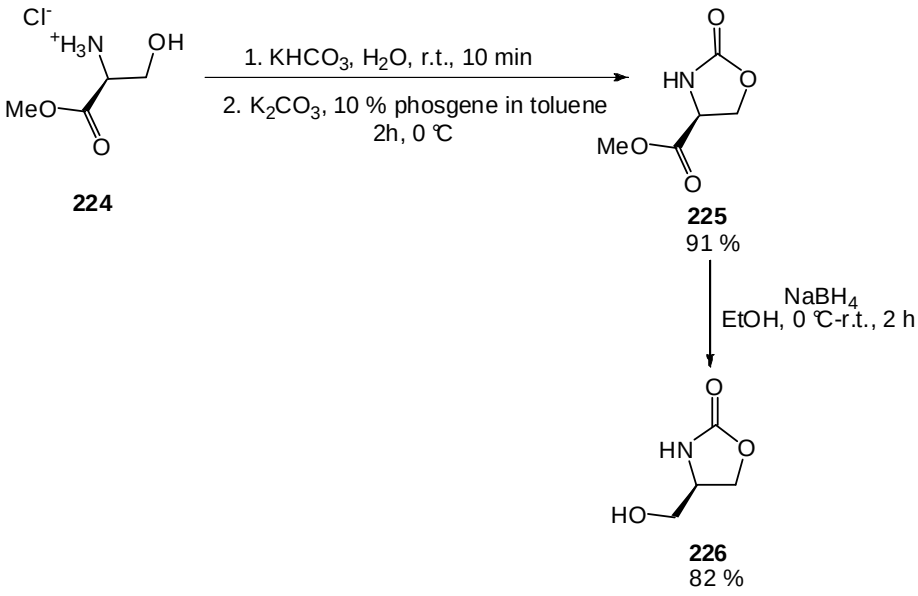
commercially available unnatural amino acids derivatives (Table 5, entries 5 and 6) by standard literature protocols involving triphosgene and triethylamine (Table 5).



Entry	Aminoalcohol	R^1	R^2	Yield	Product
1	**216**	^{i}Pr	H	89%	**199**
2	**217**	CH_2 ^{i}Pr	H	99%	**221**
3	**218**	CH_2Ph	H	99%	**198**
4	**219**	CH_3	Ph	99%	**222**
5	**220**	C_2H_5	H	99%	**223**

Table 5

The oxazolidinone **226** was obtained in 75% over 2 steps by reduction of the oxazolidinone **225** obtained by treatment with phosgene of serine methyl ester hydrochloride **224** (Scheme 108)

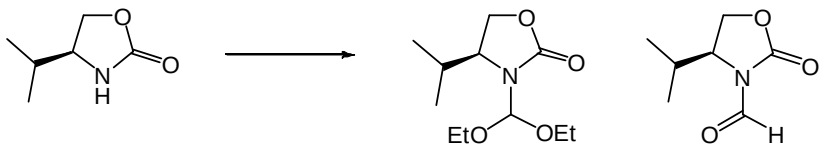


Scheme 108

As a result of the problems previously encountered in the synthesis of enantiopure carbenoid precursors and in light of the encouraging preliminary observations noted above, we therefore decided to investigate alternative conditions for the synthesis of other enantiopure precursors using three different chiral oxazolidinones (Tables 6, 7 and 8). The major problem of this reaction is that the corresponding orthoamide is not the exclusive product.

2.2.1.1. Optimisation of reaction conditions using the oxazolidinone derived from L-valine

The synthesis of orthoamide **201** from oxazolidinone **199** was performed using a range of different catalytic systems with different ratios, temperatures and in different solvents (Table 6).



199 **201** **227**

entry	$(EtO)_3CH$ eq.	catalyst	T	solvent	t	NMR observations
1	10	AcCl (1 eq.)	50 °C	neat	2 h	mixture of **199**/**227** (1:2)
2	10	AcCl (2 eq.)	90 °C	neat	1 h	mixture of **199**/**201**/**227** (4.8:2:1)
3	30	$AlCl_3$ (0.15 eq.)	100 °C	neat	16 h	mixture of **199**/**201**/**227** (14.8:1:2)
4	10	BF_3 (1 eq.)	40 °C	CH_2Cl_2	16 h	decomposition
5	2.6	TMSCl (1.1 eq.)*	40 °C	CH_2Cl_2	16 h	mixture of **199**/**227** (1:1.4:3)
6	3	$AlCl_3$ (0.15 eq.)	110 °C	toluene	16 h	80 % conversion to **201**

*PPh_3 used as catalyst (0.15 eq.)

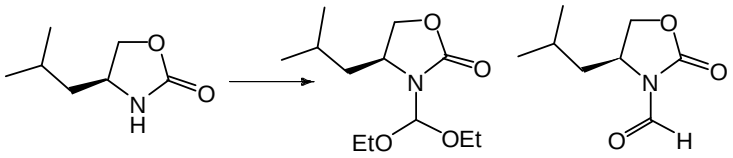
Table 6

Under the conditions employed using the oxazolidinone derived from *L*-valine, the formation of **201** was observed only at high temperature (T>90 °C, Table 6, entries 2, 3 and 6). Changing the Lewis acid used did not improve the conversion, and led to decomposition of the starting material in the case of BF_3 (Table 6, entry 4). Finally the best result (Table 6, entry 6) was observed at high temperature (110 °C) with a catalytic

amount of aluminium chloride (0.15 eq.) as Lewis acid and 3 equivalents of triethyl orthoformate in toluene.

2.2.1.2. Optimisation of reaction conditions using the oxazolidinone derived from L-Leucine

A similar study was also performed on the synthesis of orthoamide **229** through modification of the reactions conditions (Lewis acid, temperature, solvent and reaction time) (Table 7).



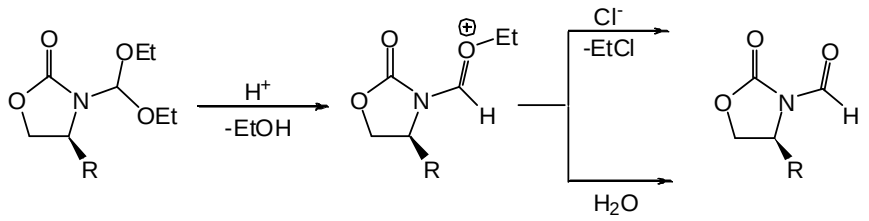
221 **228** **229**

entry	$(EtO)_3CH$ eq.	LA	T	solvent	reaction time	NMR observations
1	30	$AlCl_3$(0.15 eq.)	150 °C	/	18 h	completion 48% yield
2	4	$TiCl_4$ (0.15 eq.)	40 °C	CH_2Cl_2	16 h	mixt. **221**/**229** (1.7:1)
3	4	$TiCl_4$ (1 eq.)	40 °C	CH_2Cl_2	16 h	**221**
4	6	$AlCl_3$ (0.15 eq.)	110 °C	toluene	16 h	50% conversion
5	6	BF_3 (0.15 eq.)	110 °C	toluene	16 h	no reaction

Table 7

Studies carried out with compound **221** and triethyl orthoformate again demonstrated the importance of high temperatures (table 7, entries 1 and 4). As before, catalytic aluminium chloride was the best Lewis acid found.

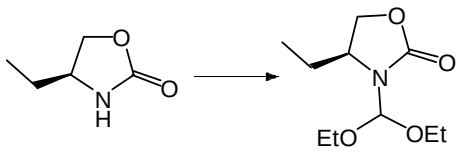
Formamides **227** and **229** were formed either by hydrolysis of the corresponding diethoxymethylamide in the presence of a proton source and water during the work up or by nucleophilic attack using chloride anion (Scheme 109).[122]



Scheme 109

2.2.1.3. Optimisation of reaction conditions using the oxazolidinone derived from 2-amino-1-butanol

Finally, some experiments were performed on the oxazolidinone **223** using trimethylsilyl chloride as Lewis acid (Table 8).



223 **230**

entry	$(EtO)_3CH$ eq.	TMSCl eq.	T	solvent	t	NMR observations
1	2.6	1.1	r.t.	CH_2Cl_2	16 h	51% conversion
2	2.6	1.1	40 °C	CH_2Cl_2	16 h	73% conversion *
3	6.5	4.25	40 °C	CH_2Cl_2	72 h	88% conversion *
4	3	3	r.t.	Toluene	16 h	61% conversion
5	6	6	40 °C	CH_2Cl_2	16 h	50% conversion

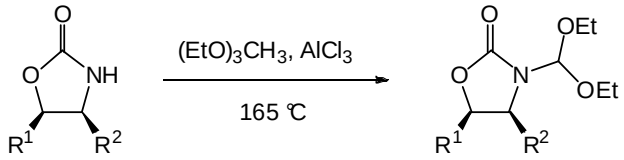
*PPh_3 used as catalyst (0.15 eq.)

Table 8

The side product formamide was never observed following these conditions. Surprisingly when oxazolidinone **223**, derived from 2-amino-1-butanol **220** was used, good conversion was obtained at 40 °C using only trimethylsilyl chloride and triphenylphosphine in dichloromethane (Table 8, entry 3). This result was unexpected considering the small difference in the structure of the starting materials **223** compared to **199** (Tables 6 and 8).

Despite further investigation into a range of reaction conditions no significantly better results than the current literature procedure was found.[121] Due to time constraints, we therefore decided to continue our investigations using the classical methodology.

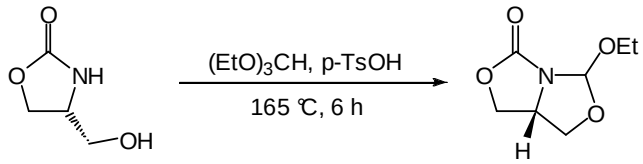
Finally, improved yields of the carbenoid precursors were achieved using a large excess of triethyl orthoformate (up to 40 equivalents) under acidic conditions at 165 °C for at least 18 hours. Working on small scale with very pure starting materials (less than 10 mmol of the oxazolidin-2-one derivatives) was the best way to obtain the chiral carbenoid precursors in moderate to good yields. We found that it was important to remove excess triethyl orthoformate under high vacuum, prior to further purification, since it could not be completely separated from the desired product by flash chromatography (Table 9).



Oxazolidinone	R_1	R_2	Yield	Product
199	H	^{i}Pr	55%	**201**
221	H	$CH_2{}^{i}$Pr	63%	**228**
198	H	Bn	53%	**200**
222	Ph	Me	53%	**231**
223	H	Et	55%	**230**

Table 9

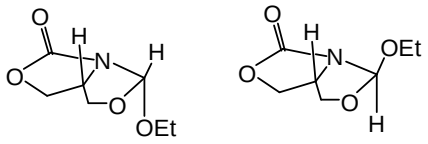
Carbenoid precursor **232** could not be synthesised using the literature conditions with aluminium chloride as the Lewis acid. Therefore **232** was synthesised in 22% yield from an alternative procedure using triethyl orthoformate and *para*-toluenesulfonic acid heated to reflux (Scheme 110).



226 **232**

Scheme 110

Two diastereoisomers could have been obtained depending on the position of the ethoxy group (Figure 8).



A B

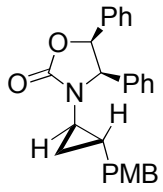
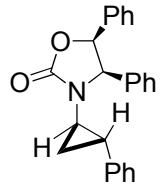
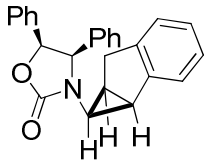
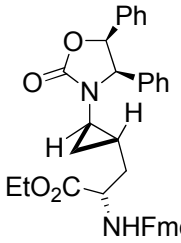
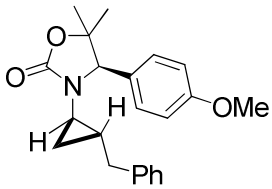
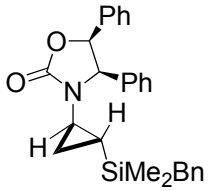
Figure 8

However, the isolated product was not stable and further NMR analysis could not be performed to determine the major isomer obtained.

2.2.2. Synthesis of chiral *N*-cyclopropyloxazolidinones

With the chiral carbenoid precursors in hand, we turned our attention towards the synthesis of *N*-cyclopropyl oxazolidinones *via* their reaction with different alkenes.

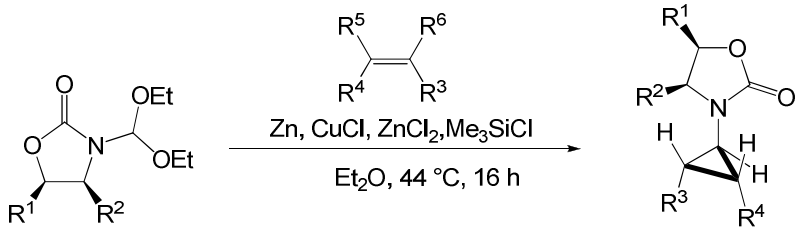
Previously within the group, only two chiral oxazolidinone had been used as organozinc carbenoid precursors for preparation of enantiopure cyclopropanes from a limited selection of alkenes (Table 10).[115,117]

Entry	Product (major)	dr[a]	Yield
1	 **233**	87:9[c] **233**:**234**	63%[f]
2	 **235**	56:28[d]:6[c]:6[d] **235**:**236**:**237**:**238**	54%[f]
3	 **239**	[b]	76%[f]
4	 **240**	[b]	70%[f]
5	 **241**	[b]	36%[g]
6	 **242**	[b]	42%[f]

a. Any diastereoisomers not observed by ^{1}H NMR spectrum were considered to be <2%. b. only one diastereoisomer was observed / isolated. c The minor diastereoisomer was a *trans*/*exo* cyclopropane. d. The minor diastereoisomer was a *cis*/*endo* cyclopropane. f. Zn(Hg) was used. g. Zn/CuCl was used.

Table 10

Thus, it was of interest to extend the range of both chiral carbenoid precursors and functionalised alkenes for cyclopropanation reaction (Tables 11 and 12).



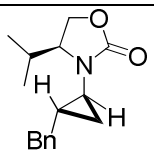
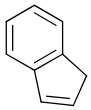
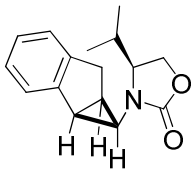
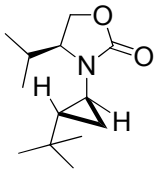
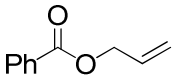
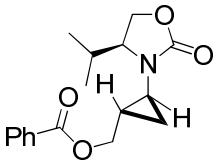
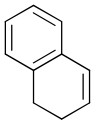
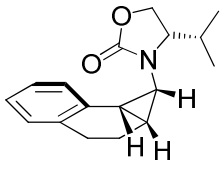
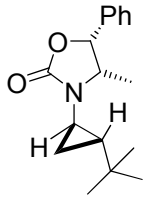
entry	alkene	Product(s)	dr[a]	Yield
1			>90:10	42% [b] (33% [b,d])
	153	**244**		
2			>90:10	40% [b]
	165	**245**		
3			>90:10	29% [b]
	164	**246**		
4			82:14[e]	13% [b]
	243	**247**	**247**:**248**	
5			59:37[f]	40% [b, g]
	166	**249**	**249**:**250**	
6			[h]	20% [b]
	164	**251**		

Table 11

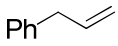
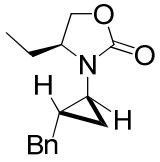
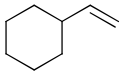
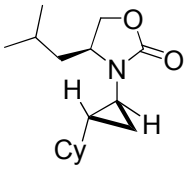
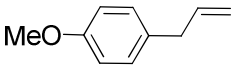
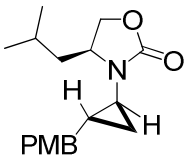
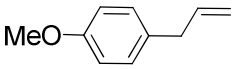
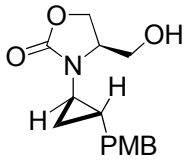
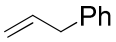
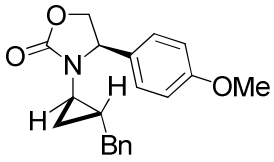
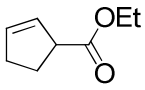
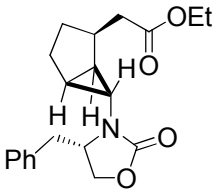
entry	alkene	Product(s)	dr	Yield
1			92:4[e]	44%[b]
	153	**254**		
2			>90:10	47%[c]
	252	**255**		
3			[h]	44%[c]
	253	**256**		
4			[h]	23%[b]
	253	**257**		
5			82:14[f]	29%[b,g]
	154	**258**	**258**:**259**	
6				26%[b,g]
	163	**260**		

Table 12

Table 11 and **Table 12**: a. Any diastereoisomers not observed by ^{1}H NMR were considered to be <2%. b. Zn/CuCl method. c. Zn(Hg) method. d. Reaction carried out as a one-pot procedure from the oxazolidinone **199** and triethyl orthoformate. e. The stereochemistry of the minor diastereoisomer was not determined. f. The minor diastereoisomer was a *trans*/*exo* cyclopropane. g. yield calculated on the total of isomers obtained after purification by flash column chromatography. h. No other diastereoisomers were observed/isolated.

The cyclopropanes were obtained in moderate to good yield with good stereoselectivity. Examination of these results in the tables 11 and 12 reveals that similar diastereoselectivities were observed for the same alkene when cyclopropanated using different oxazolidinones (Table 11, entry 1 and Table 12 entry 1 and entry 5, Table 11, entries 3 and 6 and Table 12 entries 3 and 4). Even in the case of very hindered system the stereoselectivity of the reaction does not seem to be affected (Table 12, entry 5). In general monosubstituted alkenes led to the formation of the *trans* cyclopropane (Table 11, entries 1, 3, 4, 6, Table 12, entry 1-5). However, with more substituted alkenes, stereoselectivity was dependant on the nature of the alkene. When a cyclic disubstituted alkene was used, the *endo* cyclopropane was obtained as the major product (Table 11, entries 2, 5).

As shown previously for the cyclopropanation reactions using a non chiral oxazolidinone precursor, functional groups such as ester are tolerated under the conditions reactions (Table 11, entry 4 and Table 12, entry 6).

In most of the cases, only one product was isolated out of the four potential isomers. The minor products are different depending on the nature of the oxazolidinone and the alkene. The cyclopropanation of **153** gave an inseparable mixture of the two *trans* diastereoisomers **258** and **259** (Table 12, entry 5) after purification by column chromatography whereas the cyclopropanation of **166** gave a mixture of the *endo* **249** and the *exo* **250** isomers (Table 11, entry 5).[126]

Cyclopropanation of the alkene **163** (Table 12, entry 6) could give eight possible diastereoisomers as shown in Figure 9. Unfortunately we were not able to isolate the major diastereoisomer in sufficient purity for characterization and instead only cyclopropane **260** (Table 12, entry 6) was isolated in pure form. The absolute geometry of the major diastereoisomer could not be therefore determined. The reaction was repeated using a large excess of the alkene to encourage the isolation of the major isomer but unfortunately none of diastereoisomers could be isolated pure.

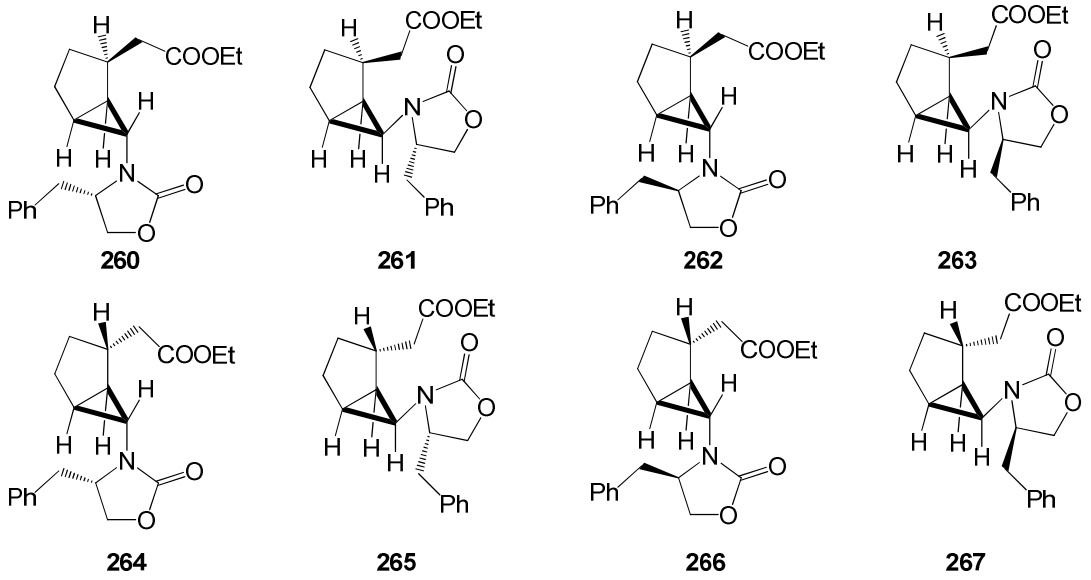
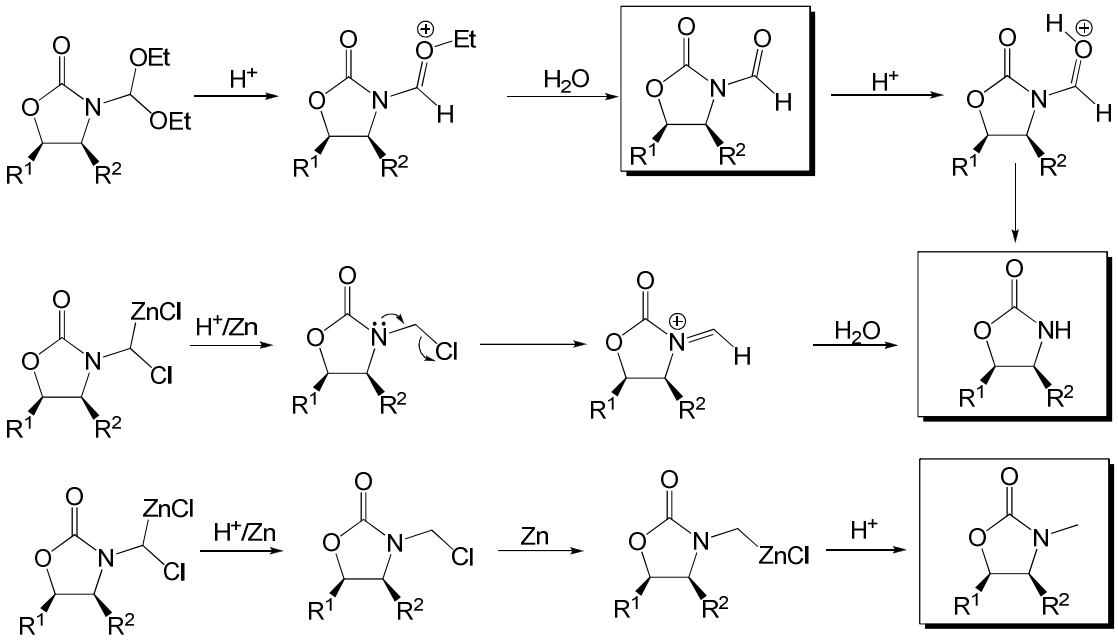


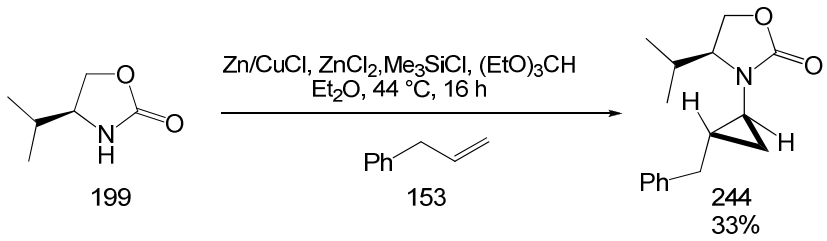
Figure 9

Three minor products were often present in the crude NMR spectrum and could not always be removed by purification. These were the formamide formed by "hydrolysis" of the unreacted carbenoid precursor during work up, the oxazolidinone which arose either from hydrolysis of the unreacted carbenoid precursor or organozinc carbenoid intermediate and the *N*-methyl oxazolidinone probably formed by protonation of the organozinc carbenoid (by traces of HCl present in the reaction) followed by its reduction by zinc (Scheme 111).[126]



Scheme 111

From a practical point of view, it would be more convenient to avoid the preparation of the orthoamide derived carbenoid precursors. As both the introduction of the diethoxymethyl group itself and the subsequent cyclopropanation reaction were carried out in the presence of Lewis acids, we therefore investigated whether the two processes could be combined into a one-pot reaction. Pleasingly in a preliminary experiment the cyclopropane **244** was obtained in 33% yield directly from the oxazolidinone **199** using zinc, copper chloride, zinc chloride, chlorotrimethylsilane and triethyl orthoformate in one pot. This compares favourably to the 28% yield previously obtained over two steps (Scheme 112).

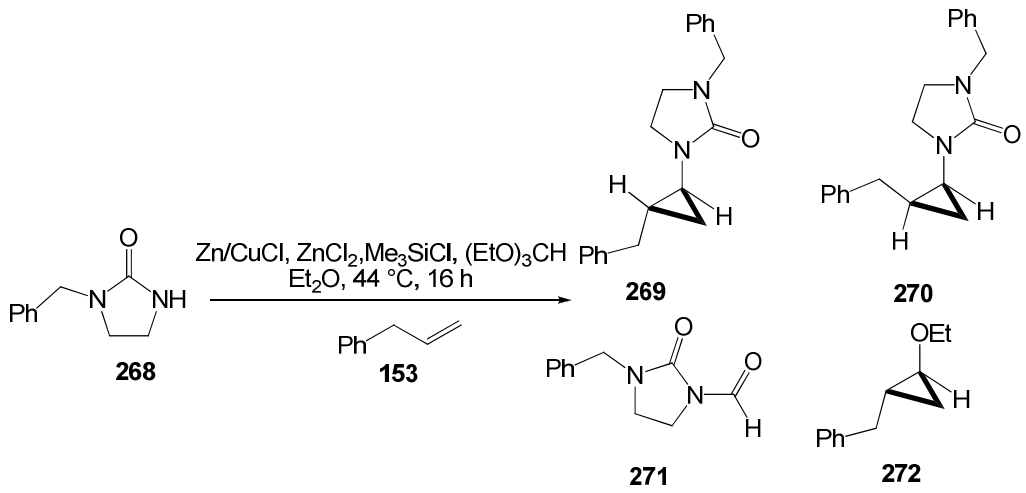


Scheme 112

Two modifications to the reaction procedure were then investigated in order to obtain the corresponding cyclopropane in one step from the oxazolidinone.

Initially a mixture of zinc chloride, trimethylsilyl chloride, and oxazolidinone **199** were heated to 44 °C in order to activate the carbenoid precursor and make it more reactive to zinc, copper chloride and the alkene **153** in diethyl ether added later on. However at this stage the resulting mixture was a semi-solid unsoluble in diethyl ether. Triethyl orthoformate was then added dropwise over 6 hours to the resulting mixture in order to form the organozinc carbenoid in situ which could then react with the alkene **153**. This modification led to formation of the *N*-cyclopropyl oxazolidinone **244** in 13% yield. In a second attempt, to obviate the problem of insolubility, addition of a solution of oxazolidinone **199** in triethyl orthoformate and dichloromethane dropwise over 6 hours to a mixture of zinc, copper chloride, zinc chloride, chlorotrimethylsilane and allylbenzene in diethyl ether followed by heating at reflux for 16 hours furnished *N*-cyclopropyl oxazolidinone **244** in 33 % yield.[126] With the benefit of hindsight it might have been interesting to examine an experimental method involving the addition of triphenylphosphine in order to further aid the formation of the organozinc carbenoid during this one pot process.

The cyclopropanation reaction of the alkene **153** was also performed following the first procedure but using the cyclic urea, 1-benzyl-imidazolidin-2-one **268**. A mixture of products was formed including the desired *trans* cyclopropane **269** and the *cis* cyclopropane **270**, the starting material **268**, *N*-formyl compound **271** and the alkoxy cyclopropane **272** formed *via* the normal formation of the alkoxy organozinc carbenoid (Scheme 113).

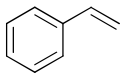
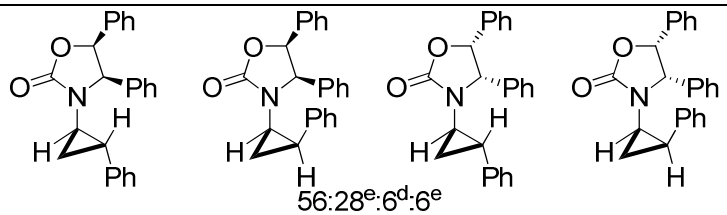
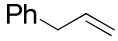
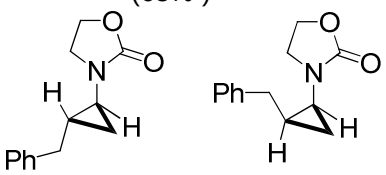
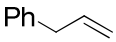
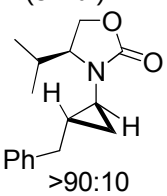
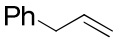
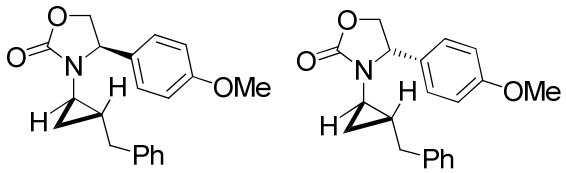
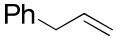
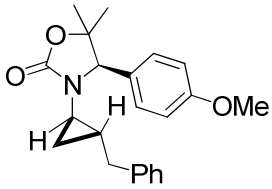
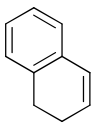
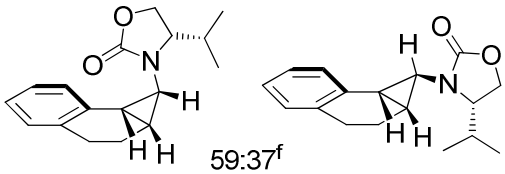


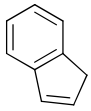
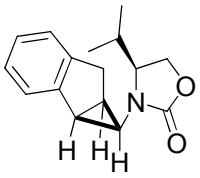
Scheme 113

The *trans*-cyclopropane was the major product formed, from ^{1}H NMR spectroscopic analysis of the crude reaction mixture, but only 10% could be isolated in pure form after extensive chromatography. Due to time constraints however, this potentially interesting molecular scaffold was not pursued further.

2.2.3. Stereochemistry

The geometry of the cyclopropane was determined to be *trans, cis, exo* or *endo* by ^{1}H NMR spectroscopy analysis. The examples shown below show again all the complexity of the stereoselectivity (Table 13).[115,116,117,122,126]

entry	alkene	Product(s)
1[a]		 56:28[e]:6[d]:6[e]
	33	**235** **236** **23** **238**
2[a]		(63%[c])  15 : 1
	153	**273** **274**
3		(57%[b])  >90:10
	153	**244** (42%[b])
4		 82:14[d]
	153	**258** **259**
5[a]		**(29%[b,f])**  >90:10
	153	**241** (36%[b])
6		 59:37[f]
	166	**249** **250** (40%[b,f])

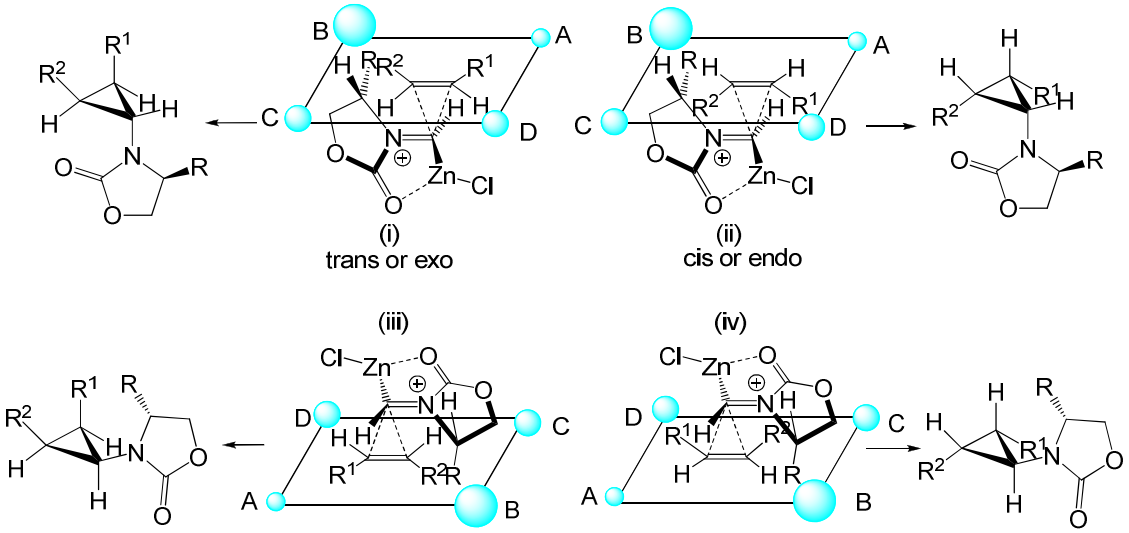
7			>90:10	**245** (40%[b])
	165			

a. cyclopropane synthesised previously in the group. b. Zn/CuCl method. c. Zn(Hg) method. d. The minor diastereoisomer was a *trans*/*exo* cyclopropane. e. The minor diastereoisomer was a *cis*/*endo* cyclopropane. f. yield calculated on the total of isomers obtained after purification by flash column chromatography.

Table 13

As highlighted earlier in our examination of the results obtained for the cyclopropanation reaction using chiral organozinc precursors, monosubstituted alkenes seems to lead to the formation of the *trans* cyclopropane and with more substituted alkenes, stereoselectivity was dependant on the nature of the alkene.

When the reaction was performed using a chiral carbenoid precursor for alkene **153** the selectivity seems to be greater than with non-chiral precursors (Table 13, entries 2, 3, 4 and 5). Moreover, ancillary functionality in the chiral oxazolidinone influenced the selectivity (Table 13, entries 4 and 5) with the formation of the two possible *trans* diastereoisomers favoured. At this stage, the stereoselectivity of the reaction was not easy to predict. Therefore, we investigated a more advanced quadrant model to explain the results observed. Cyclopropanation of alkenes using chiral organozinc carbenoid can potentially afford four diastereoisomers. The stereochemistry of these isomers will be based on the geometry of the cyclopropane (*cis*/*endo* or *trans*/*exo*) and on the position of the cyclopropane formed, relative to the chiral group of the oxazolidinone (Scheme 114).[126]



Scheme 114

The R group of the oxazolidinone controls which face of the alkene was cyclopropanated: the alkene preferred to approach the carbenoid from the opposite face to the R group [transition state (i) and (ii)] which explained the strong preference for one of the 4 diastereoisomers observed in most cases (Table 13).

In the case of the cyclopropanation of a monosubstituted alkene (R^2=H), transition state (i) is preferred with R_1 fitting well in the less sterically hindered quadrant A, leading to the *trans* cyclopropane. In the case of a disubstituted alkene (R^2≠H) the transition (ii) is preferred (R_1 and R_2 occupying quadrants C and D), to the transition states (i) and (iii) in which R^2, in quadrant B, would undergo a steric interaction with the oxazolidinone ring.

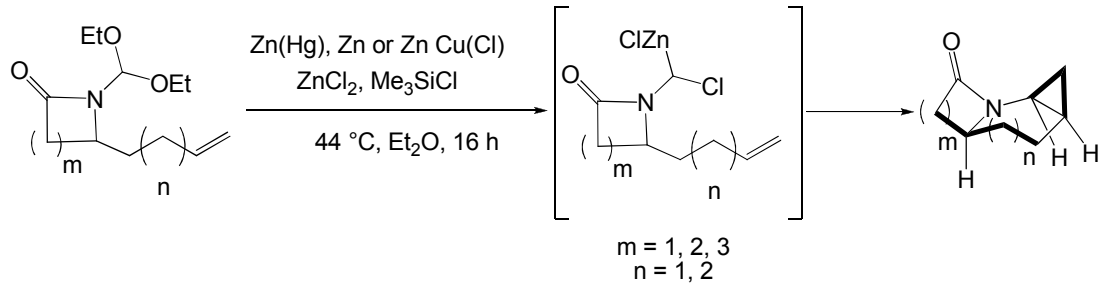
As outlined earlier, the minor products seem to depend on the nature of the oxazolidinone and the alkene (Table 13). The formation of the two possible *trans* cyclopropanes was favoured for the monosubstituted alkenes, except in the case of styrene **33** which showed a greater selectivity for the formation of the *cis* cyclopropane (Table 13, entry 1). The difference in the selectivity between the cyclopropane **241** and cyclopropanes **258**, **259** is probably due to the difference in size of the susbstituent group on the oxazolidinone which is bigger in the case of the cyclopropane **241** (Table 13, entries 5 and 4).

The geometry of the cyclopropanes were determined by ^{1}H NMR spectrum analysis considering the coupling constant of the cyclopropyl protons. However the relative stereochemistry between the chiral centre of the oxazolidinone and those on the cyclopropane could not be determined from ^{1}H NMR spectrum but was assigned by analogy with the X-ray crystal structures obtained for **247** and **239**[115,117] which also confirmed the absolute stereochemistry of the cyclopropane (Appendix 1).

In summary the synthesis of enantiopure *N*-cyclopropyl oxazolidinones was successful and the stereoselectivity of the reaction was rationalised by a further variant of our quadrant model.

2.3. Intramolecular cyclopropanation

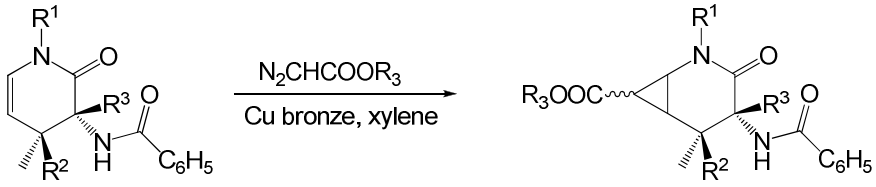
In view of the significant number of antiviral, [127] antibacterial[128] and antitumor compounds[129] which contain an aminocyclopropyl ring within a polycyclic framework it was of particular interest to investigate the potential of the intramolecular variant of our organozinc carbenoid reaction on suitably substituted lactams (Scheme 115).



Scheme 115

In recent times, a variety of approaches for the preparation of polycyclic aminocyclopropranes *via* intramolecular reactions have been reported, including elegant variants of the Kulinkovich[74,75] reaction developed by de Meijere[76] using Ti(II) mediated coupling of tethered *N*,*N*-dialkylamides as shown in Chapter 1 Scheme 57.[80] It should be noted however, as highlighted in Scheme 115, that the tricyclic products produced in the present method also contain useful lactam functionality for further elaboration, and that, in contrast to the titanium mediated intramolecular cyclopropanation of ω-vinylimides,[80a] a linearly fused tricyclic system is obtained.

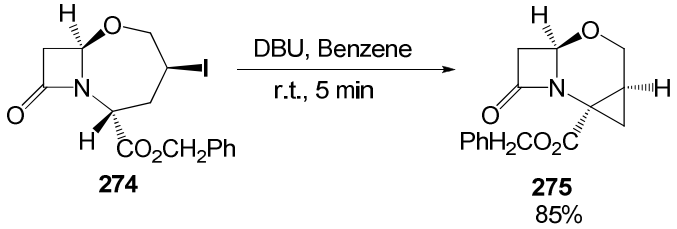
An alternative approach *via* intermolecular transition metal-mediated cyclopropanation of enamines has also been used to provide access to a limited range of such polycyclic systems. Thus, the reactions of enamide derivative with diazoacetates in the presence of a catalytic amount of copper-bronze, gave 3-oxo-2-azabicyclo [4.1.0] heptane derivatives with high *exo*-selectivity (Scheme 116).[130]



Scheme 116

Other strategies such as ionic 1,3-ring closure reactions can also be used to access the same scaffold. However, this method requires the formation of a ring large enough to enable 1,3 ring closure thus restricting the scope of the reaction.

For example, the synthesis of polycyclic product **275** containing a three membered ring by 1,3 *syn*-substitution of an iodide from a bicyclic precursor has been reported (Scheme 117).[131]



Scheme 117

In the case of the bicyclic compound **275**, the cyclopropanation reaction occurred in 5 minutes due to the favourable geometry between the proton and iodo group. These 2 substituents are *trans* and can easily form the W-shaped transition state needed for a 1,3 ring closure (Figure 10).

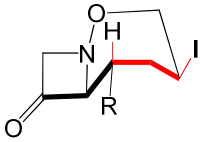
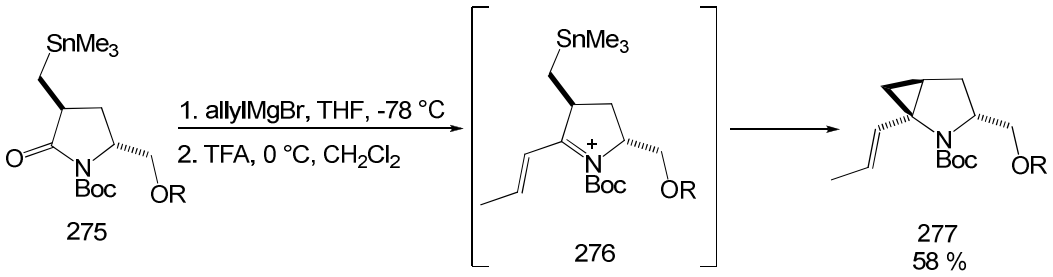


Figure 10

Another example using a trimethylstannyl group and an adjacent iminium ion has been reported by Hanessian *et al.* [132] Reaction of **275** with the Grignard reactant afforded a hemiaminal which when treated with TFA at 0 °C gave *trans*-cyclopropane **277**. This

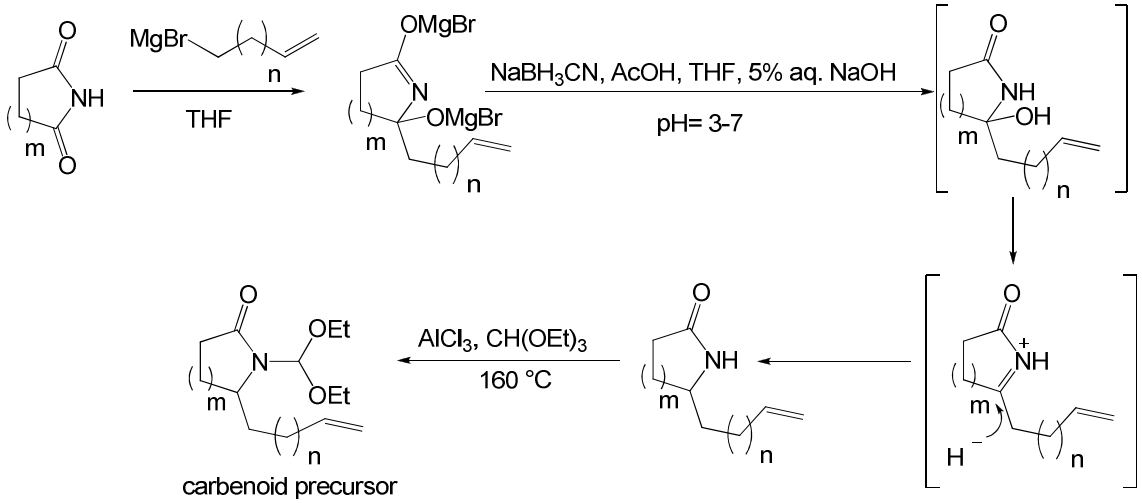
method required the presence of a stannane group on the molecule which required several steps to synthesise (Scheme 118).[132]



Scheme 118

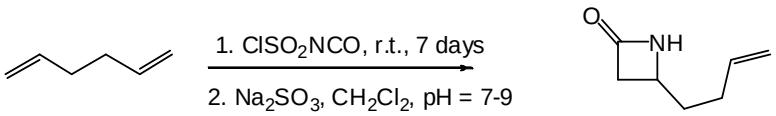
2.3.1. Synthesis of the carbenoid precursors

Five diethoxymethylamide carbenoid precursors were prepared in straightforward fashion by the reaction of cyclic imides with an excess of the appropriate Grignard reagent derived from either 4-bromobutene or 5-bromopentene. This synthesis gave firstly the magnesium salt which by further reduction, acidification and neutralisation affords the corresponding lactams in moderate to good yield (47%-73%).[133] The lactams were then heated at 160 °C in triethyl orthoformate using a catalytic amount of aluminium chloride (0.15 eq.) to obtain the carbenoid precursors (Scheme 119). The yields for these steps are given in Table 14.[121]



Scheme 119

An alternative procedure was used to synthesise the lactam **279** (m=0 and n=1) using the [2+2] cycloaddition of hexa-1,5-diene and chlorosulfonyl isocyanate.[134] The corresponding diethoxymethylamide was then prepared as described above in 32% yield (Scheme 120).



278 **279** 37%

Scheme 120

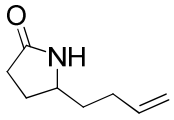
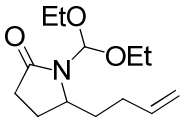
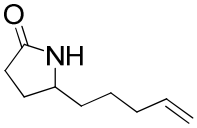
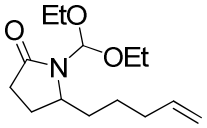
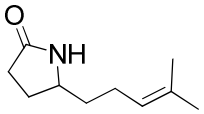
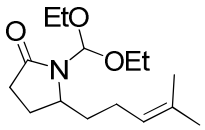
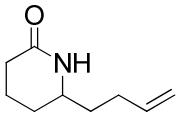
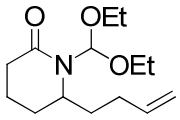
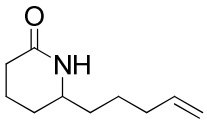
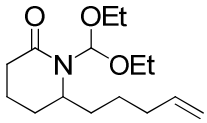
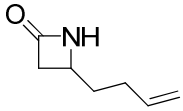
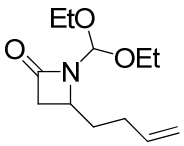
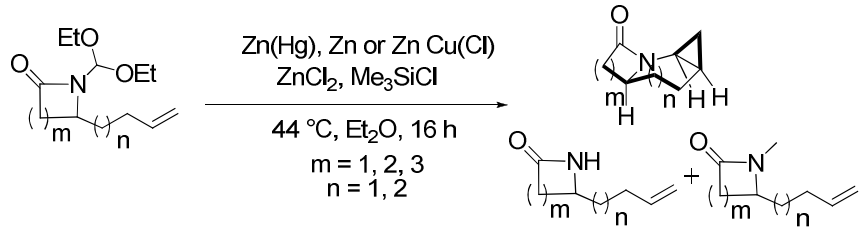
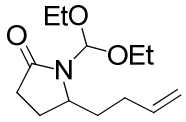
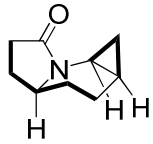
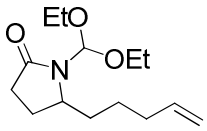
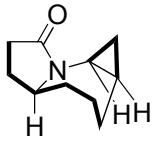
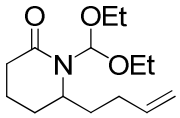
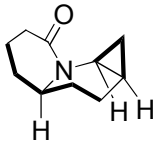
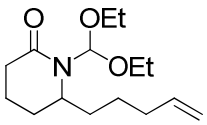
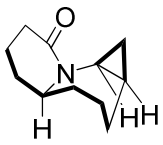
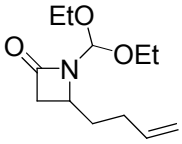
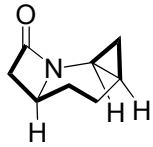
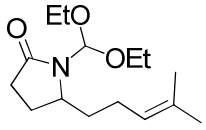
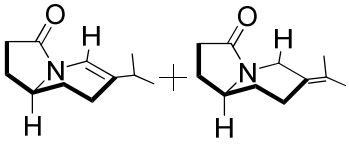
Entry	amide	orthoamide
1		
	280 (64 %)	**285** (46 %)
2		
	281 (73 %)	**286** (59 %)
3		
	282 (47 %)	**287** (90 %)
4		
	283 (66 %)	**288** (42 %)
5		
	284 (68 %)	**289** (55 %)
6		
	279 (37 %)	**290** (32 %)

Table 14

2.3.2. Intramolecular cyclopropanation reactions

With the carbenoid precursors in hand the cyclopropanation reaction was carried out using Zn(Hg), zinc or zinc/copper couple, trimethylsilyl chloride and zinc chloride, and heated at reflux in diethyl ether for 16 hours. After purification by flash column chromatography the polycyclic cyclopropanes were formed with good stereoselectivity in moderate to good yields. Traces of side products were present *viz*, the NH compound from hydrolysis of the unreacted carbenoid precursor or the organozinc carbenoid intermediate and the *N*-methyl oxazolidinone due probably to the protonation of the organozinc carbenoid (by traces of HCl present in the reaction) followed by its reduction by zinc (Table 15).[135]

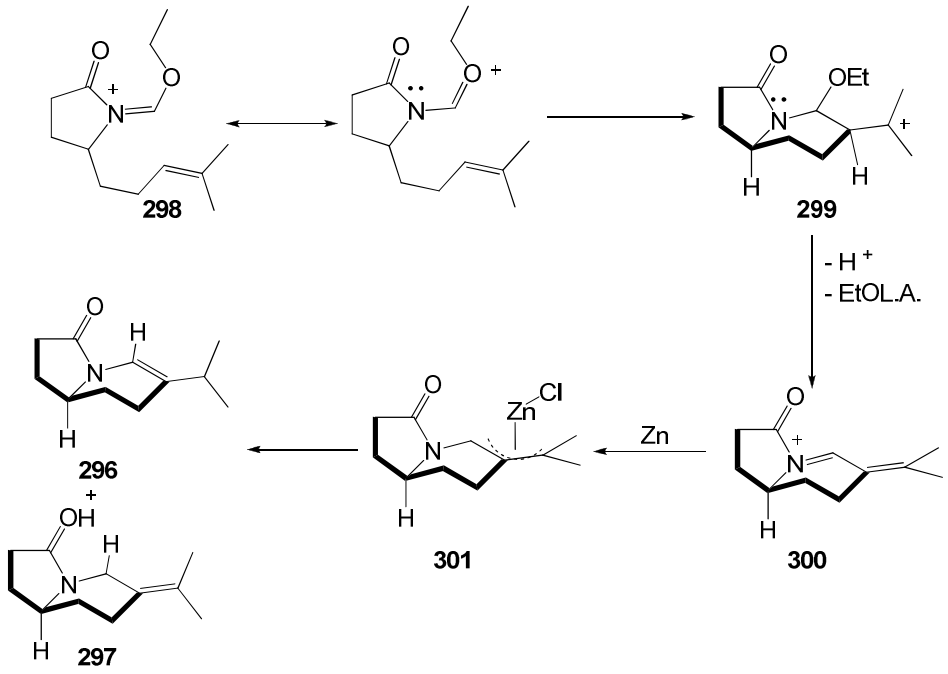


Entry	orthoamide	product	Yield
1			41%[a]
	285	**291**	
2			41%[b]
	286	**292**	
3			21%[c]
	288	**293**	
4			26%[c]
	289	**294**	
5			21%[c]
	290	**295**	
6			not isolated[c]
	287	**296** **297**	

a. Zn(Hg) method. b. Zn dust without CuCl. c. Zn/CuCl method

Table 15

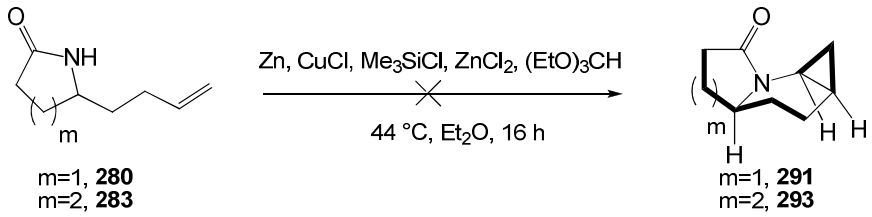
It is noteworthy that the stereoselective formation of 6- and 7- membered rings was equally viable. Selection of a tethered γ-lactam derivative provided the highest yields (Table 15, entries 1 and 2) irrespective of whether the organozinc carbenoid was participating in formation of a bicyclo [4.1.0] (six membered ring) or a [5.1.0] (seven membered ring) subunit. In all cases, only one diastereoisomer was obtained. By way of contrast the use of either the more conformationally mobile tethered δ-lactams (Table 15, entries 3 and 4) or of the relatively rigid β-lactam (Table 15, entry 5) led to a significant reduction in yield. Attempted cyclisation of compound **287**, containing a trisubstituted alkene tether (Table 15, entry 6) did not however lead to the formation of desired substituted cyclopropane ring. In this instance a mixture of the cyclic alkenes **296** and **297** was observed as evidenced by NMR analysis of the crude reaction mixture. The following mechanism is suggested to explain their formation (Scheme 121).



Scheme 121

In this case, the cyclisation of the trisubstituted alkene onto the low energy *N*-acyl iminium cation **298** must be faster than two electron reduction by zinc presumably as a consequence of the favourable formation of a tertiary carbocation. Proton loss followed by Lewis acid mediated departure of the second ethoxy group will then furnish the conjugated acyl iminium ion **300**, which can then be reduced to give the allylzinc species **301**. Protonation of **301** gave then a mixture of the two alkenes **296** and **297**.[135]

The cyclopropanation reaction was also investigated from the lactams **280** and **283** avoiding the synthesis of the orthoamide but in contrast to our earlier success in the intermolecular case, did not give satisfactory results. Only recovered starting material was obtained after the reaction (Scheme 122).



Scheme 122

2.3.3. Stereochemistry

Due to steric constraints only a *cis* substituted cyclopropane can be formed and this was confirmed by ^{1}H NMR spectroscopy studies. The H_{6b} signal is a doublet of doublets of doublets with two *cis* coupling constants and one *trans* confirming the indicated stereochemistry. From a stereochemical standpoint, it was important to determine whether the cyclopropane unit was the more hindered *endo* isomer **291** *i.e* located on the more hindered concave face, as opposed to the sterically less congested *exo* diastereoisomer **302** (Figure 11).

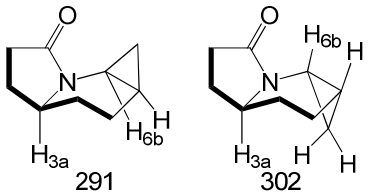


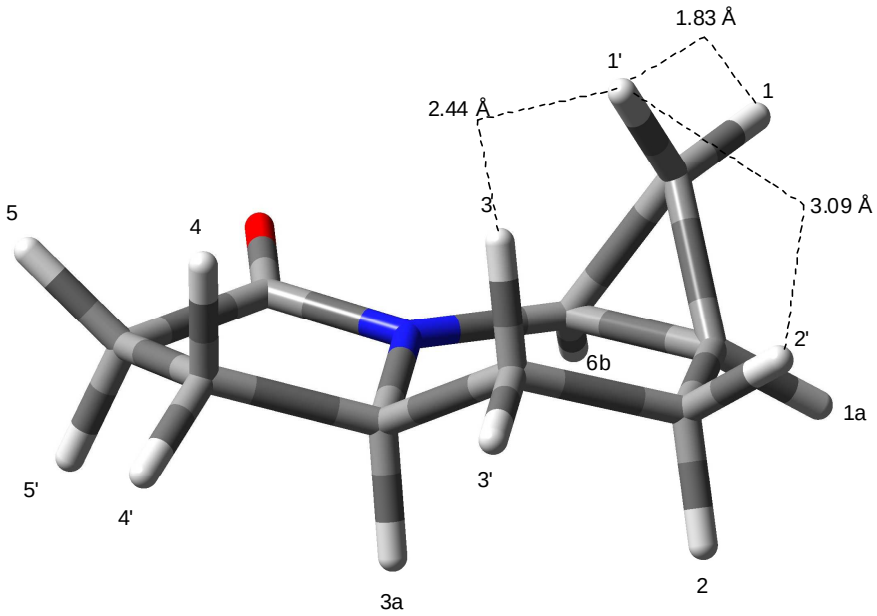
Figure 11

Since these two isomers were not likely to be distinguishable using simple NMR techniques, a combined NMR calculation and molecular modelling approach was used to determine which structural isomer provided the best fit with the NMR data.

The analysis undertaken to identify the stereochemistry of product formed is detailed below, a similar process was applied to all compounds to assign the correct configuration.

A detailed comparison of the observed ^{1}H-^{1}H coupling constants and nuclear Overhauser enhancements (nOe) with values obtained from molecular mechanics calculations using the MMX force field[136] followed by DFT calculations using B3LYP/6-31G(d) level of theory was done for each compound by Dr A. Aliev to determine the orientation of H_{3a} related to the cyclopropane.[137] Computational studies allowed prediction of the nOe ratios, dihedral angles, chemical shifts and coupling constants for both conformations (Table 16), showing two large ^{3}J couplings on proton 3aH. Irradiation of proton $H_{1'}$ enhanced protons H_1, H_3, H_{1a} and $H_{2'}$ and the corresponding enhancement ratio for protons $H_3/H_{2'}$($\eta_{1'\rightarrow 3}/\eta_{1'\rightarrow 2'}$) was 3.4 (Figure 12). From the B3LYP/6-31G(d) optimised geometry, the internuclear distances, between $H_{1'}$ and H_3 and between $H_{1'}$ and $H_{2'}$ in the *endo*-C_1,C_3 conformation were found to be 2.44 Å and 3.09 Å, respectively (Figure 12). Thus, using the initial rate approximation,[138] based on the r^{-6} dependence of nOes as shown in the Figure 12, the expected enhancement ratio is 4.1 which compared well with the measured value of 3.4. The expected nOe ratio is only 0.1 in the alternative *exo*-C_1,C_3 conformation (Figure 12).

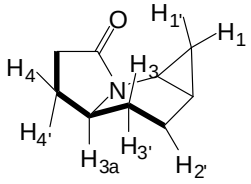
$$\frac{\eta_{1'-2}}{\eta_{1'-3}} = \left(\frac{r_{1'-3}}{r_{1'-2}}\right)^{6}$$



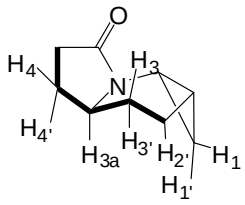
291

Figure 12

This study compared with the experimental results confirms that we have the *endo* configuration of the 3-CH_2 and the cyclopropane ring (noted endo-C_1,C_3).



291
endo-C_1,C_3



302
exo-C_1,C_3

	NOE ratio	Dihedral angles/°		Coupling constants/Hz	
	$\eta_{1'\rightarrow 3}$/ $\eta_{1'\rightarrow 2'}$	H^3CCH^{3a}	$H^{3a}CCH^4$	$J_{3,3a}$	$J_{3a,4}$
Predicted for endo **291**	4.1	177	154	11.8 (9.6)	10.3 (8.2)
Predicted for exo **302**	0.1	177	153	11.8 (9.6)	10.2 (7.9)
Observed	3.4			11.5	8.8

Table 16

Table 16 NMR assignment of stereochemistry. The predicted values are for the B3LYP/6-31G(d) optimised geometries. Vicinal $^3J_{HH}$ couplings were predicted using a Karplus-type equation,[139] accounting for the dependence of $^3J_{HH}$ on both the dihedral angle and the substituent electronegativities. The values shown in brackets are from the B3LYP/6-311+G(2d,p) calculations of the *J*-couplings.

The preference for formation of the more hindered product may possibly be rationalised by consideration of the two possible transition states shown in Figure 13 both of which feature an “amidoorganozinc carbenoid” in which the oxygen atom of the lactam is coordinated to the zinc atom. The observed stereochemical outcome would result from the less strained and less sterically congested approach of the alkene to the carbenoid (A), rather than the somewhat more hindered approach (B) which would lead to the *exo* isomer (Figure 13). [135]

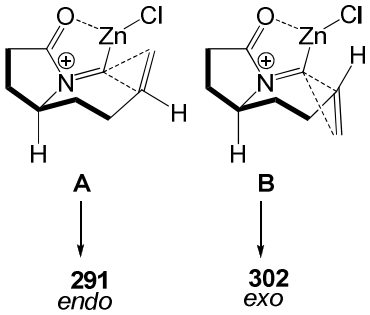


Figure 13

In a similar manner Dr Abil Aliev confirmed the geometry of the predominant conformation of each polycylic compound shown in Figure 14 by a detailed comparison of the observed ^{1}H-^{1}H coupling constants and nOe with values obtained from molecular mechanics calculations using the MMX force field[136] followed by DFT calculations (Figure 14).

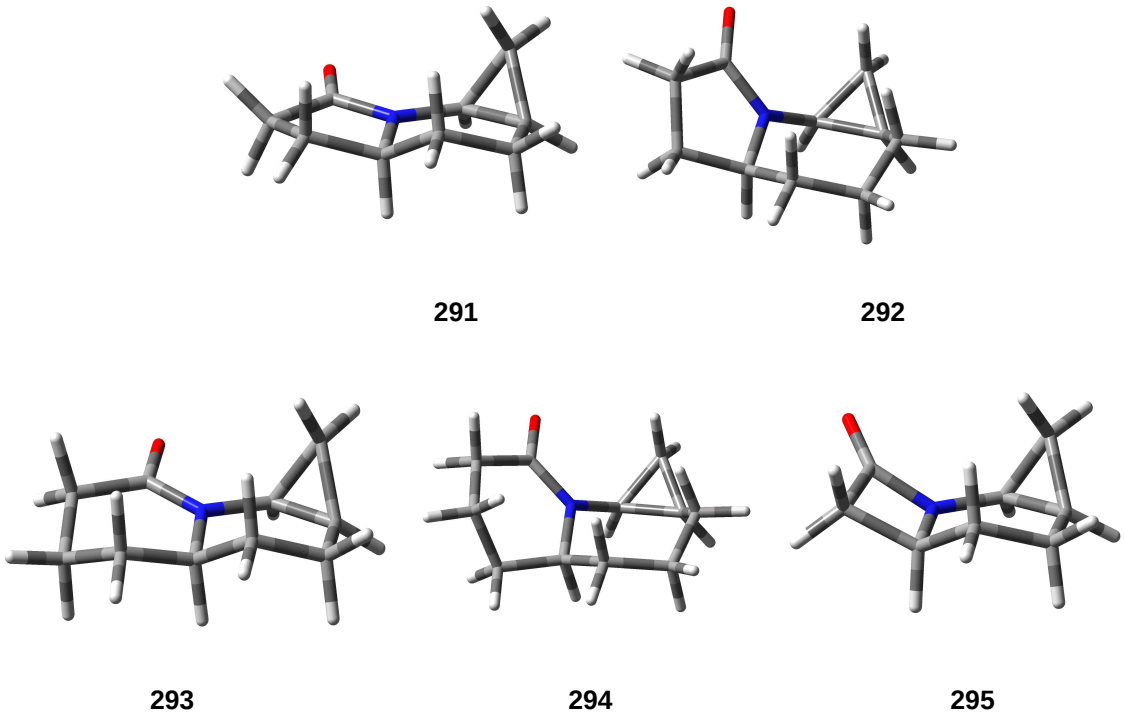


Figure 14

Figure 14. The predominant conformations of polycylic compounds **291-295** determined from the combined analysis of the vicinal ^{1}H-^{1}H coupling constants, nOes and DFT calculations.

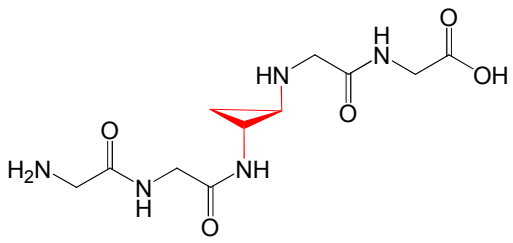
The results of this preliminary study clearly indicate that the amidoorganozinc carbenoids derived from suitably constituted *N*-diethoxymethyl lactams can successfully participate in intramolecular reactions with simple monosubstituted alkene tethers.

2.4. Studies towards the preparation of novel aminocyclopropyl functionalised compounds

In light of the good results obtained for the formation of *N*-cyclopropyl oxazolidinone in only two steps from readily available oxazolidinones, we decided to apply our methodology to the synthesis of other highly functionalised molecules which could in turn, be used to generate interesting structural skeletons containing an aminocyclopropyl unit.

2.4.1. Amino acid derived building blocks

The incorporation of a rigid aminocyclopropyl unit into a peptide backbone could provide a control clement for a particular conformation and thus enable the incorporation of specific functionalities in a selected direction. An example is shown in Figure 15.



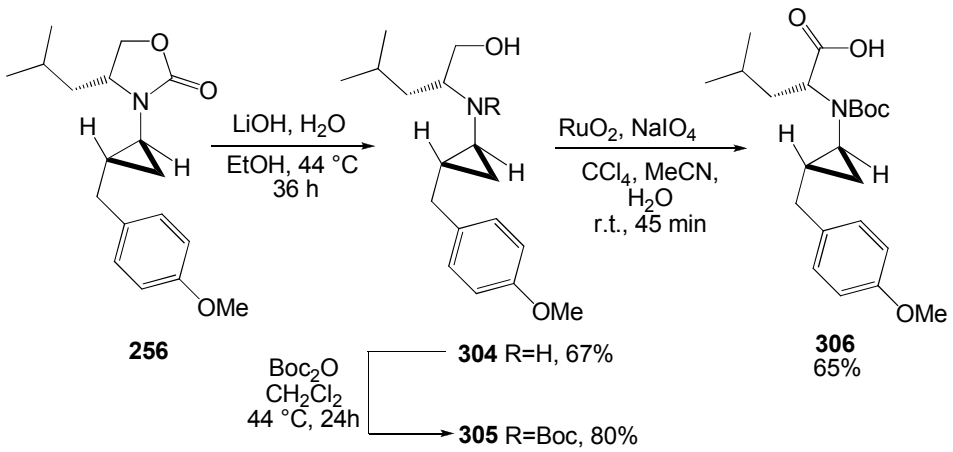
303

Figure 15

We therefore wished to explore cyclopropanes containing amino alcohol and amino acid units *via* ring opening of the enantiopure *N*-cyclopropyl oxazolidinone which had previously been prepared.

The amino alcohols **304** and **305** and the cyclopropyl amino acid **306** were accordingly synthesised from *N*-cyclopropyl oxazolidinone **256** by the short sequence shown in

Scheme 123. After the deprotection of the methoxy group such compounds were of interest as unusual tyrosine analogues.

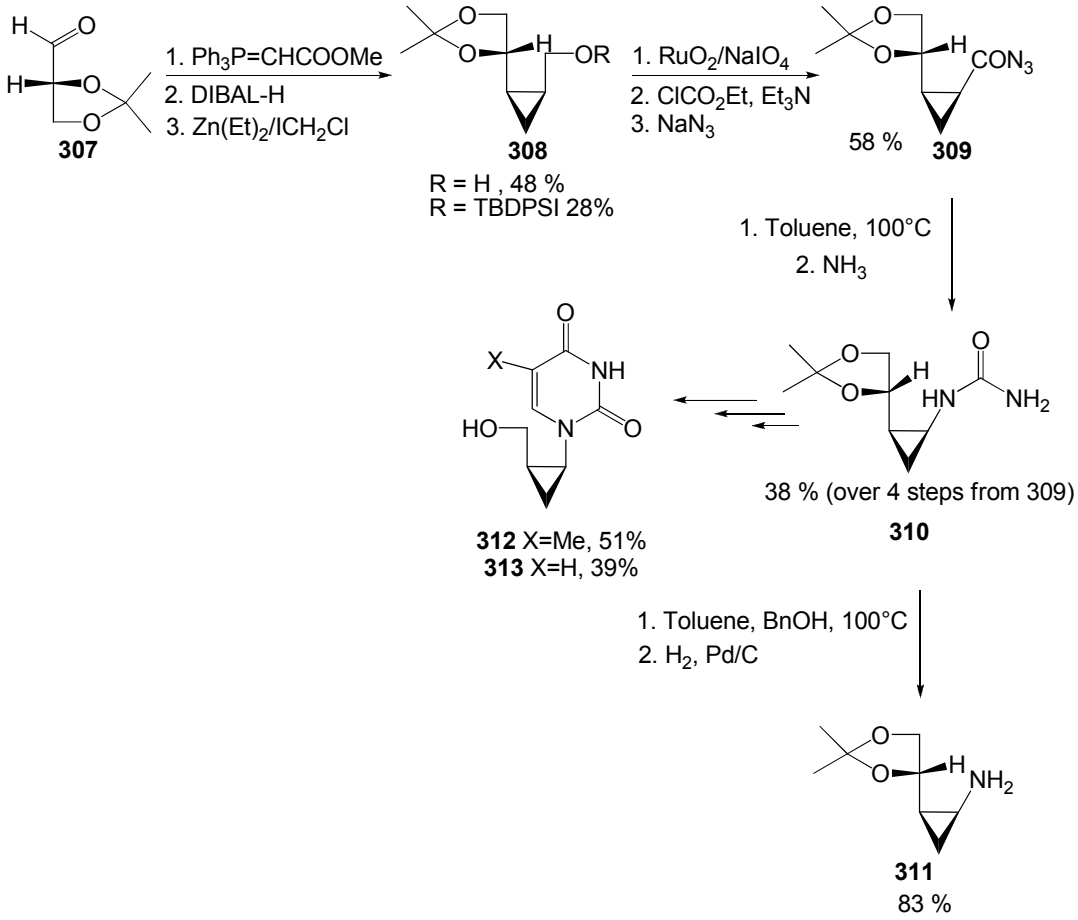


Scheme 123

Thus, oxazolidinone **256** was initially cleaved under basic conditions with LiOH to afford the amino alcohol **304** in good yield. The secondary amine thus obtained was then protected under standard conditions with Boc anhydride and the primary alcohol oxidised to afford the *trans N*-cyclopropyl substituted amino-acid **306**.[126] This compound could be used for further peptide coupling reactions.

2.4.2. Carbocyclic nucleoside building blocks

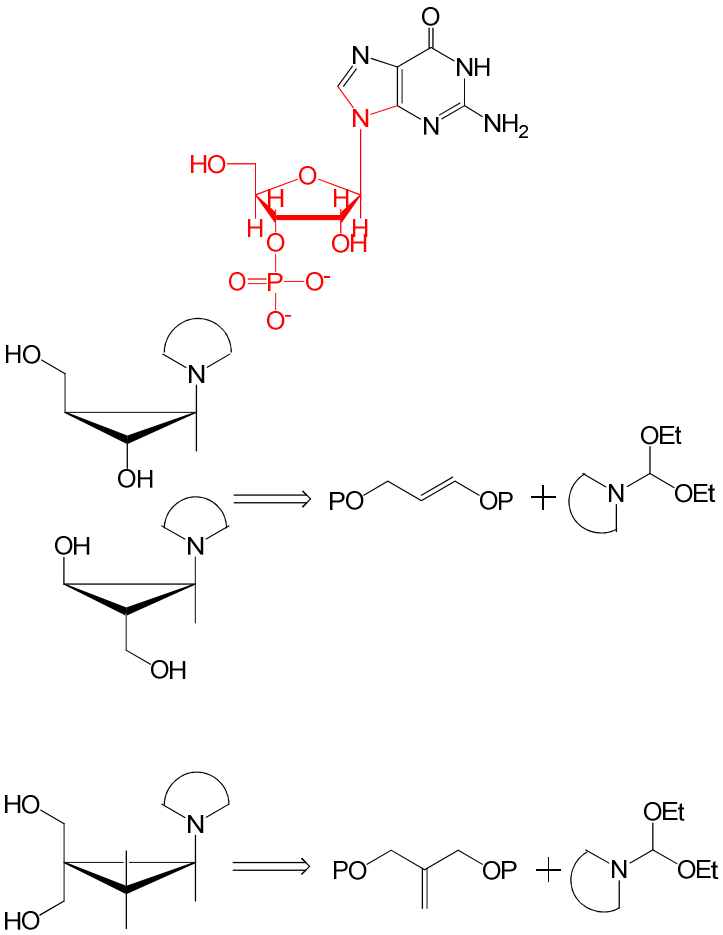
There are many reports of the activity of carbocyclic nucleosides as antiviral compounds in the literature.[140,141142] Chu *et al.* investigated the biological activity of cyclopropyl carbocyclic nucleosides such as **312** and **313** (Scheme 124) as potential antiviral compounds. [143,144,145] In their research, the cyclopropanes were synthesised from (D)-glyceraldehyde acetonide using the Denmark variant of the Furukawa modification of the Simmons-Smith reaction as the key step on an alkene containing a dioxolane group which was then converted to the key aminocyclopropane protected with a *cis*-hydroxymethyl group (Scheme 124).



Scheme 124

In the event, cyclopropane **308** required seven steps for elaboration to the *N*-cyclopropyl heterocycles **312** and **313**. [143]

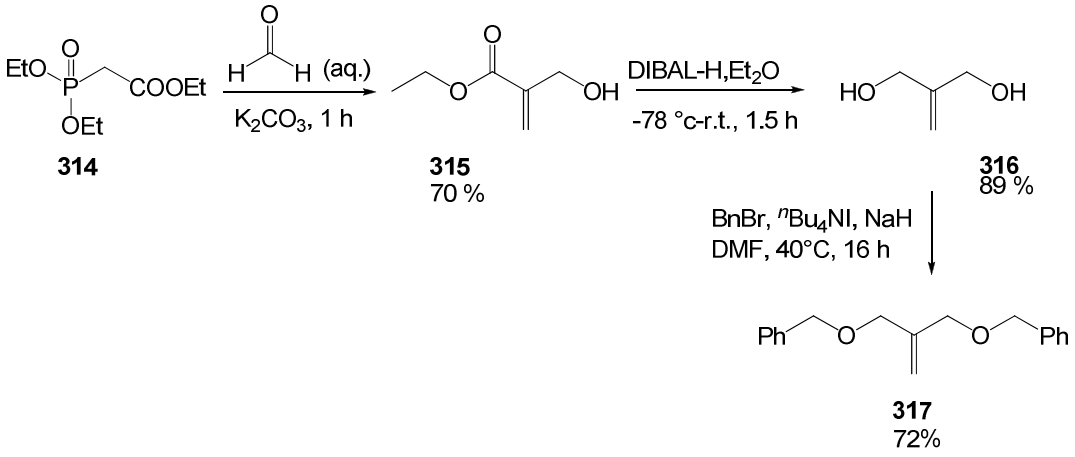
We therefore considered that it would be useful to reproduce this type of skeleton by applying our methodology to alkenes containing alcohol functionalities in order to obtain such carbocyclic analogues of the ribose unit since these new mimics could be interesting targets for anti-viral activity assays (Scheme 125).



Scheme 125

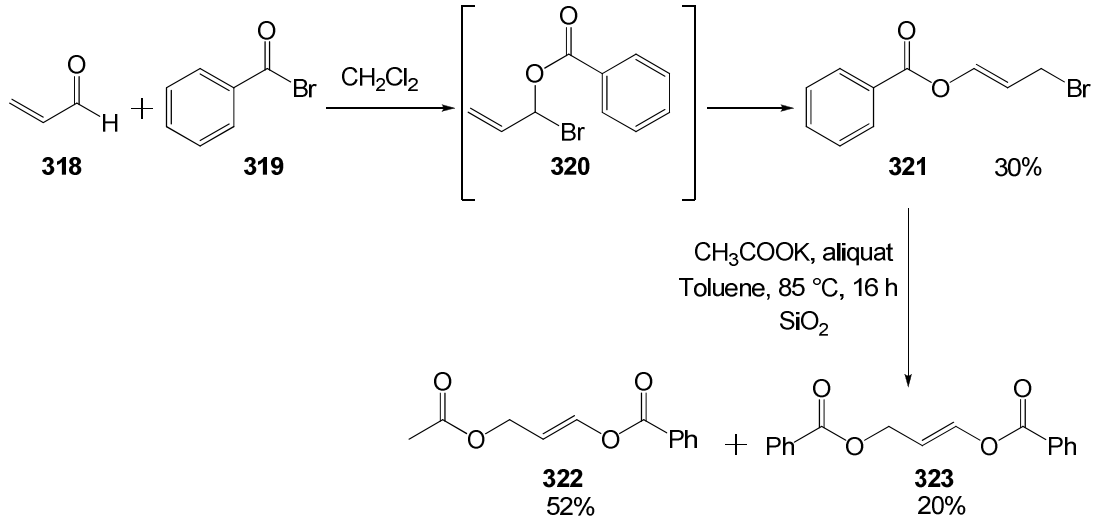
We anticipated that these alkenes would be readily trapped by an organozinc carbenoid to give interesting amido and aminocyclopropanes functionalised with hydroxyl groups after deprotection.

In consequence, the necessary alcohol **315** was synthesised in 70% yield following a literature procedure starting from triethyl phosphonoacetate and formaldehyde under basic conditions.[146] The ester was converted to 2-methylenepropane-1,3-diol **316** by reduction using DIBAL-H in 89% yield. Diol **316** was then converted to the protected dibenzyl ether **317** by treatment with sodium hydride and benzyl bromide (Scheme 126).[147]



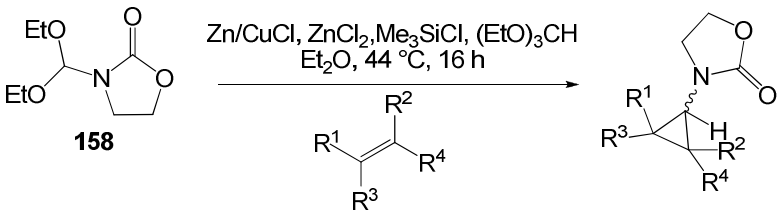
Scheme 126

The protected alcohol **322** was also synthesised by a literature procedure applied to the bromide **321**,[148] which itself was synthesised from acrolein and benzoyl bromide according to a literature method.[149] The protected alcohol **323** was obtained as a side product (Scheme 127).



Scheme 127

With our alkene substrates in hand, we then attempted the cyclopropanation reactions using *N*-diethoxyoxazolidin-2-one **158** as the carbenoid precursor. The results of these reactions are shown in Table 17.



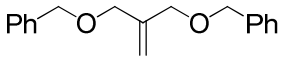
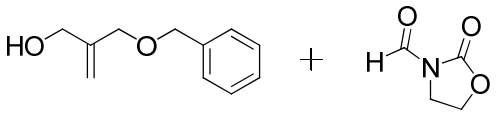
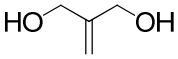
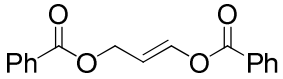
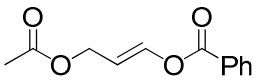
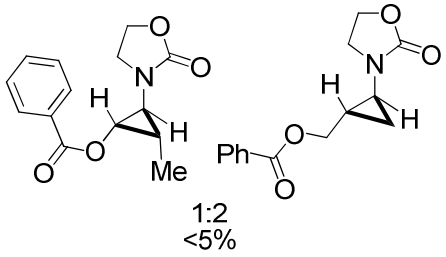
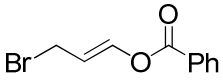
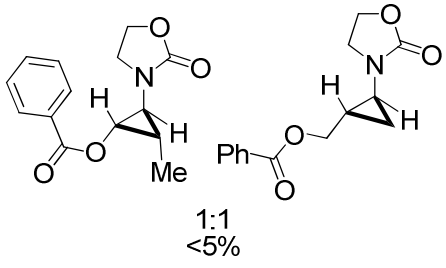
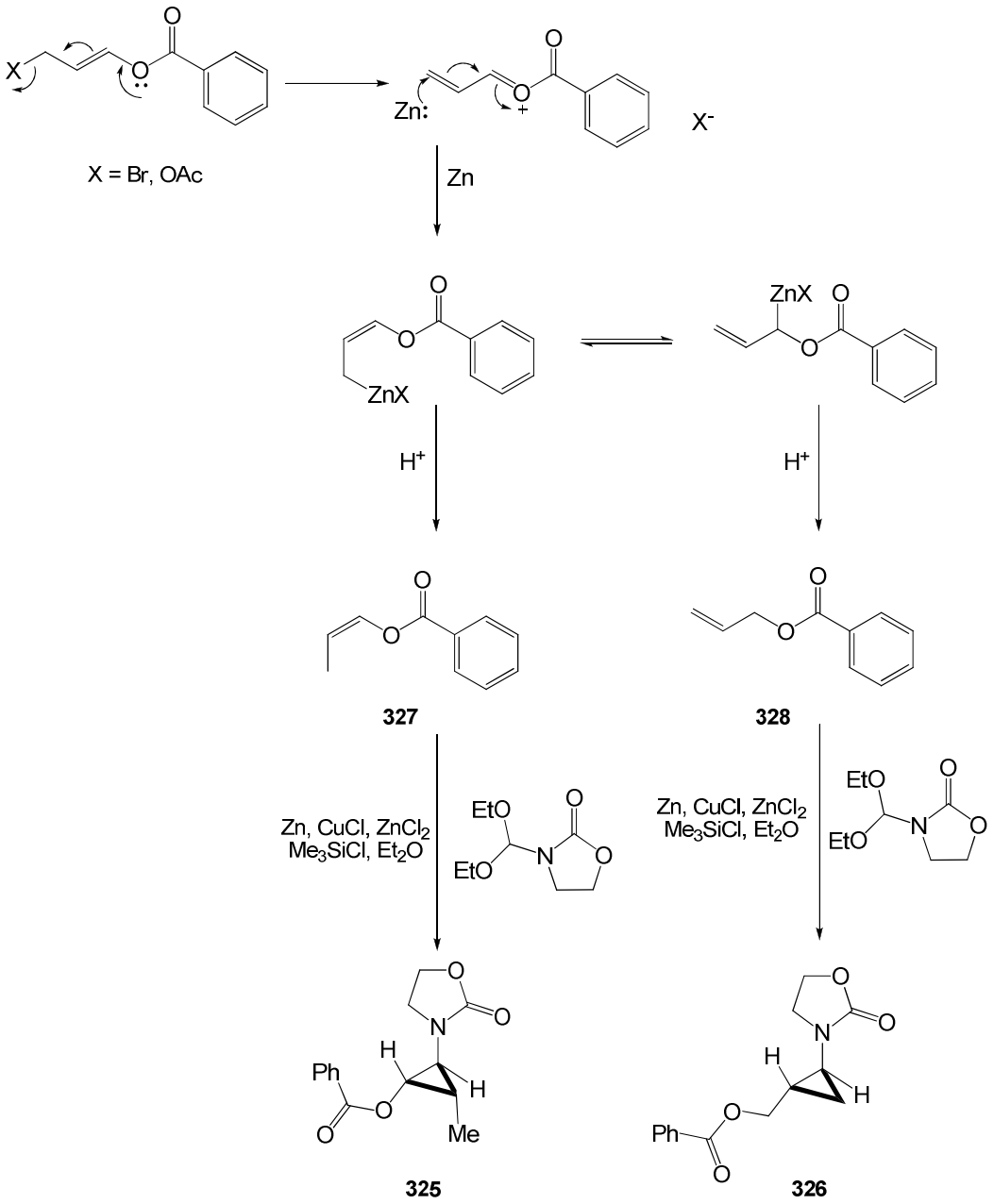
entry	alkene	NMR observations
1		Complex mixture No identified products + 
	317	**324**
2		Complex mixture No identified products
	316	
3		Complex mixture No identified products
	323	
4		 1:2 <5%
	322	**325** **326**
5		 1:1 <5%
	321	**325** **326**

Table 17

Unfortunately none of the expected cyclopropanes were obtained. To our surprise the protected alcohol **317** was mono deprotected under the reactions conditions (Table 17, entry1) and the previously observed *N*-formyl derivative of the oxazolidinone was the only detectable product from the carbenoid precursor. Cyclopropanation of **316** and **323** was also attempted but gave an intractable mixture of products and no identifiable products (Table 17, entry 2 and entry 3). The reaction undertaken with alkenes **322** and **321** led to the formation of the cyclopropanes **325** and **326**, as determined from NMR analysis of the crude reaction product (Table 17, entries 4 and 5).

Under the reaction conditions, **321** and **322** were initially converted to the alkenes **327** and **328** before undergoing cyclopropanation. We propose the following mechanism to explain these results. In the alkenes **322** and **321** the allylic acetate and bromide groups were too labile under the reaction conditions and after reduction of the oxonium by zinc in presence of acidic proton gave alkenes **327** and **328** which afford the cyclopropanes **325** and **326** (Scheme 128).

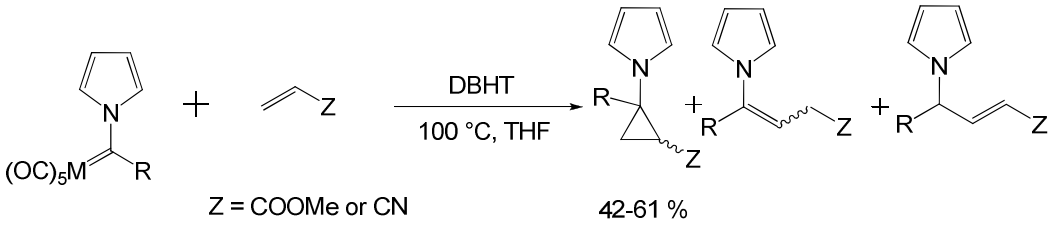


Scheme 128

2.4.3. *N*-cyclopropyl heterocyclic carbenoids

Molecules containing a nitrogen-based heterocycle attached through nitrogen to a cyclopropyl unit are potentially very interesting in drug discovery programmes.[143,144,145] As outlined in section **2.4.2**, Chu *et al*. accessed such *N*-cyclopropyl heterocycle nucleoside mimics by construction of the heterocycle from an aminocyclopropyl unit.[143,144] However Hegedus et *al*. have developed the cyclopropanation of electron-deficient olefins using group 6 pyrrolocarbene complexes (Scheme 129). The

pyrrolocarbene complexe was obtained from the corresponding alkoxycarbene complexes by exchange with the lithium or potassium salt of the pyrrole. The cyclopropane was obtained as a mixture of diastereoisomers together with side products resulting from CH insertion (Scheme 129).[150]

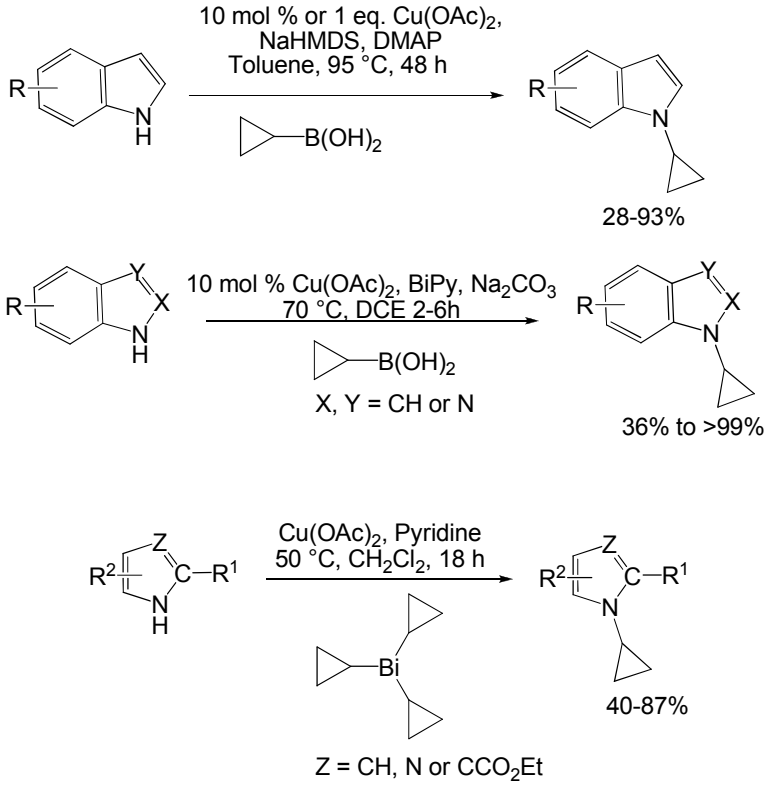


Scheme 129

The free-radical scavenger, DBHT, was used to suppress polymerisation of the olefinic substrates.[150]

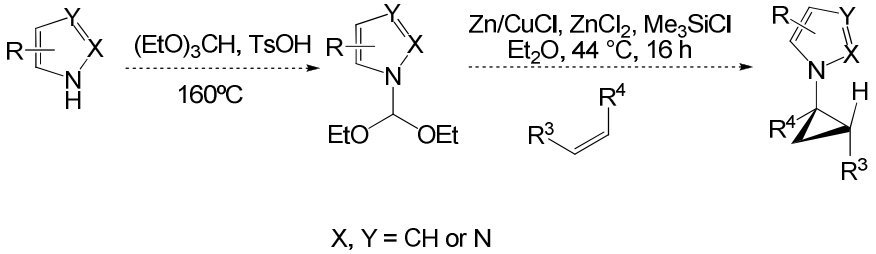
The synthesis of *N*-cyclopropyl heterocycles by these two methods is not very convenient: the first synthetic route is long, whilst the second one is limited to electron deficient alkenes and requires the synthesis and use of the stoichiometric transition metal *N*-heterocyclic Fischer carbenoid. Moreover the cyclopropanation reaction using the *N*-heterocyclic carbenes has to be carried out under harsh conditions, in a sealed pressure tube heated at 100 °C.

More recent studies were published on the direct *N*-cyclopropanation of heterocycles such as pyrroles or indoles employing a cyclopropylboronic acid[151] or a cyclopropylbismuth reagent (Scheme 130).[152] However, a major drawback of this approach is that they utilise a cyclopropyl ring that does not possess any substituents. The major disadvantage of this latter method relates to the preparation of the tricyclopropylbismuth reagent which is not stable for storage.[151,152]



Scheme 130

To overcome the problems associated with these literature methods our idea was to use the methodology we had developed to access *N*-cyclopropyl heterocycles from *N*-diethoxymethyl heterocycles as carbenoid precursors and functionalised alkenes. The desired *N*-cyclopropyl heterocycles containing substituents present on the cyclopropane ring could therefore be obtained in only two steps from the *N*-starting heterocycle (Scheme 131).



Scheme 131

In the event, seven carbenoid precursors derived from readily-available *N*-heterocycles were synthesised using literature or modified literature procedures (Table 18).[153,154,155,156,157] The carbenoid precursors were obtained in moderate to good yield and were found to be stable at room temperature. As expected, heterocycles containing an electron-withdrawing group make the nitrogen atom more reactive which facilitates incorporation of the *N*-diethoxy methyl group (Table 18).

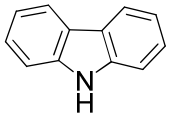
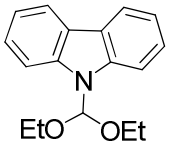
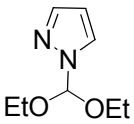
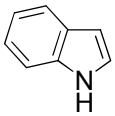
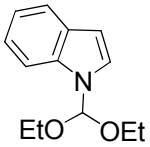
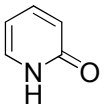
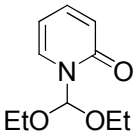
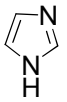
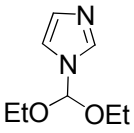
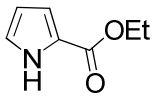
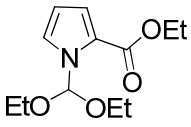
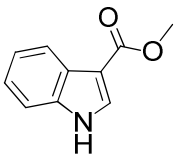
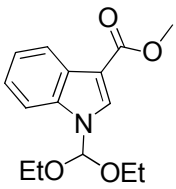
entry	heterocycle	Conditions	Product(s)	Yield
1		$(EtO)_3CH$ 10 eq. *p*-tosic acid 0.1 eq. 85℃, 36 h		42%
	329		**336**	
2		$(EtO)_3CH$ 1 eq. 140℃, 16 h		50%
	330		**337**	
3		$(EtO)_3CH$ 10 eq. 160℃, 48 h		13%
	331		**338**	
4		$(EtO)_3CH$ 15.4 eq. 155℃, 24 h		46%
	332		**339**	
5		$(EtO)_3CH$ 4.25 eq. *p*-tosic acid 0.03 eq. 130℃, 16 h		45%
	333		**340**	
6		$(EtO)_3CH$ 10 eq. 165℃, 6 days		73%
	334		**341**	
7		$(EtO)_3CH$ 10 eq. 165℃, 60 h		85%
	335		**342**	

Table 18

The zinc/Me_3SiCl-mediated cyclopropanation reaction was then attempted using a variety of alkenes. To our initial surprise however, only carbenoid precursor **342** was able to trap an alkene to form the desired cyclopropane (Table 19).

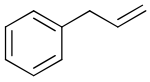
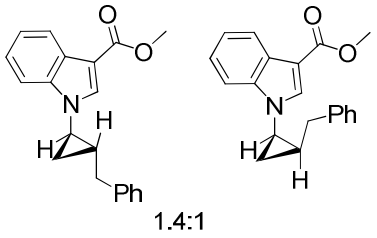
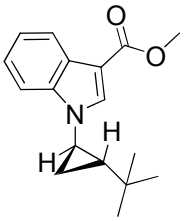
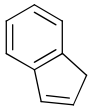
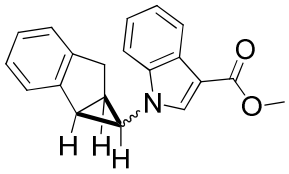
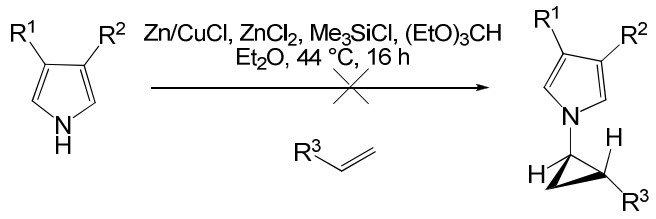
Entry	alkene	Product	Yield
1		 1.4:1	18 %
	153	**343** **344**	
2			11 %
	164	**345**	
3			Not isolated
	165	**346**	

Table 19

Although these novel *N*-cyclopropyl heterocycles were only obtained in low yield, depending on the nature of the alkene, the overall sequence requires only 2 steps and hence is competitive with existing multistep alternatives.

In order to increase the yield of the reaction, the reaction was attempted using a larger excess of the carbenoid precursor **342** (4 eq. instead of 2 eq.), but only the parent *N*-heterocycle **335** was observed in the crude ^1H NMR spectrum with no trace of cyclopropane. At the present time, in spite of several attempts to correlate the success or failure of the various *N*-diethoxymethyl heterocyclic systems prepared in terms of leaving group ability, acidity, or other parameters we have no satisfactory explanation for the above results.

The cyclopropanation reaction was also attempted directly from the *N*-heterocycles to avoid the synthesis of the *N*-diethoxymethyl heterocycles but the results obtained were not conclusive and only recovered starting material was obtained as evidenced by NMR examination of the crude reaction product (Scheme 132).

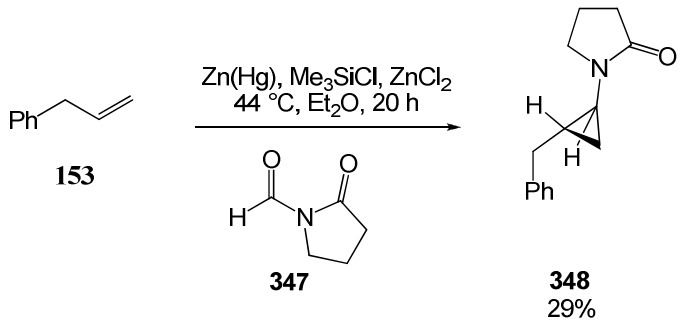


Scheme 132

2.5. A miscellany of novel carbenoid precursors

2.5.1. More highly functionalised derivatives

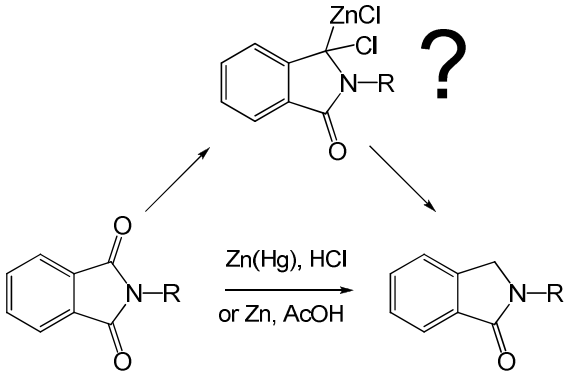
Previous research within our group had demonstrated that an amidocyclopropanation reaction using an *N*-formyl amide **347** as the carbenoid precursor was a viable route to a carbenoid but led to lower yield of the cyclopropane **348** than the reaction using the *N* diethoxymethyl derivative **157** (88%) (Scheme 133).[115]



Scheme 133

We therefore decided to investigate precursors derived from a cyclic imide and a cyclic amide or oxazolidinone and further functionalised by a second electron-withdrawing group such as the carboethoxy or trifluoroacetyl group.

Our inspiration for this idea came from an observation in the early literature by Brewster who reported that the reduction of phthalimides under Clemmensen reduction conditions using zinc and a source of protons led to lactam formation (Scheme 134).[158]

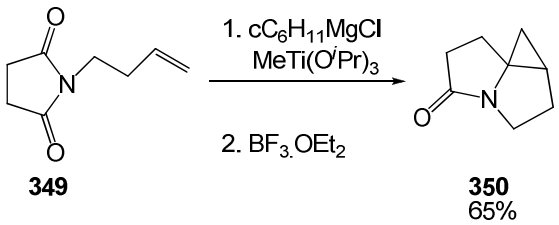


Scheme 134

Given that we now know that the combination of zinc and a silicon electrophile leads to the formation of an organozinc carbenoid from a carbonyl group, it was therefore reasonable to propose such an intermediate from the cyclic imide, and this is, of course, an α amidoorganozinc carbenoid.

The idea was to use the same conditions to trap an alkene in the intramolecular mode to obtain a tetracyclic compound.

Recently Bertus *et al.* have developed an intramolecular titanium- and Lewis acid-mediated cyclopropanation of imides, but this of course proceeds *via* a different mechanism (Scheme 135).[80a]

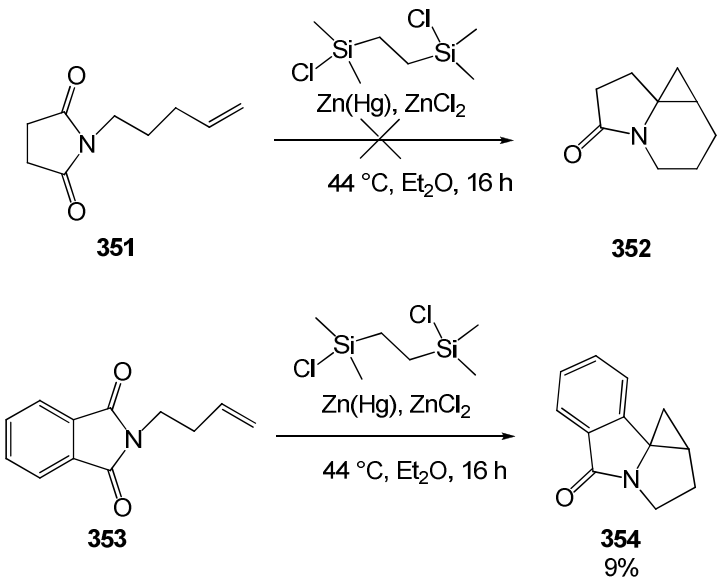


349 **350** 65%

Scheme 135

Therefore, cyclopropanation reactions were attempted on compounds **351** and **352** containing an alkene and a carbenoid precursor group. Compound **351** was synthesised in 85% yield by treatment of succinimide with sodium hydride and 5-bromopentene and **353**

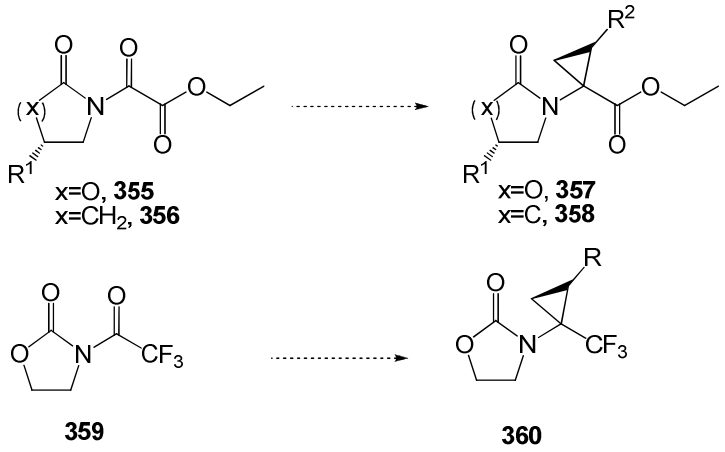
was synthesised previously in the lab by treatment of phthalimide with sodium hydride and 4 bromobutene (Scheme 136).



Scheme 136

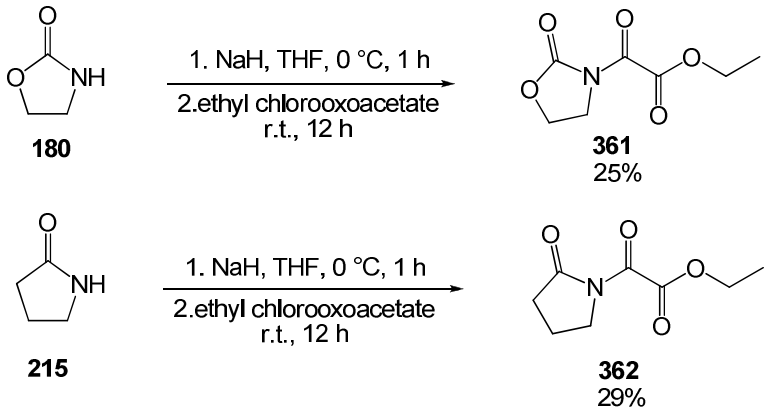
In contrast to the Bertus procedure, the intramolecular cyclopropanation of the parent succinimide derivative **351** did not give any satisfactory results, and only starting material was recovered at the end of the reaction. However, the phthalimide congener led to the tetracyclic system **354** albeit in only 9% yield. This promising result needs further investigation to improve the yield and to understand the role of the aromatic ring in the process. This result adds further weight to our hypothesis that an organozinc carbenoid was probably an intermediate in the reduction of the phthalimide using a source of zinc under acidic conditions. However due to time constraints, this avenue was not pursued further.

An additional electron-withdrawing group adjacent to the carbenoid should make it even more susceptible both to reduction and to formation of a tetrahedral centre both in the intermediates and in the cyclopropanated product. Furthermore, chiral oxazolidinones of the types **355** were considered to be of special interest as a potential source of a “chiral glycine” carbenoid (Scheme 137).



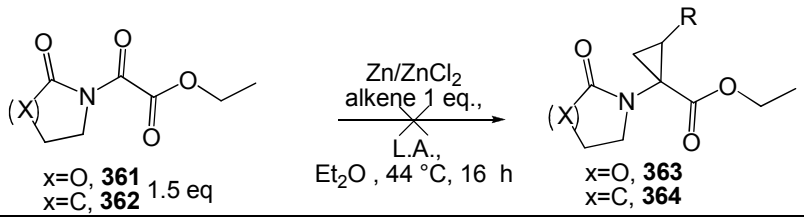
Scheme 137

Carbenoid precursors **361** and **362** were accordingly synthesised from 2-oxazolidinone and 2-pyrrolidinone (Scheme 138).



Scheme 138

A range of conditions using different alkenes, Lewis acid and zinc were then investigated in order to synthesise cyclopropanes from these carbenoid precursors **361** and **362** and the observations are outlined below (Table 20).



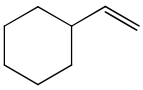
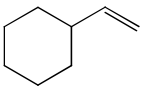
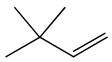
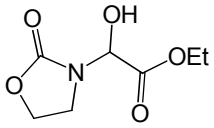
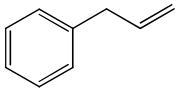
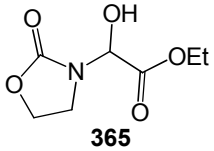
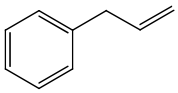
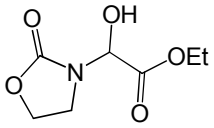
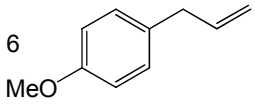
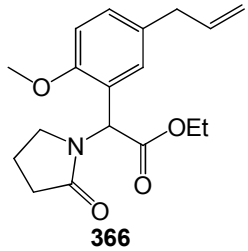
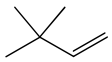
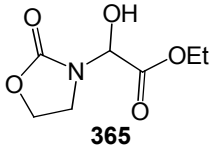
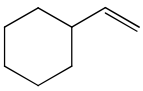
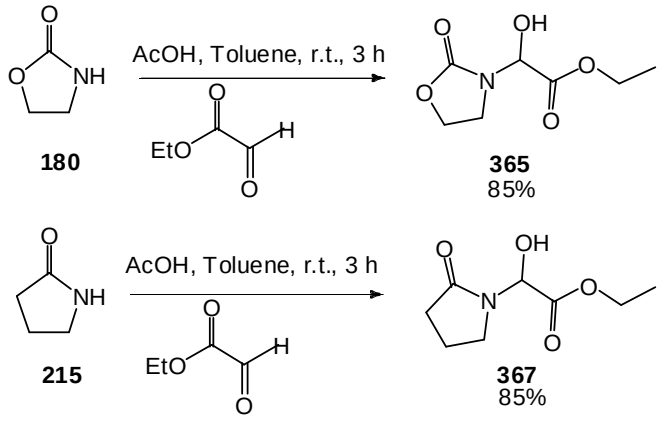
entry	alkene	X	reagents	Lewis acid	NMR observations
1	 **252**	CH_2	Zn 13 eq./$ZnCl_2$ 1.5 eq.	Me_3SiCl 6.4 eq.	no reaction
2	 **252**	O	Zn(Cu) 12.6 eq./$ZnCl_2$ 1.5 eq.	Me_3SiCl 6.4 eq.	no reaction
3	 **164**	O	Zn(Hg) 12.5 eq./$ZnCl_2$ 3 eq.	BF_3 2 eq.	 **365**
4	 **153**	O	Zn(Hg) 12.5 eq./$ZnCl_2$ 3 eq.	BF_3 6.4 eq.	 **365**
5	 **153**	O	Zn(Hg) 12.5 eq./$ZnCl_2$ 3 eq.	$AlCl_3$ 6 eq.	 **365**
6	 **253**	CH_2	1. Zn(Hg) 12.5 eq./$ZnCl_2$ 1.5 eq. 2. Zn 12.5 eq./CuCl 0.8 eq.	Me_3SiCl 6.3 eq.	 **366**
7	 **164**	O	1. Zn(Hg) 12.5 eq./$ZnCl_2$ 1.5 eq. 2. Zn 12.5 eq./CuCl 0.8 eq.	Me_3SiCl 6.3 eq.	 **365**
8	 **252**	O	Zn(Hg) 12.5 eq./$ZnCl_2$ 1.5 eq.	$Si_2C_6H_{16}Cl_2$ 6.4 eq.	no reaction

Table 20

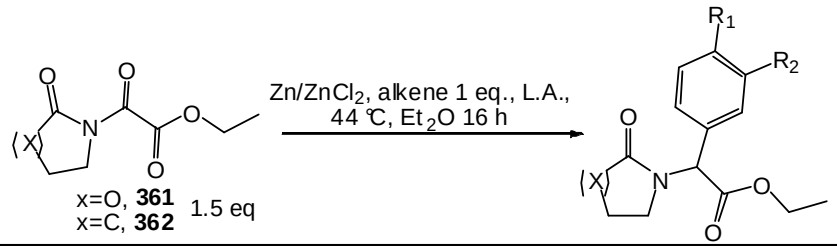
To our disappointment, in all cases, the cyclopropane was not formed but the use of Zn(Hg) led to reduction of one carbonyl group to the alcohol (Table 20, entries 3, 4, 5, 7). The presence of the alcohol was clearly determined from the ^1H NMR spectrum and was

also confirmed by a straightforward synthesis of the product *via* the alternative route shown in Scheme 139.



Scheme 139

The alkene possessing an activated aromatic ring (Table 20 entry 6) led surprisingly to a Friedel-Crafts type addition and so we investigated more substrates, reagents and conditions to confirm this initial finding (Table 21).



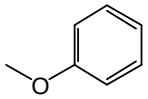
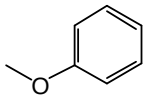
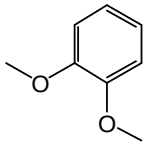
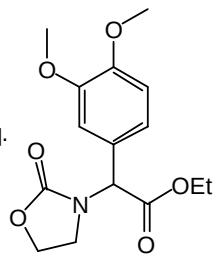
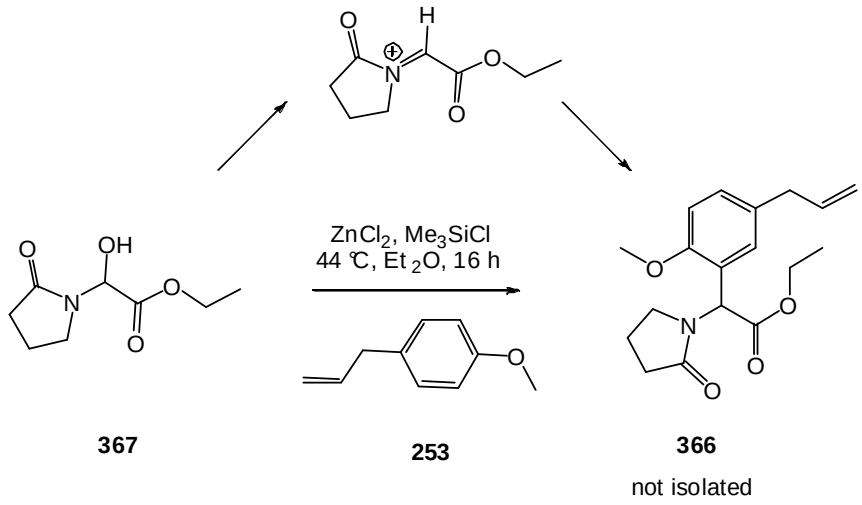
entry	alkene	X	Zn/$ZnCl_2$	L.A.	NMR observations
1	 **368**	C	Zn 13 eq./$ZnCl_2$ 1.5 eq.	Me_3SiCl 6.4 eq.	no reaction
2	 **368**	O	Zn(Cu) 12.6 eq./$ZnCl_2$ 1.5 eq.	Me_3SiCl 6.3 eq.	no reaction
3	 **369**	O	Zn(Hg) 12.5 eq./$ZnCl_2$ 1.5 eq.	$C_6H_{16}Cl_2Si_2$ 6.4 eq.	 **370** 56%

Table 21

As in the case of reaction with allyl anisole (Table 20, entry 6) only very electronic rich aromatic compounds underwent the Friedel-Crafts reaction (Table 21). The successful reaction of the allyl anisole derivative (Table 20, entry 6) stands in contrast to the failure of anisole itself, and at this time, we have no satisfactory explanation for this particular observation.

In order to confirm that the Friedel-Crafts reaction occurred *via* an *N*-acyl iminium cation, compound **367** was added to a solution of zinc chloride, trimethylsilyl chloride and 4-allylanisole **253** (Scheme 140). As observed by ^{1}H NMR spectroscopy, the same product resulted from this more classical Friedel-Crafts reaction.

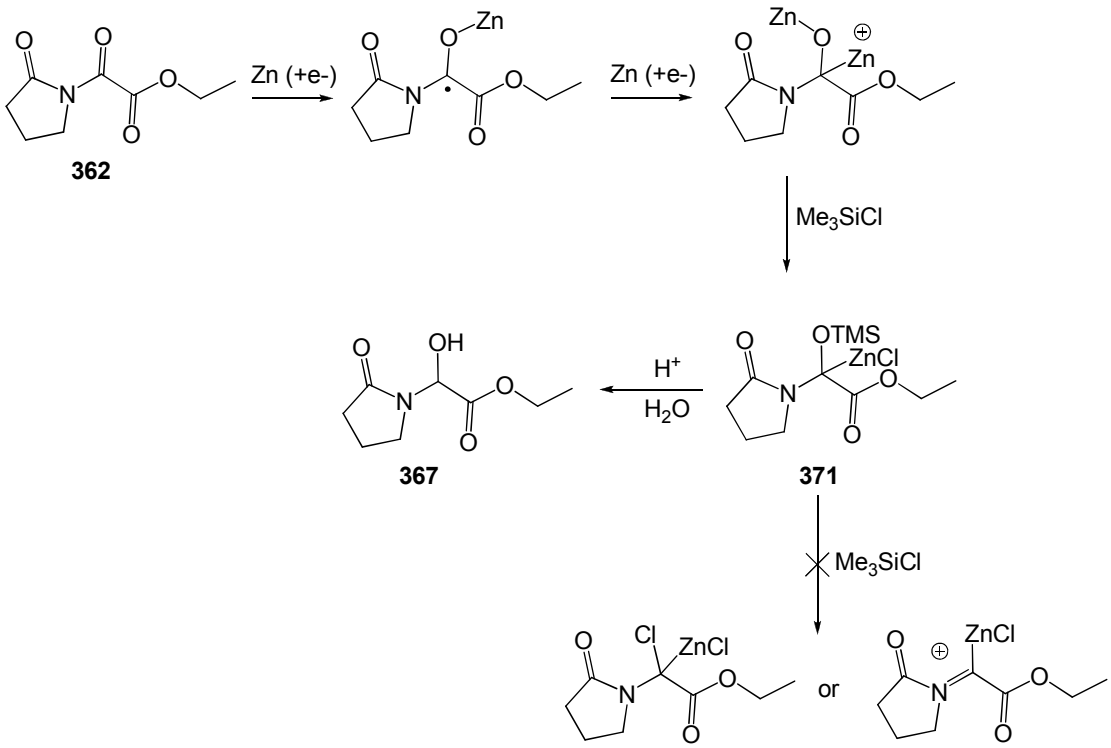


367 **253** **366**

not isolated

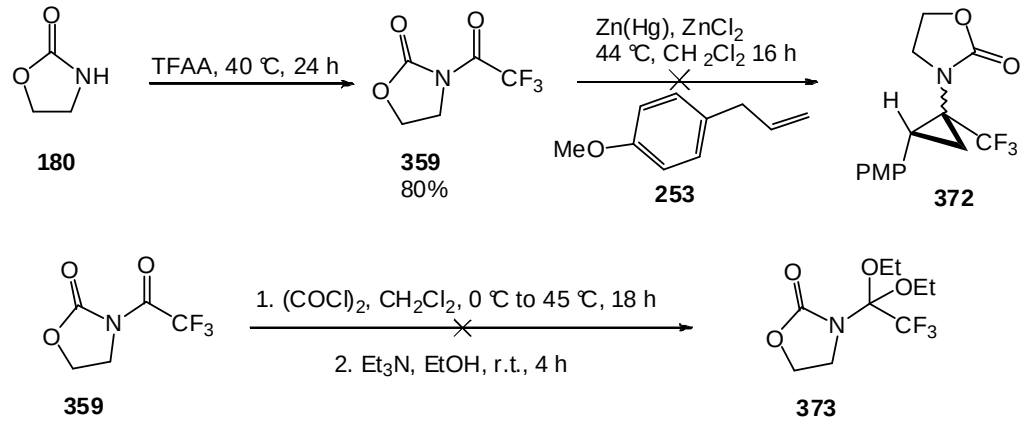
Scheme 140

In essence, these observations would seem to imply that two electron delivery from zinc to the desired carbonyl group is, as expected, a favourable process. Further evolution involving cleavage of the carbon oxygen bond appears to be much more problematic and hence the desired carbenoid reactivity is not observed and intermediate **371,** on hydrolytic work up gives the observed alcohol **367** (Scheme 141).



Scheme 141

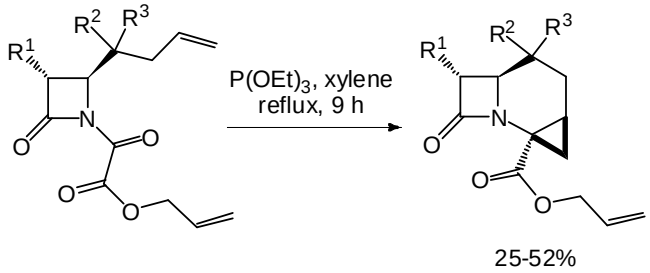
The trifluoroacetyl derivative was also examined as a carbenoid precursor for cyclopropanation reaction and efforts were also made to prepare the functionalised diethoxytrifluoroethyl congener **373** (Scheme 142).



Scheme 142

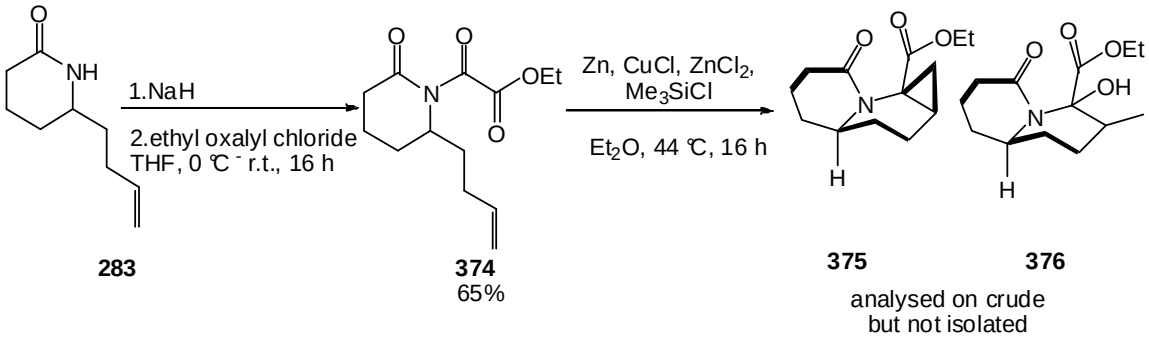
Unfortunately, in all of these cases, formation of the desired product was never observed. The attempted cyclopropanation of **359** gave a mixture of the 2-oxazolidinone **180** and recovered allyl anisole **253**. Further investigations are therefore required to allow cyclopropanation using more substituted amidocarbenoid precursors.

Within the framework of such donor acceptor carbenoids we were also intrigued by a literature reaction in which a carbene species derived from an oxalamide substrate by treatment with triethylphosphite afforded a tricyclic compound containing an aminocyclopropyl group in an intramolecular reaction as shown in Chapter 1 Scheme 42 and outlined again below (Scheme 143).[59,159]



Scheme 143

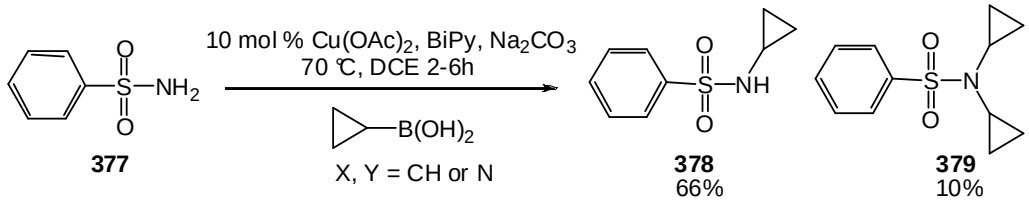
We therefore applied our methodology to an imide **374**, containing an electron-withdrawing group (an ester) in the alpha position, as a carbenoid precursor. The carbenoid precursor **374** was synthesised from lactam **283** using sodium hydride and ethyl oxalyl chloride in 65% yield. When the intramolecular cyclopropanation reaction was attempted, a mixture of two products including the desired product was formed (Scheme 144). Only a small amount of material was obtained (34 mg) after the first purification by flash chromatography and due to time constraints the reaction was not repeated and the desired cyclopropane could not be isolated. This reaction also requires further investigation.



Scheme 144

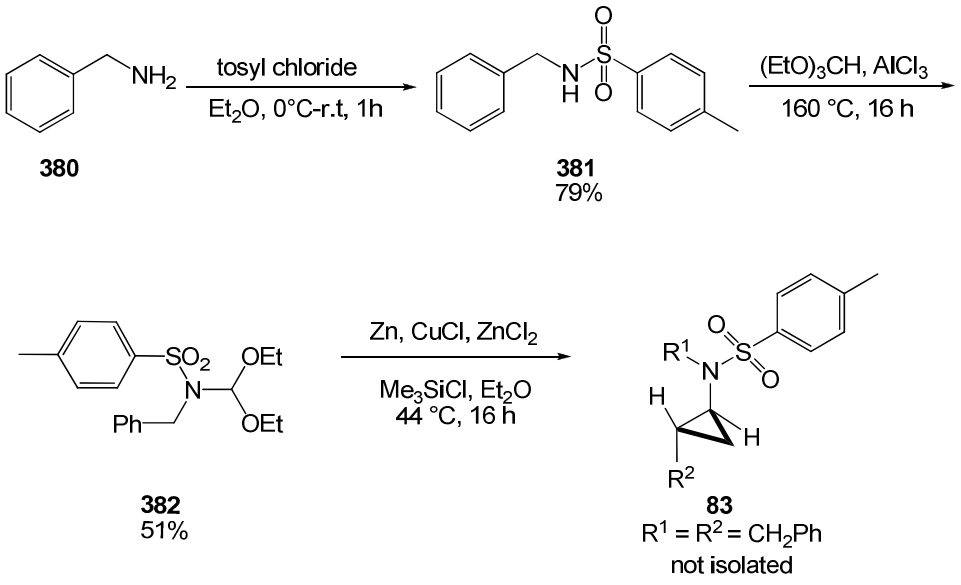
2.5.2. Sulfonamido organozinc carbenoids

Instead of having a carbonyl group as the electron-withdrawing group on the carbenoid carbon we decided to design a new carbenoid precursor functionalised with a sulfonyl group. Zhu *et al.* have reported the *N*-cyclopropanation of sulfonamides by cyclopropylboronic acid to yield unfunctionalised sulfonamidocyclopropanes (Scheme 145).[151b]



Scheme 145

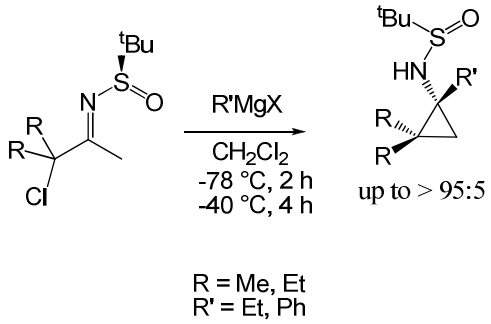
Using our methodology we could potentially obtain sulfonamide-functionalised three membered rings. A novel carbenoid precursor **382** was therefore synthesised and the cyclopropanation reaction was attempted (Scheme 146).



Scheme 146

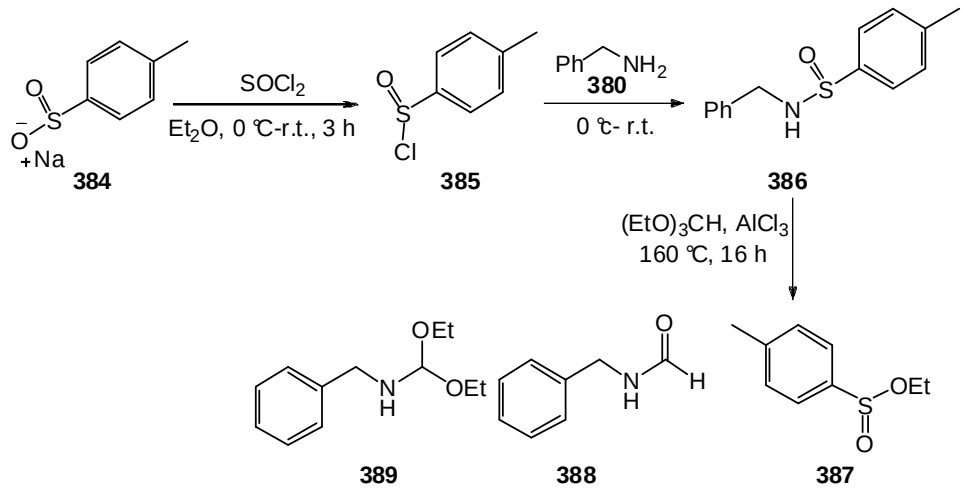
Compound **382** was synthesised in 40 % overall yield from benzylamine **380** *via N*-benzyl-4-methyl-benzenesulfonamide **381**[160] and subsequently reacted with triethyl orthoformate in the presence of a Lewis acid. When the cyclopropanation reaction on **382** was attempted, the crude ^{1}H NMR spectrum showed signals indicating the presence of a cyclopropane (doublet of triplets at 1.83 ppm resulting from the NCH and two doublets of doublets resulting from the CH_2Ph at 2.15 ppm and 2.6 ppm). Unfortunately we were unable to isolate the compound in pure form due to the very small amount of material obtained after the first purification by flash chromatography and because of time constraints, the reaction was not repeated. However this initial result was very encouraging.

In similar vein, we were impressed by a recent publication from De Kimpe *et al.*, who developed an asymmetric synthesis of *N*-cyclopropyl sulfinamides in good yield and with high diastereoselectivity from chiral *N*-sulfinyl α-chloro ketimines (Scheme 147).[161]



Scheme 147

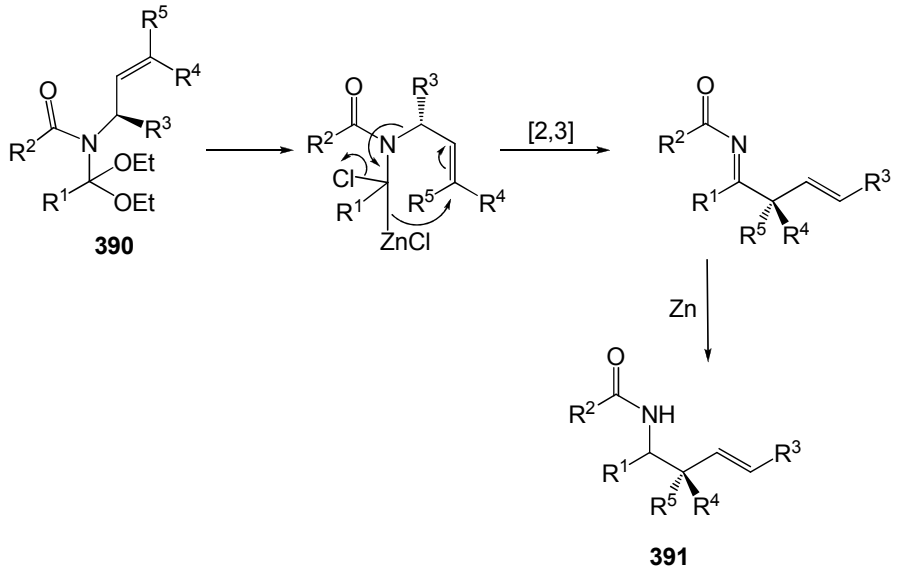
Thus, we decided to examine our cyclopropanation methodology to gain access to a functionalised cyclopropyl unit from a carbenoid precursor containing a sulfinic acid group. Accordingly 4-methylbenzenesulfinic acid benzylamide **386** was synthesised in 33% from **384.**[162,163] However when we investigated the conversion of **386** into a carbenoid precursor we obtained **387**, **388** and a trace of the orthoamine **389**. Therefore, the subsequent cyclopropanation was not attempted (Scheme 148).



Scheme 148

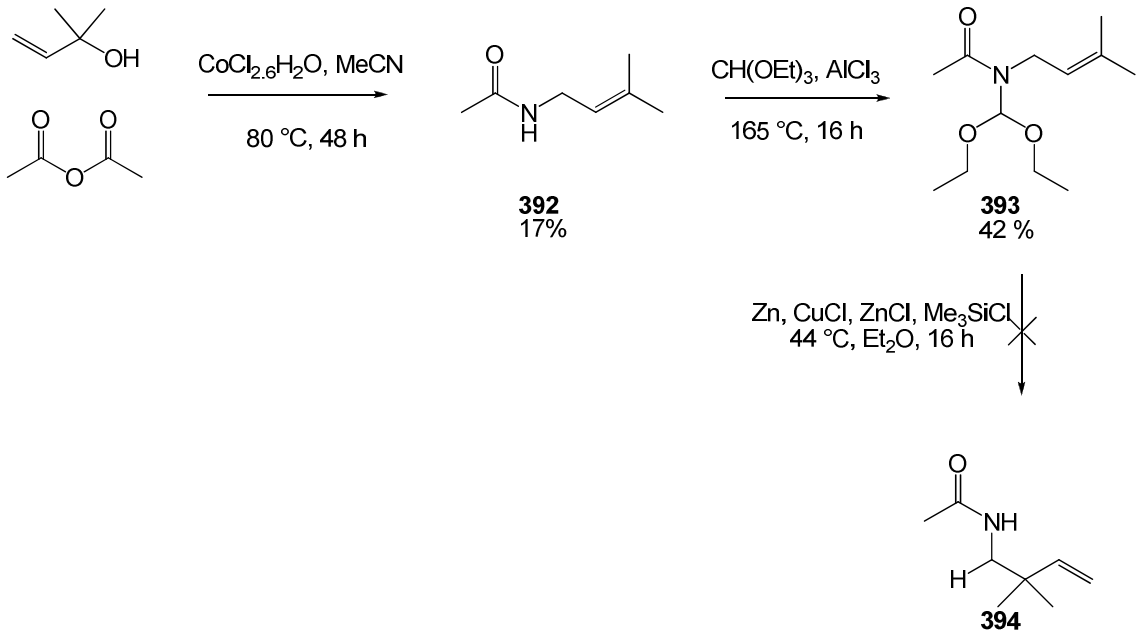
2.6. Attempted rearrangement studies

In a further extension of our work on amidoorganozinc carbenoids we wished to prepare a compound such as **390** which could pleasingly undergo a subsequent [2,3] sigmatropic rearrangement as outlined below and, in the ideal scenario, generate a chiral quaternary centre (Scheme 149).



Scheme 149

We therefore prepared **392** following an interesting literature procedure using a mixture of cobalt chloride, 2 methyl but-3ene-1 ol, and acetic anhydride in acetonitrile at 80°C for 48 hours.[164] The subsequent reaction with triethyl orthoformate then furnished the desired precursor **393** in acceptable yield. This product was then subjected to the same conditions as for the cyclopropanation reaction, but unfortunately, examination of the NMR spectrum of the crude product did not give any conclusive results and only the amide **392** was obtained. Under the reaction conditions attempted, either the orthoamide **393** did not lead to the formation of an organozinc carbenoid and was hydrolysed under the reactions conditions, or the organozinc carbenoid was formed but hydrolysed prior to intramolecular trapping of the alkene to give the expected amide **394** (Scheme 150).



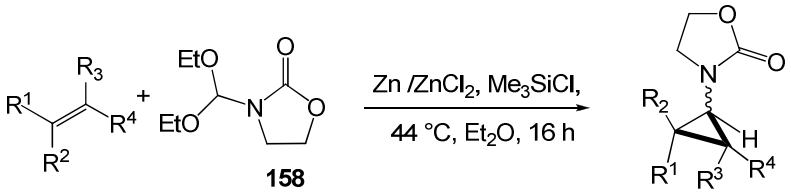
Scheme 150

This reaction certainly requires much further investigation. It would also be interesting to try the reaction with a carbenoid precursor containing a stronger electron-withdrawing group alpha to the nitrogen atom in order to attenuate the reactivity of the lone pair and avoid hydrolysis.

Chapter 3: Conclusions and Future Perspectives

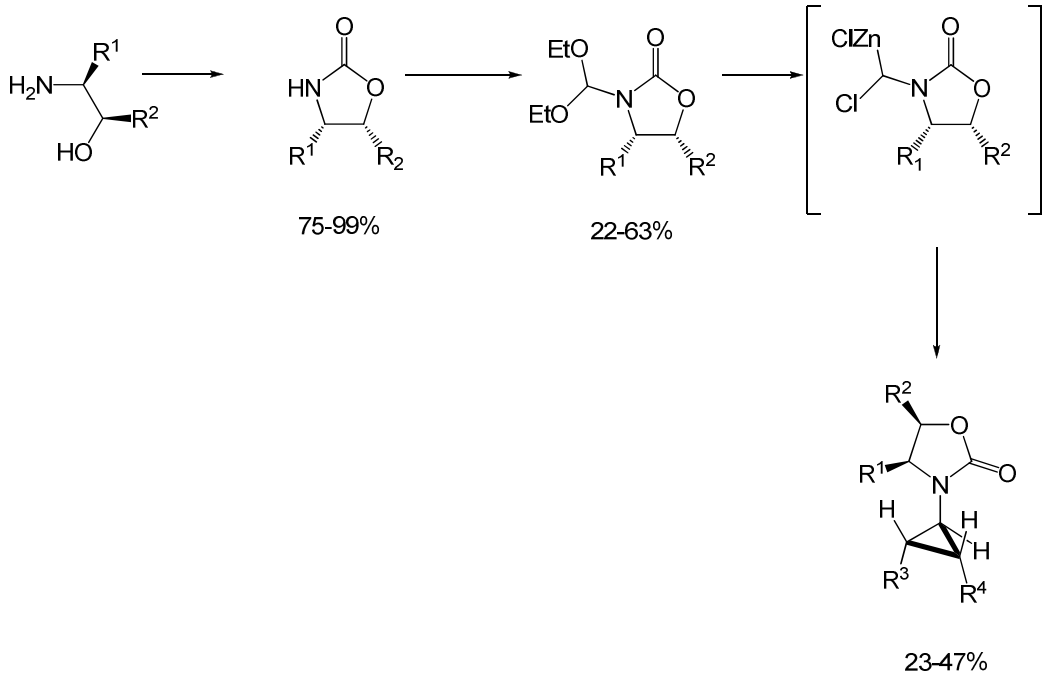
3. Conclusions and future perspectives

In summary, we have investigated the scope of the direct cyclopropanation of alkenes using racemic organozinc carbenoids derived from oxazolidinones in detail in terms of chemoselectivity and stereoselectivity, and as a consequence the results have been rationalised using a quadrant model to explain the observed geometry of the cyclopropane as a function of the nature of the alkene (Scheme 151). In terms of chemoselectivity, as expected more electron-rich alkenes are preferred over electron-deficient ones.



Scheme 151

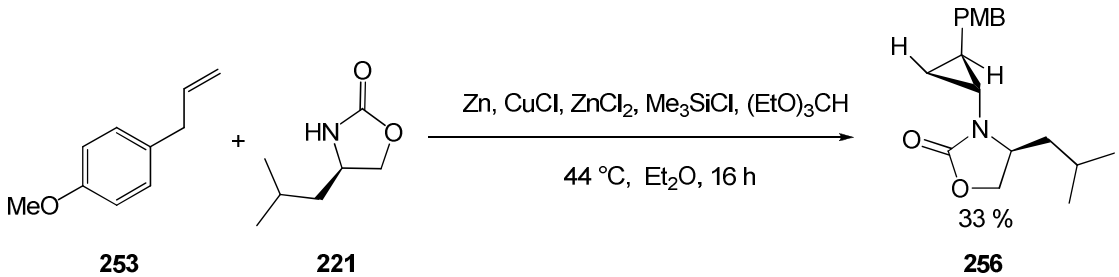
In order to study the asymmetric version of this cyclopropanation reaction, we prepared a wide range of highly functionalised zinc carbenoid precursors as their dialkoxymethylamide derivatives using both natural and unnatural amino-acid derivatives in moderate to excellent yield. From an experimental standpoint, the overall sequence is simple, inexpensive and robust and the zinc chlorotrimethylsilane mediated cyclopropanation reaction occurs under mild conditions, thus paving the way for the enantiopure preparation of novel highly functionalised *N*-cyclopropyl oxazolidinone systems that could not be readily obtained using existing methods (Scheme 152).



Scheme 152

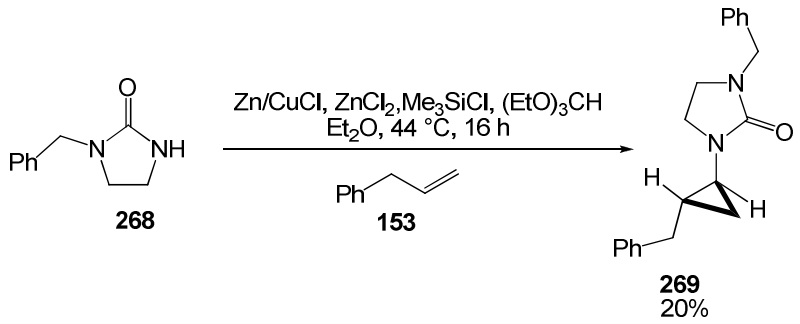
In most cases, only one diastereoisomer was isolated with diastereoselectivities of up to 95:5. The particular stereoselectivity in these reactions was also rationalised using the quadrant model previously established for the racemic version.

The direct synthesis of a *N*-cyclopropyl oxazolidinone without the need for preparation of the intermediate orthoamide derived carbenoid precursors was pleasing. The two processes were successfully combined into a one-pot reaction and the cyclopropane **256** was obtained in 33 % yield from an oxazolidinone in one step (Scheme 153). Further optimisation of this protocol should certainly be considered.



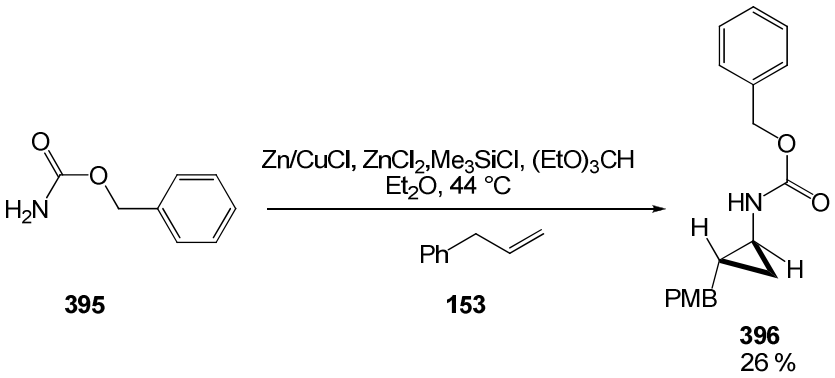
Scheme 153

This “one-pot process” was also a success for the synthesis of cylopropane **269** containing a functionalised urea group, and although only one example was studied, this represents an interesting molecular scaffold (Scheme 154).



Scheme 154

Moreover, for the sake of completeness, we include an initial result from Dr. Tom Sheppard who showed that the synthesis of a carbamate functionalised cyclopropane was possible using the same conditions from the carbamate **395.** A mixture of rotamers of the *trans*-cyclopropane **396** was obtained (Scheme 155).

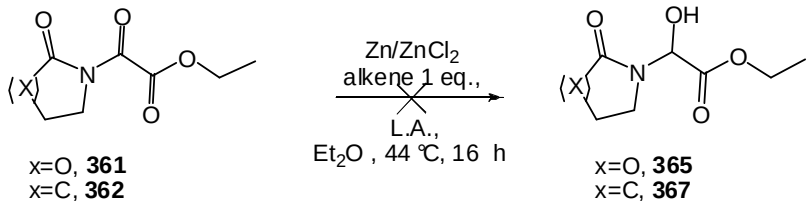


Scheme 155

The synthesis of a cyclopropane functionalised with a carbamate is, of course of great interest since they can potentially lead to an aminocyclopropane in one step by simple deprotection.

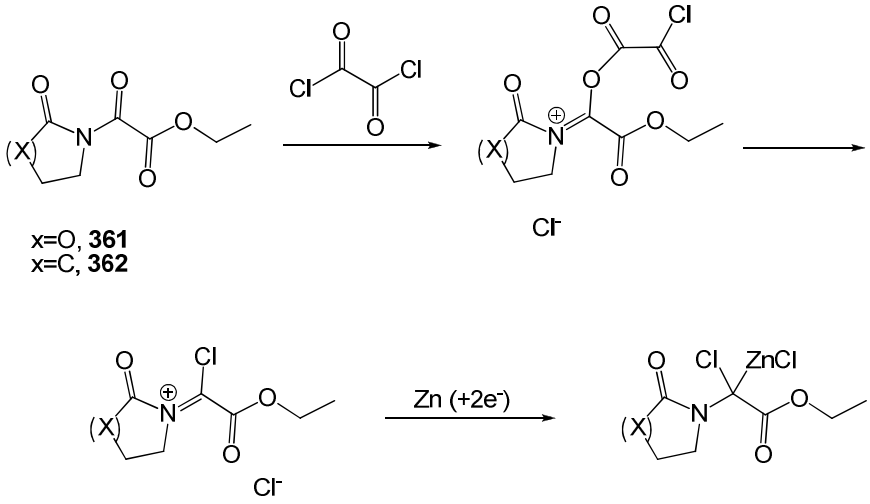
These results are very encouraging and this approach for the direct preparation of amido and aminocyclopropanes from readily available amides or carbamates should be optimised in the future.

The investigation of new source of organozinc carbenoid from a carbonyl group attached to a nitrogen atom such a **361** and **362** did not give any satisfactory results in terms of intermolecular cyclopropanation reaction and the desired carbonyl group was reduced to an alcohol (Scheme 156).



Scheme 156

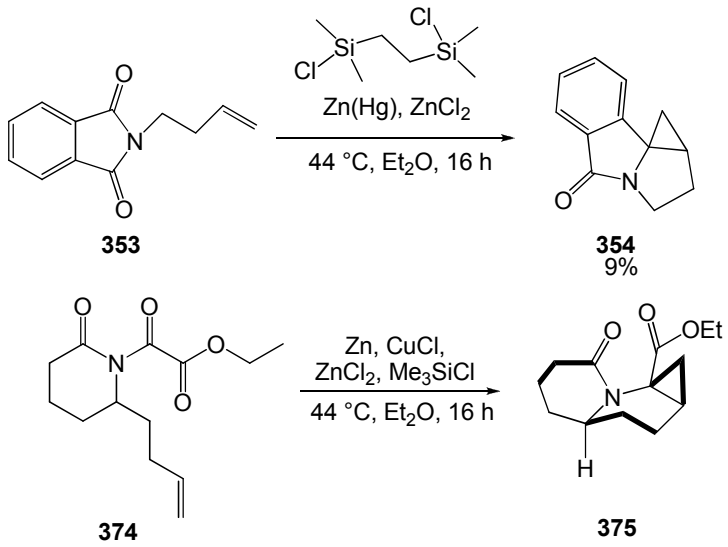
The C-OSiMe$_3$ bond seems difficult to break to form the organozinc carbenoid, hence it would be interesting to use ethyl 2-chlorooxoacetate or a sulfonyl chloride instead of trimethylsilyl chloride in order to encourage the formation of an organozinc carbenoid (Scheme 157).



Scheme 157

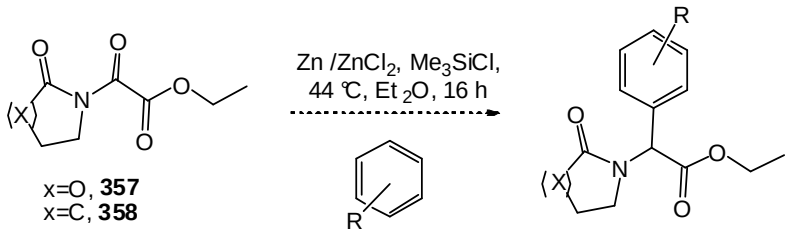
These conditions could also be interesting for investigation in the case of the imide functionalised with a trifluoroacetyl group

However, the generation of an organozinc carbenoid from the carbonyl group attached to the nitrogen atom of a cyclic imide can undergo intramolecular cyclopropanation in some cases (Scheme 158). At this stage however, this approach is not competitive with the Kulinkovich-based alternative.



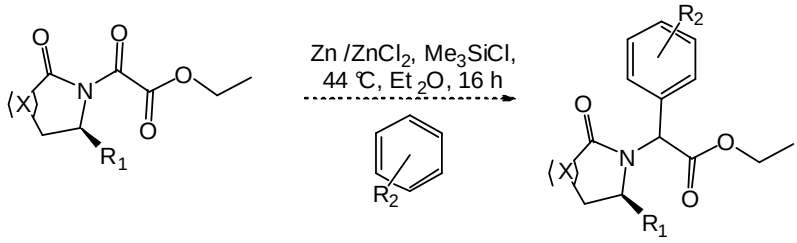
Scheme 158

As a "divertissement", the discovery of the Friedel-Crafts reaction observed under the cyclopropanation conditions with electron-rich aromatic rings could be investigated for a wider range of substrates (Scheme 159).



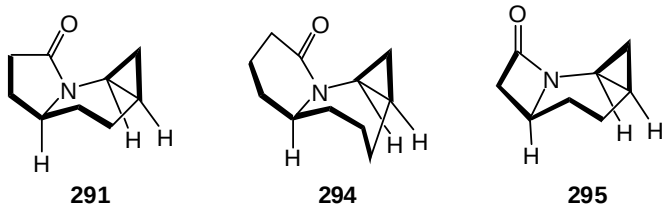
Scheme 159

It will also be interesting to know if this reaction works with an enantiopure substrate and to determine if there is any preferred stereoselectivity in the reaction (Scheme 160).



Scheme 160

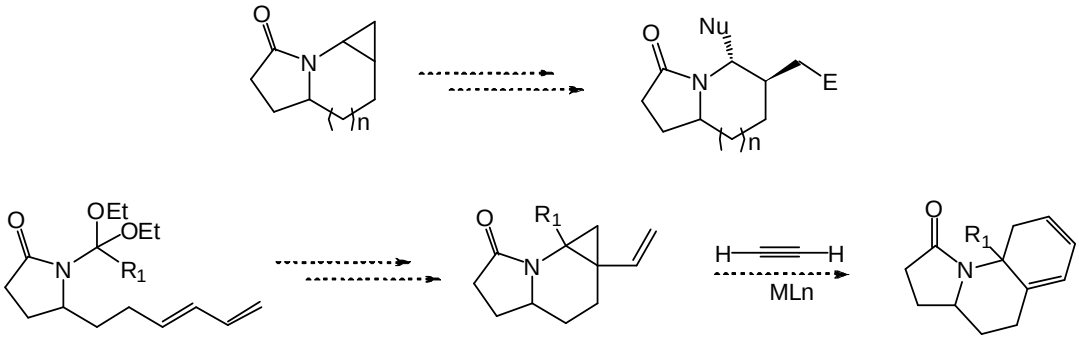
The possibility of intramolecular cyclopropanation using our methodology from diethoxymethyl lactams as organozinc carbenoid precursors was successfully achieved for the construction of a range of usefully functionalised polycyclic amidocyclopropane systems in moderate yield (21%-41%). The organozinc carbenoid was participating in formation of a bicyclo [4.1.0] (six membered ring) or a [5.1.0] (seven membered ring) subunit. In all cases thus for studied, only one diastereoisomer was isolated and the stereochemical preference was for formation of the cyclopropane on the more hindered concave face of the molecule (Figure 16).



291 **294** **295**

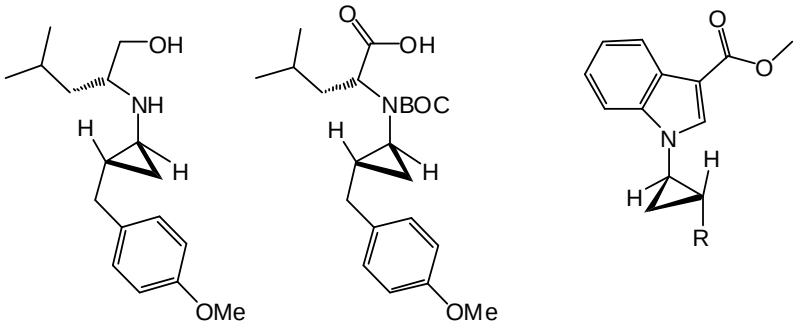
Figure 16

The novel compounds obtained by the intramolecular variant of the amidocyclopropanation reaction could potentially afford a new range of products *via* subsequent stereoselective cycloaddition or ring-opening reactions (Scheme 161).



Scheme 161

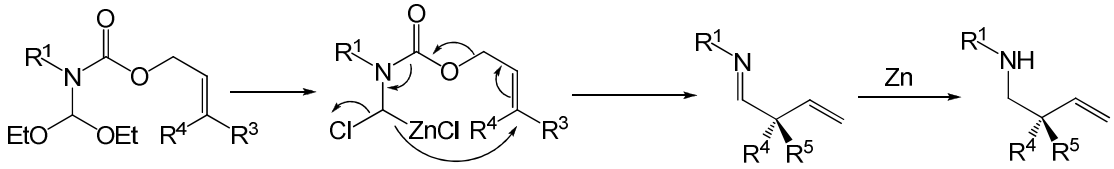
The further application of these results for the development of novel targets containing the aminocyclopropyl motif was also a success through the synthesis of cyclopropanes containing aminoalcohols, amino acid motifs and an *N*-cyclopropyl indole in two steps allowing the design of further complex compounds (Figure 17).



304 **306** **343-346**

Figure 17

Finally due to lack of time, the study of the rearrangement reaction could not be investigated in detail and was only tried once. It would be very interesting to prepare more material and also to try the reaction with other carbenoid precursors such as **397**. The N-COO bond should be easier to break than the corresponding NC-C one and, although no longer a sigmatropic rearrangement, the reaction could give some satisfactory results (Scheme 162).



397 **398**

Scheme 162

Chapter 4: Experimental

Experimental

Melting points were determined using a Reichert hot-stage apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter or a Perkin Elmer Model 343 Polarimeter (using the sodium D-line, 529 nm) and $[\alpha]_D^T$ values are given in 10^{-1} deg $cm^2.g^{-1}$, concentration (*c*) in g per 100 ml. Infrared (IR) spectra were recorded on a Perkin-Elmer 1605 Fourier transform spectrometer or on a PerkinElmer spectrum 100 FT-IR spectrometer as thin films. Absorption maxima are reported in wavenumbers (cm^{-1}). Only selected absorbances are reported.

^{1}H NMR spectra were recorded at 300 MHz on a Bruker AMX300 spectrometer, at 400 MHz either on a Bruker AMX400 or Avance 400 spectrometer, at 500 MHz on a Bruker Avance 500 spectrometer or at 600 MHz on a Bruker Avance 600 spectrometer in the stated solvent using residual protic solvent $CHCl_3$ (δ = 7.26 ppm, s), DMSO (δ = 2.56 ppm, qn) or D_2O (δ = 4.79, s) as the internal standard. Chemical shifts are quoted in ppm using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad or a combination of these. The coupling constants (*J*) are reported as measured and recorded in Hertz. Chemical shifts (δ) are quoted as parts per million relative to TMS (tetramethylsilane) downfield from δTMS = 0 ppm.
^{13}C NMR spectra were recorded at 75 MHz on a Bruker AMX300 spectrometer, at 100 MHz either on a Bruker AMX400 or Avance 400 spectrometer, at 125 MHz on a Bruker Avance 500 spectrometer or at 150 MHz on a Bruker Avance 600 spectrometer in the stated solvent using the central reference of $CHCl_3$ (δ = 77.0 ppm, t), DMSO (δ = 39.52 ppm, septet) as the internal standard. Chemical shifts are reported to the nearest 0.1 ppm.

Mass spectra and accurate mass measurements were recorded on a Micromass 70-SE Magnetic Sector spectrometer at the University College London Chemistry Department either by electrospray ionisation (ESI), fast atom bombardment (FAB) using a cesium ion gun in a thioglycerol matrix or were ionised electronically (EI) with an accelerating voltage of approximately 6 kV.

Elementary analyses were performed at University College London Chemistry Department. The X-Ray crystal structure was determined using a Diffractometer: Nonius KappaCCD area detector (ϕ scans and ω scans to fill asymmetric unit sphere) at the University of Southampton, School of Chemistry, EPSRC National Crystallography Service.
Purification was carried out by column chromatography using silica gel BDH (40-60 µm). Analytical thin layer chromatography was carried out using Merck Kieselgel aluminium-backed plates coated with silica gel 60 F_{254}. Components were visualised using combinations of ultra-violet light, iodine, ceric ammonium molybdate and permanganate solutions.

All reactions using dry solvents were carried out in oven-dried glassware under a nitrogen atmosphere. Diethyl ether, tetrahydrofuran, toluene and dichloromethane were used following purification from Anhydrous Engineering zeolite drying apparatus. *N*,*N* dimethylformamide was distilled under reduced pressure from calcium hydride and stored over 4Å molecular sieves. Triethylamine was distilled from potassium hydroxide. Petroleum ether refers to the fraction of petroleum ether that was distilled between 40 °C and 60 °C. Chlorotrimethylsilane was distilled from calcium hydride immediately prior to use. 3-Carene was distilled prior to use. Sodium *para*-toluenesulfinate was dried under vacuum at 120 °C prior to use. Cobalt(II) chloride hexahydrate was dried at 100 °C for 4 hours prior to use.

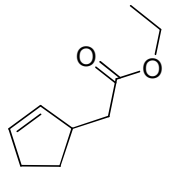
Zinc amalgam

Zinc dust (10.0 g, 153 mol) was added to a vigorously stirred solution of mercury (II) chloride (2.0 g, 7.20 mmol) and a solution of hydrochloric acid (0.5 ml of a 12M solution) in water (30 ml). The mixture was stirred for 10 minutes, the zinc amalgam filtered off and then washed with water (3 x 20 ml), acetone (3 x 20 ml), ethanol (3 x 20 ml) and diethyl ether (3 x 20 ml) before being dried under high vacuum. The zinc amalgam was thereafter stored under vacuum, and flame dried under a stream of nitrogen immediately prior to use.

Zinc dust

A suspension of commercially available zinc dust (5 g, 76.5 mmol) in 2% aqueous hydrochloric acid (15 ml) was stirred for 10 min, filtered and washed with water (3 × 20 ml), acetone (3 × 20 ml), ethanol (3 × 20 ml) and diethyl ether (3 × 20 ml) and then dried under vacuum.

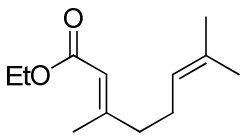
Ethyl 2-(cyclopent-2-enyl)acetate 163[118]



Acetyl chloride (3.00 ml, 42.4 mmol, 2.7 eq.) was added dropwise to a solution of ethanol (30 ml) at 0 °C. 2-(Cyclopent-2-enyl)acetic acid **178** (2.00 g, 15.9 mmol, 1 eq.) was added dropwise to this solution at 0 °C, and the resulting mixture allowed to warm to room temperature then heated at reflux for 4 hours. After concentration under reduced pressure the residue was diluted with chloroform (15 ml) and concentrated again under reduced pressure to give a biphasic mixture. The mixture was extracted with dichloromethane (10 ml) and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether: diethyl ether 4:1) to give the ester **163** as a pale yellow oil (1.6 g, 65%).

IR (film): υ_{max} 2907 (s), 1732 (s), 1614 (w), 1259 (s), 1148 (s), 1032 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.26 (t, J=7.2 Hz, 3H, CH_3), 1.42–1.50 (m, 1H, C*H*HCHCH$_2$), 2.07–2.16 (m, 1H, CH*H*CHCH$_2$), 2.25–2.33 (m, 2H, CH_2C=O), 2.33–2.42 (m, 2H, C*H*$_2$CH=CH), 3.04–3.12 (m, 1H, C*H*CH=CH), 4.14 (q, J=7.2 Hz, 2H, C*H*$_2$CH$_3$), 5.65–5.68 (m, 1H, C*H*=CH), 5.74–5.78 (m, 1H, C*H*=CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3 (CH_3), 29.6 (CH_2), 31.8 (CH_2), 40.5 (CH_2), 41.8 (CH), 60.2 (CH_2), 131.4 (*C*H=CH), 133.7 (CH=*C*H), 173.0 (C=O); MS (EI) m/z (%): 153 (M-H, 33), 79 (75), 57 (100); HRMS:M-H, found 153.09115, $C_9H_{13}O_2$ requires 153.09101.

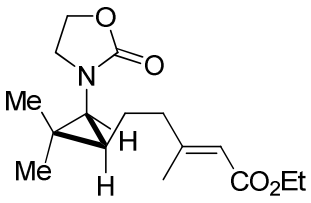
(*E*)-Ethyl 3,7-dimethylocta-2,6-dienoate 159[119]



Sodium hydride (60% mineral oil dispersion, 0.31 g, 7.80 mmol, 1.3 eq.) was washed three times with hexane. The resulting solid was suspended in dry tetrahydrofuran (10 mL) and cooled to 0 °C. A solution of triethyl phosphonoacetate (1.75 g, 7.80 mmol, 1.3eq.) in tetrahydrofuran (6 ml) was added at 0 °C, and the mixture was stirred at this temperature for a further 30 min. A solution of 6-methyl-5-hepten-2-one **179** (0.74 g, 5.90 mmol, 1eq.) in tetrahydrofuran (5 ml) was added and the resulting mixture was stirred at 0 °C for 1 hour and then allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was then poured into a mixture of diethyl ether (50 ml) and a saturated aqueous solution of ammonium chloride (20 ml). The ether layer was separated and the aqueous layer extracted with diethyl ether (2 × 20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product (approximately 75:25 *E*:*Z*) was purified by column chromatography (3% ^{t}BuOMe in hexane) to give 1.03 g of a mixture of (*E*) and (Z) isomers (64:36 *E*:*Z*) as a colourless oil and 187 mg of the pure *E* isomer as a colourless oil (89% overall yield). The pure *E* isomer was used in the cyclopropanation reaction.

IR (film): υ_{max} 1643 (s), 1385 (w), 1223 (w), 1142 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J*=7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.60 (s, 3H, C*H*$_3$CCH$_3$), 1.68 (s, 3H, CH$_3$CC*H*$_3$), 2.15 (s, 3H, C*H*$_3$C=CH), 2.16 (m, 4H, 2 × CH$_2$), 4.15 (q, *J*=7.1 Hz, 2H, C*H*$_2$CH$_3$), 5.03–5.1 (m, 1H, CHCOO), 5.66 (br s, 1H, Me$_2$C=C*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3 (CH_3), 17.7 (CH_3), 18.8 (CH_3), 25.7 (CH_3), 26.0 (CH_2), 40.9 (CH_2), 59.5 (CH_2), 115.6 (*C*H=C), 123.0 (*C*H=C), 132.5 (*C*=CH), 159.8 (*C*=CH), 166.9 (C=O); MS (EI) m/z (%): 196 (M^+,10), 151 (33), 123 (60), 97 (52), 83 (100); HRMS: $[M]^+$, found 196.14572, $C_{12}H_{20}O_2$ requires 196.14632.

cis (_E_)-Ethyl 5-(2,2-dimethyl-3-(2-oxooxazolidin-3-yl)cyclopropyl)-3-methylpent-2-enoate 181

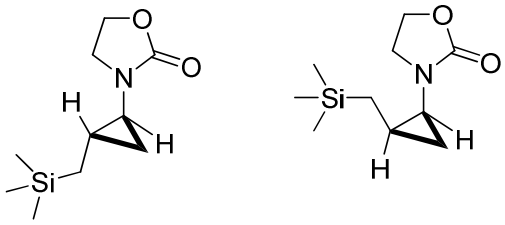


A solution of 3-diethoxymethyloxazolidin-2-one **158** (342 mg, 1.81 mmol, 2 eq.) in diethyl ether (3 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (1.19 g, 18.2 mmol, 20 eq.), copper(I) chloride (119 mg, 1.20 mmol, 1.3 eq.), zinc chloride (1.0 M solution in diethyl ether, 1.8 ml, 1.8 mmol, 2 eq.), chlorotrimethylsilane (1.16 ml, 9.00 mmol, 10 eq.) and (*E*)-ethyl-3,7-dimethyl-octa-2,6-dienoate **159** (178 mg, 0.90 mmol, 1 eq.) in diethyl ether (10 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (15 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (3 ×15 ml) and the combined organic extracts washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product (**181**:**182** 11:1 as determined by ^{1}H NMR spectrum) was purified by column chromatography (diethyl ether:petroleum ether 1:1) to give the *N*-cyclopropyl oxazolidinone **181** as a pale yellow liquid (101 mg, 38%).

IR (mixture of *trans* and *cis*, film): υ_{max} 2955, 1759, 1709, 1643 (s) cm^{-1}; ^{1}H NMR (*cis*, 500 MHz, $CDCl_3$): δ 0.74 (ddd, *J*=8.9, 7.6, 5.4 Hz, 1H, C*H*CHN), 1.07 (s, 3H, CH_3CCH_3), 1.09 (s, 3H, CH_3CCH_3), 1.25 (br t, *J*=7.1 Hz, 3H, CH_3CH_2), 1.34–1.44 (m, 1H, C*H*HCH_2), 1.76– 1.84 (m, 1H, CH*H*CH_2), 2.10 (d, *J*=7.6 Hz, 1H, CHN), 2.14 (s, 3H, CH_3C=CH), 2.16–2.22 (m, 1H, C*H*HC=CH), 2.23–2.31 (m, 1H, CH*H*C=CH), 3.43–3.56 (m, 2H, CH_2N), 4.12 (q, *J*=7.1 Hz, 2H, C$H_2$$CH_3$), 4.22–4.30 (m, 2H, CH_2OC=O), 5.64 (br s, 1H, CHCOO); ^{13}C NMR (*cis*, 125 MHz, $CDCl_3$): δ 14.3 (CH_3), 14.9 (CH_3), 18.9 (CH), 19.5 (CH_3), 22.8 (C), 22.9 (CH_2), 27.0 (CH_3), 27.8 (CH), 40.9 (CH_2), 46.9 (CH_2), 59.5 (CH_2), 62.2 (CH_2), 115.8 (*C*H=C), 159.5 (*C*=CH), 160.4 (C=O), 166.7 (C=O); ^{1}H NMR (*trans*, 500 MHz, $CDCl_3$): δ 0.52-0.57 (m, 1H), 3.94 (dd,

2H), 4.49 (dd, 2H); MS (FAB) m/z (%): 296 (MH^+, 28), 250 (70), 219 (100), 163 (66), 154 (72); HRMS: $[MH]^+$, found 296.18541, $C_{16}H_{26}O_4N$ requires 296.18617.

***trans* 3-[2-((trimethylsilyl)methyl)cyclopropyl]oxazolidin-2-one 183 and *cis* 3-[2-((trimethylsilyl)methyl)cyclopropyl]oxazolidin-2-one 184**

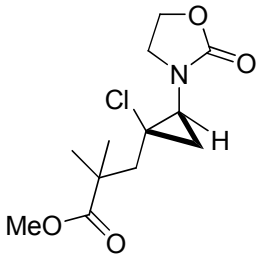


A solution of 3-diethoxymethyloxazolidin-2-one **158** (497 mg, 2.60 mmol, 2 eq.) in diethyl ether (2 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (1.72 g, 26.3 mmol, 20 eq.), copper(I) chloride (172 mg, 1.74 mmol, 1.4 eq.), zinc chloride (1.0 M solution in diethyl ether, 2.6 ml, 2.6 mmol, 2 eq.), chlorotrimethylsilane (1.67 ml, 13.2 mmol, 10 eq.) and allyltrimethylsilane **160** (0.20 ml, 1.26 mmol, 1 eq.) in diethyl ether (5 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (15 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (3 ×15 ml) and the combined organic extracts washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (diethyl ether:petroleum ether 3:2) to give the *trans N*-cyclopropyl oxazolidinone **183** as a pale yellow liquid (41 mg, 15%) and the *cis N*-cyclopropyl oxazolidinone **184** as a pale yellow solid (26 mg, 10%)

IR (*trans*, film): υ_{max} 2953 (w), 1748 (s), 1483 (w), 1417, 1246, 1037, 835 (s); ^{1}H NMR (*trans*, 500 MHz, $CDCl_3$): δ 0.01 (s, 9H, 3 × CH_3), 0.33 (dd, *J*=14.8, 8.4 Hz, 1H, C*H*HSi), 0.48-0.52 (m, 1H, C*H*HCHN), 0.75 (dd, *J*=14.8, 6.1 Hz, 1H, CH*H*Si), 0.87 (ddd, *J*=9.3, 5.5, 3.6 Hz, 1H, CH*H*CHN), 0.92-0.99 (m, 1H, C*H*CHN), 2.15 (dt, *J*=6.8, 3.4 Hz, 1H, CHN), 3.42-3.52 (m, 2H, CH_2N), 4.22 (t, *J*=8.0 Hz, 2H, CH_2O); ^{13}C NMR (*trans*, 125 MHz, $CDCl_3$): δ – 1.5 (3 × CH_3Si), 14.6 (CH_2), 15.0 (CH), 20.1 (CH_2), 33.5 (CH), 45.7 (CH_2), 61.7 (CH_2), 158.3 (C=O);

M.p. 93-96 °C (Et_2O); IR (*cis* , film): υ_{max} 2956 (w), 1744 (s), 1430 (w), 1243 (s), 1136, 1082, 1033 (s), 839 (s) cm^{-1}; ^1H NMR (*cis*, 500 MHz, $CDCl_3$): δ 0.02 (s, 9H, 3 × CH_3), 0.04-0.08 (m, 1H, C*H*HSi), 0.38-0.44 (m, 1H, C*H*HCHN), 0.95-1.04 (m, 3H, CH*H*Si, C*H*CHN, CH*H*CHN), 2.41 (td, *J*=7.3, 4.3 Hz, 1H, CHN), 3.58 (td, *J*=8.7, 7.2 Hz, 1H, C*H*HN), 3.64 (td, *J*=8.7, 7.1 Hz, 1H, CH*H*N), 4.26-4.30 (m, 2H, CH_2O); ^{13}C NMR (*cis*, 125 MHz, $CDCl_3$): δ – 1.5 (3 × CH_3Si), 12.1 (CH_2), 13.9 (CH), 14.7 (CH_2), 30.3 (CH), 46.6 (CH_2), 61.9 (CH_2), 159.4 (C=O); MS (CI^+) m/z (%): 214 (MH^+, 82), 198 (100), 159 (20), 144 (27); HRMS: $[MH]^+$, found 214.12740, $C_{10}H_{20}O_2NSi$ requires 214.12633.

***cis* Methyl 3-(1-chloro-2-(2-oxooxazolidin-3-yl)cyclopropyl)-2,2-dimethyl-propanoate 185**

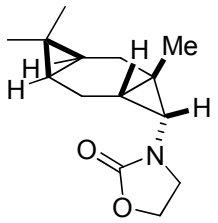


A solution of 3-diethoxymethyloxazolidin-2-one **158** (427 mg, 2.26 mmol, 2 eq.) in diethyl ether (4 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (1.48 g, 22.6 mmol, 20 eq.), copper(I) chloride (148 mg, 1.50 mmol, 1.3 eq.), zinc chloride (1.0 M solution in diethyl ether, 2.2 ml, 2.2 mmol, 2 eq.), chlorotrimethylsilane (1.45 ml, 11.3 mmol, 10 eq.) and methyl 4-chloro-2.2-dimethylpent-4-enoate **161** (200 mg, 1.13 mmol, 1eq.) in diethyl ether (8 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (15 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 ×15 ml) and the combined organic extracts washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated under vacuum. The crude product (**185**:**186** 16:1 as determined by ^1H NMR spectrum) was purified by column chromatography (diethyl ether:petroleum ether 1:1) to give the *N*-cyclopropyl oxazolidinone **185** as a colourless solid (33 mg, 11%).

M.p. 46–49 °C (petroleum ether); IR (film): υ_{max} 1634 (s), 1427 (w) cm^{-1}; 1H NMR (*trans*, 500 MHz, $CDCl_3$): δ 1.28 (s, 3H, CH_3CCH_3), 1.29 (s, 3H, CH_3CCH_3), 1.36 (dd, *J*=9.0, 7.9 Hz, 1H, C*H*HCHN), 1.59 (ddd, *J*=7.9, 5.5, 1.0 Hz, 1H, CH*H*CHN), 2.01 (d, *J*=15.2 Hz, 1H, C*H*HCCHN), 2.11 (dd, *J*=15.2, 1.0 Hz, 1H, CH*H*CCHN), 2.51 (dd, *J*=9.0, 5.5 Hz, 1H, CHN), 3.56–3.64 (m, 1H, C*H*HN), 3.68 (s, 3H, CH_3O), 3.74–3.80 (m, 1H, CH*H*N), 4.25–4.37 (m, 2H, CH_2OCO); ^{13}C NMR (*cis*, 125 MHz, $CDCl_3$): δ 22.0 (CH_2), 25.8 (CH_3), 25.8 (CH_3), 36.7 (CH), 42.2 (C), 44.5 (C), 45.6 (CH_2), 48.5 (CH_2), 51.9 (CH_3), 61.9 (CH_2), 158.5 (C=O), 177.1 (C=O); MS (CI^+) m/z (%): 278

(MH^{+} ^{37}Cl, 5), 276 (MH^{+} ^{35}Cl, 15), 244 (28), 216 (100), 180 (16); HRMS: $[MH]^{+}$, found 276.09988, $C_{12}H_{19}O_4NCl$ requires 276.10025.

8-*endo*-(2-Oxooxazolidin-3-yl)-1,4,4-trimethyltricyclo[5.1.0.0]octane 187

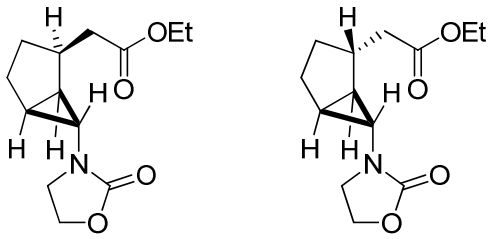


A solution of 3-diethoxymethyloxazolidin-2-one **158** (568 mg, 3.00 mmol, 2 eq.) in diethyl ether (4 ml) was added dropwise *via* syringe pump (0.6 ml.h^{-1}) to a vigorously stirred refluxing mixture of zinc dust (1.96 g, 30.0 mmol, 20 eq.), copper(I) chloride (196 mg, 1.98 mmol, 1.3 eq.), zinc chloride (1.0 M solution in diethyl ether, 3.0 ml, 3.0 mmol, 2 eq.), chlorotrimethylsilane (1.90 ml, 15.0 mmol, 10 eq.) and 3-carene **162** (200 mg, 1.50 mmol, 1 eq.) in diethyl ether (10 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (15 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 15 ml) and the combined organic extracts washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product (**187** and minor undetermined diastereoisomers) was purified by column chromatography (ethyl acetate:petroleum ether 1:4) to give the *N*-cyclopropyl oxazolidinone **187** as a colourless solid (205 mg, 58%).

M.p. 60– 64 °C (petroleum ether); $[\alpha]_D^{20}$ –27.1 (*c* 1, $CHCl_3$); IR (mixture, film): υ_{max} 2864 (w), 1755, 1634, 1404 cm^{-1}; ^{1}H NMR (*endo*, 500 MHz, $CDCl_3$): δ 0.37 (td, *J*=9.4, 3.2 Hz, 1H, $CHCMe_2$), 0.43 (td, *J*=9.4, 3.2 Hz, 1H, $CHCMe_2$), 0.77 (s, 3H, C*H*$_3$CCHN), 0.82 (m, 1H, C*H*CHN), 0.98 (s, 3H, C*H*$_3$CCH$_3$), 1.02 (s, 3H, CH$_3$CC*H*$_3$), 1.30 (dd, *J*=15.7, 3.2 Hz, 1H, C*H*HCCH$_3$), 1.63 (ddd, *J*=15.7, 5.8, 3.2 Hz, 1H,C*H*HCHCHN), 2.08 (d, *J*=7.7 Hz, 1H, CHN), 2.27 (dd, *J*=15.7, 9.4 Hz, 1H, CH*H*CCH$_3$), 2.28 (dd, *J*=15.7, 9.4 Hz, 1H, CH*H*CHCHN), 3.63 (t, *J*=7.8 Hz, 2H, CH_2N), 4.24–4.28 (m, 2H, CH_2O); ^{13}C NMR (*cis*, 125 MHz, $CDCl_3$): δ 13.9 (CH_2), 15.1 (CH_3), 16.1 (CH), 16.9 (C), 17.1 (C), 17.7 (CH), 20.3 (CH_2), 21.3 (CH), 26.5 (CH_3), 27.8 (CH_3), 38.1 (CH), 46.5 (CH_2), 62.4 (CH_2), 159.8 (C=O); MS (CI$^+$) m/z (%): 236 (MH$^+$, 43), 149 (100),

100 (22), 88 (48); HRMS: $[MH]^+$, found 236.16482, $C_{14}H_{22}O_2N$ requires 236.16505. Anal. Calcd for $C_{14}H_{21}O_2N$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.54; H, 9.12; N, 5.90.

(±)-Ethyl 2-((1*R*,2*S*,5*S*,6*R*)-6-(2-oxooxazolidin-3-yl)bicyclo[3.1.0]hexan-2-yl)acetate 188 and (±)-ethyl 2-((1*R*,2*R*,5*S*,6*R*)-6-(2-oxooxazolidin-3-yl)bicyclo[3.1.0]hexan-2-yl)acetate 189

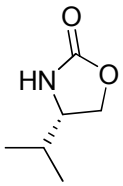


A solution of 3-diethoxymethyloxazolidin-2-one **158** (491 mg, 2.60 mmol, 2 eq.) in diethyl ether (4 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (1.70 g, 26 mmol, 20 eq.), copper(I) chloride (170 mg, 1.72 mmol, 1.3 eq.), zinc chloride (1.0 M solution in diethyl ether, 2.6 ml, 2.6 mmol, 2 eq.), chlorotrimethylsilane (1.66 ml, 13.1 mmol, 10 eq.) and ethyl 2-cyclopent-2-enyl-acetate **163** (200 mg, 1.30 mmol, 1 eq.) in diethyl ether (7 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (15 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 15 ml) and the combined organic extracts washed with brine (15 ml), dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by column chromatography (diethyl ether:petroleum ether 9:1) to give pure *N*-cyclopropyl oxazolidinone **188** as a yellow oil (24 mg) and a mixture of **188**, **189** and other diastereoisomers (80 mg). This mixture was further purified by column chromatography (ethyl acetate:petroleum ether 4:1) to give *N*-cyclopropyl oxazolidinone **189** (28mg, >90% purity) as an pale yellow oil (combined yield of diastereoisomers 104 mg, 34%).

IR (**188**:**189** mixture 2.6:1, film): υ_{max} 2954, 1732 (s), 1417 (s) cm^{-1}; ^1H NMR (**188**, 500 MHz, $CDCl_3$): δ 1.20 (t, *J*=7.2 Hz, 3H, CH_3), 1.28–1.33 (m, 1H, C*H*HCHCH_2), 1.35–1.45 (m, 1H, CH*H*CHCH_2), 1.45–1.49 (m, 1H, C*H*CHCH_2), 1.69–1.72 (m, 1H, C*H*CHN), 1.78–1.84 (m, 1H, C*H*HCHCHN), 1.84–1.91 (m, 1H, CH*H*CHCHN), 2.20 (dd, *J*=15.1, 8.2 Hz, 1H, C*H*HCOO), 2.28 (t, *J*=1.9 Hz, 1H, CHN), 2.32 (dd, *J*=15.1, 7.1 Hz, 1H, CH*H*COO), 2.62 (br q, *J*=7.5 Hz, 1H, C*H*CH_2CO), 3.47–3.51 (m, 2H, CH_2N),

4.14 (q, *J*=7.2 Hz, 2H, C*H*$_2$CH$_3$), 4.22–4.27 (m, 2H, C*H*$_2$OCON); ^{13}C NMR (**188**, 125 MHz, $CDCl_3$): δ 14.2 (CH_3), 24.7 (CH), 24.8 (CH_2), 27.0 (CH_2), 29.7 (CH), 33.4 (CH), 36.5 (CH), 39.8 (CH_2), 45.7 (CH_2), 60.3 (CH_2), 61.8 (CH_2), 158.3 (C=O), 172.5 (C=O). ^{1}H NMR (**189**, 500 MHz, $CDCl_3$): δ 0.68–0.77 (m, 1H, C*H*HCHCH$_2$), 1.26 (t, *J*=7.1 Hz, 3H, CH_3), 1.60–1.65 (m, 1H, C*H*CHCH$_2$), 1.69–1.73 (m, 1H, C*H*CHN), 1.73–1.79 (m, 1H, CH*H*CHCH$_2$), 1.79–1.88 (m, 1H, C*H*HCHCHN), 1.95 (dd, *J*=12.9, 8.1 Hz, 1H, CH*H*CHCHN), 2.28 (br t, *J*=1.9 Hz, 1H, CHN), 2.40 (dd, *J*=15.2, 7.1 Hz, 1H, C*H*HCOO), 2.46 (dd, *J*=15.2, 7.6 Hz, 1H, CH*H*COO), 2.56–2.65 (m, 1H, C*H*CH$_2$CO), 3.43–3.51 (m, 2H, CH_2N), 4.14 (q, *J*=7.1 Hz, 2H, C*H*$_2$CH$_3$), 4.19–4.28 (m, 2H, CH_2OCON); ^{13}C NMR (**189**, 125 MHz, $CDCl_3$): δ 14.3 (CH_3), 25.5 (CH), 27.0 (CH_2), 27.6 (CH_2), 28.9 (CH), 30.8 (CH), 36.6 (CH), 37.8 (CH_2), 45.7 (CH_2), 60.3 (CH_2), 61.8 (CH_2), 158.4 (C=O), 173.0 (C=O); MS (CI^+) m/z (%): 254 (MH^+, 100), 208 (95), 166 (60), 88 (14); HRMS: $[MH]^+$, found 254.13872, $C_{13}H_{20}O_4N$ requires 254.13923.

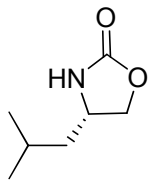
(*S*)-4-Isopropyloxazolidin-2-one 199[165]



Triphosgene (6.0 g, 20 mmol, 0.35 eq.) was added portionwise to a suspension of L-valinol **216** (6.0 g, 58 mmol, 1 eq.) and triethylamine (18.0 ml, 129 mmol, 2.2 eq.) in dry dichloromethane (210 ml) at 4 °C. The reaction mixture was stirred for 15 min at this temperature and then allowed to warm to room temperature and stirred for 16 hours before being quenched with a saturated aqueous solution of ammonium chloride (200 ml). The aqueous layer was separated and the organic layer washed with water (100 ml). The aqueous layer was extracted with dichloromethane (150 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the title oxazolidinone **199** as a yellow solid (6.68 g, 89%) used without further purification.

M.p. 65-68 °C, lit.,[165] 67-70 °C (Et_2O); $[\alpha]_D^{16}$ +8.92 (*c* 1.1, $CHCl_3$), lit.,[165] $[\alpha]_D^{26}$ + 15.5 (*c* 5.2, $CHCl_3$); IR (film): ν_{max} 3300 (w), 2963, 1753 (s), 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (d, *J*=6.8 Hz, 3H, C*H*$_3$CHCH$_3$), 0.96 (d, *J*=6.8 Hz, 3H, CH$_3$CHC*H*$_3$), 1.73 (octet, *J*=6.8 Hz, 1H, $CHMe_2$), 3.53-3.65 (m, 1H, *CH*NH), 4.10 (dd, *J*=8.7, 6.3 Hz, 1H, C*H*HO), 4.44 (t, *J*=8.7 Hz, 1H, CH*H*O), 5.98 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6 (CH_3), 18.0 (CH_3), 32.7 (CH), 58.3 (CH), 68.6 (CH_2), 160.1 (C=O); MS (CI^+) *m/z* (%): 130 (MH^+, 100), 102 (2), 86 (7); HRMS: $[MH]^+$, found 130.08634, $C_6H_{12}O_2N$ requires 130.08680.

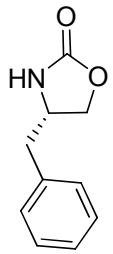
(*S*)-4-Isobutyloxazolidin-2-one 221[166]



Triphosgene (1.77 g, 5.97 mmol, 0.35 eq.) was added portionwise to a suspension of L-leucinol **217** (2.0 g, 17.0 mmol, 1 eq.) and triethylamine (5.23 ml, 37.4 mmol, 2.20 eq.) in dry dichloromethane (60 ml) at 4 °C. The reaction mixture was stirred for 15 min and then allowed to warm to room temperature before being quenched with a saturated aqueous solution of ammonium chloride (25 ml). The aqueous layer was separated and the organic layer washed with water (25 ml). The aqueous layer was extracted with dichloromethane (50 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **221** as a yellow oil (2.47 g, 99%) used without further purification

$[\alpha]_D^{16}$ −11.6 (*c* 1, $CHCl_3$), lit.,[166] (*R*)-isomer, $[\alpha]_D^{22}$ +11.9 (*c* 0.6, $CHCl_3$); IR (film): ν_{max} 3336 (s, br), 2980, 2871, 1750 (s), 1408 (w), 1235 (w), 1028 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, *J*=4.1 Hz, 3H, CH_3CHCH_3), 0.94 (d, *J*=4.1 Hz, 3H, CH_3CHCH_3), 1.34-1.44 (m, 1H, $CHMe_2$), 1.50-1.71 (m, 2H, CH_2CHMe_2), 3.89-4.00 (m, 2H, *CH*NH, C*H*HO), 4.49 (t, *J*=7.4 Hz, 1H, CH*H*O), 6.21 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1 (CH_3), 22.9 (CH_3), 25.1 (CH), 44.4 (CH_2), 51.0 (CH), 70.7 (CH_2), 159.9 (C=O); MS (EI) *m/z* (%): 143 (M^+, 23), 130 (5), 86 (100); HRMS: $[M]^+$, found 143.09423, $C_7H_{13}O_2N$ requires 143.09462.

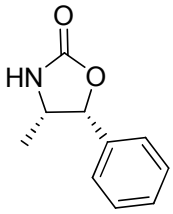
(*S*)-4-Benzyloxazolidin-2-one 198[167]



Triphosgene (1.0 g, 3.5 mmol, 0.35 eq.) was added portionwise to a suspension of L-phenylalaninol **218** (1.5 g, 9.9 mmol, 1 eq.) and triethylamine (3.02 ml, 21.7 mmol, 2.2 eq.) in dry dichloromethane (30 ml) at 4 °C. The reaction mixture was stirred for 15 min and then allowed to warm to room temperature and stirred for 2 hours before being quenched with a saturated aqueous solution of ammonium chloride (20 ml). Dichloromethane (40 ml) was added to the reaction which was then stirred for 20 min. The aqueous layer was separated and the organic layer washed with a saturated aqueous solution of sodium bicarbonate (25 ml) and brine (25 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **198** as a pale yellow solid (1.71 g, 99%). A sample was purified by column chromatography (petroleum ether:ethyl acetate 6:4).

M.p. 84-88 °C (petroleum ether) lit.,[167] 85-87 °C (CH_2Cl_2) ;$[\alpha]_D^{23}$ - 63.1 (*c* 1.02, $CHCl_3$), lit.,[167] $[\alpha]_D^{25}$ −62.0 (*c* , 1.0, $CHCl_3$; IR (film): ν_{max} 3261, 1751 (s), 1738 (s), 1700 (s), 1407, 1247, 1095 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.84 (dd, *J*=13.6, 8.2 Hz, 1H, C*H*HPh), 2.90 (dd, *J*=13.6, 5.8 Hz, 1H, CH*H*Ph), 4.05-4.12 (m, 1H, C*H*N), 4.16 (dd, *J*=8.7, 5.6 Hz, 1H, C*H*HO), 4.49 (t, *J*=8.3 Hz, 1H, CH*H*O), 4.99 (br s, 1H, NH), 7.16-7.20 (m, 2H, H-Ar), 7.26-7.30 (m, 1H, H-Ar), 7.33-7.37 (m, 2H, H-Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 41.7 (CH_2), 53.9 (CH), 69.8 (CH_2), 127.4 (CH-Ar), 129.0 (CH-Ar), 129.2 (CH-Ar), 136.0 (C-Ar), 158.9 (C=O).

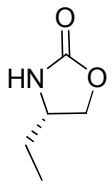
(4*S*,5*R*)-4-Methyl-5-phenyloxazolidin-2-one 222[168]



Triphosgene (1.22 g, 4.11 mmol, 0.35 eq.) was added portionwise to a suspension of (*1R, 2S*)-(-)-norephedrine hydrochloride (2.20 g, 11.7 mmol, 1 eq.) and triethylamine (5.23 ml, 37.5 mmol, 3.2 eq.) in dry dichloromethane (40 ml) at 4 °C. The reaction mixture was stirred for 30 min and then allowed to warm to room temperature and stirred for 2 hours. The Et_3N hydrochloride precipitate was removed by filtration and washed with dichloromethane (2 × 20 ml). The resulting filtrate was washed with a saturated aqueous solution of ammonium chloride (20 ml), then sodium bicarbonate (20 ml) and brine (20ml). The resulting organic extract was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the title oxazolidinone **222** as a pale yellow oil (2.12 g, 99%). A small sample was purified by column chromatography (petroleum ether:ethyl acetate 1:1) to give **222** as a pale yellow solid.

M.p. 116-119 °C (petroleum ether) lit.,[168] 116-117 °C ; $[\alpha]_D^{23}$ −163.8 (*c* 1.02, $CHCl_3$), lit.,[168] $[\alpha]_D^{20}$ −170 (*c* 1.2); IR (film): ν_{max} 3269, 1719 (s), 1383, 1353, 1238 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.07 (d, *J*=6.6 Hz, 3H, CH_3), 4.19-4.25 (m, 1H, C*H*CH_3), 5.19 (br s, 1H, NH), 5.74 (d, *J*=8.0 Hz, 1H, CHO), 7.32 (d, *J*=7.3 Hz, 2H, H-Ar), 7.35-7.39 (m, 1H, H-Ar), 7.42 (t, *J*=7.3 Hz, 2H, H-Ar); ^{13}C NMR (150 MHz, $CDCl_3$): δ 17.6 (CH_3), 52.3 (CH), 81.0 (CH), 125.9 (CH-Ar), 128.6 (CH-Ar), 134.8 (C-Ar), 158.9 (C=O).

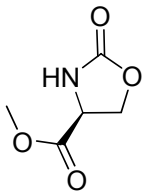
(*S*)-4-Ethyloxazolidin-2-one 223[169]



Triphosgene (5.82 g, 19.6 mmol, 0.35) was added portionwise to a suspension of S-(+)-2 amino-1-butanol **220** (5.00 g, 56.6 mmol, 1 eq.) and triethylamine (17.2 ml, 123 mmol, 2.20 eq.) in dry dichloromethane (60 ml) at 4 °C. The reaction mixture was stirred for 15 min and then allowed to warm to room temperature before being quenched with a saturated aqueous solution of ammonium chloride (50 ml). The aqueous layer was separated and the organic layer washed with water (50 ml). The aqueous layer was extracted with dichloromethane (50 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **223** as a yellow oil (3.9 g, 60%) used without further purification

$[\alpha]_D^{20}$ −7.24 (*c* 0.76, $CHCl_3$), lit.,[169] $[\alpha]_D^{30}$ −5.3 (*c* 0.6, $CHCl_3$); IR (film): ν_{max} 2247 (w), 1749, 1248 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, *J*=7.5 Hz, 3H, *CH*$_3$CH$_2$), 1.55-1.65 (m, 2H, *CH*$_2$CH$_3$), 3.76-3.85 (m, 1H, *CH*NH), 4.02 (dd, *J*=8.5 Hz, 6.1 Hz, 1H, C*H*HO), 4.48 (t, *J*=8.5 Hz, 1H, CH*H*O), 6.28 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.3 (CH_3), 28.2 (CH_2), 53.9 (CH), 70.0 (CH_2), 160.3 (C=O); MS (CI^+) *m/z* (%): 116 (MH^+,100), 99 (4), 86 (8); HRMS: $[MH]^+$, found 116.07058, $C_5H_{10}O_2N$ requires 116.07115.

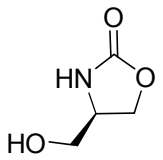
(*S*)-Methyl-2-oxazolidinone-4-carboxylate 225[170]



Serine methyl ester hydrochloride **224** (10.0 g, 64.3 mmol, 1 eq.) and potassium bicarbonate (6.69 g, 66.9 mmol, 1.04 eq.) were dissolved in water (100 ml) and the solution stirred at room temperature for 10 min. Potassium carbonate (9.38 g, 67.8 mmol, 1.05 eq.) was added to the solution which was then cooled to 0 °C and treated with a 20% solution of phosgene in toluene (44.3 ml, 84.0 mmol, 1.3 eq.) over 10 min. The resulting mixture was stirred for 2 hours at 0 °C. The toluene layer was separated from the aqueous layer which was evaporated to dryness. The resulting colourless solid was extracted with dichloromethane (60 ml) and the extract dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **225** as a colourless oil (8.5 g, 91%) used without further purification.

$[\alpha]_D^{20}$ –19.2 (*c* 4.59, CH_2Cl_2), lit.,[170] $[\alpha]_D^{25}$ –18.6 (*c* 4.52, CH_2Cl_2); IR (film): ν_{max} 3416 (s, br), 1738 (s), 1617 (w), 1436 (w), 1410 (w), 1231, 1059 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H, *CH*$_3$O), 4.42 (dd, *J*=9.1, 4.6 Hz, 1H, *CH*CH_2O), 4.52 (dd, *J*=9.1 Hz, 4.6 Hz, 1H, C*H*HO), 4.62 (t, *J*=9.1 Hz, 1H, CH*H*O), 6.05 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.1 (CH_3), 53.6 (CH), 66.6 (CH_2), 158.6 (C=O), 170.4 (C=O); MS (EI) *m/z* 145 (M^+, 36), 115 (3), 84 (100); HRMS: $[M]^+$, found 145.03789, $C_5H_7O_4N$ requires 145.0375.

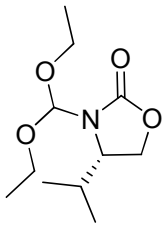
(*R*)-4-(Hydroxymethyl)oxazolidin-2-one 226[170]



Sodium borohydride (177 mg, 4.69 mmol, 1.05 eq.) was added portionwise to a solution of the ester **225** (650 mg, 4.48 mmol, 1 eq.) in ethanol (10 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature over 2 hours, then treated with a saturated aqueous solution of ammonium chloride (51 ml) and stirred at room temperature for 30 min. The colourless solid was removed by filtration and the filtrate concentrated under reduced pressure to give **226** as a colourless solid (0.43 g, 82%).

M.p. 77-81 °C, lit.,[170] 96-99 °C ($CHCl_3$); $[\alpha]_D^{20}$ +29.2 (*c* 1.0, MeOH), lit.,[170] $[\alpha]_D^{25}$ +32.25 (*c* 1.044, MeOH); IR (film): ν_{max} 3276 (br, s), 1732 (s), 1418, 1259, 1037, 939 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 3.58 (dd, *J*=12.0, 4.4 Hz, 1H , C*H*HOH), 3.67 (dd, *J*=12.0, 3.7 Hz, 1H, CH*H*OH), 4.03-4.09 (m, 1H, *CH*CH_2O), 4.29 (dd, *J*=9.0, 5.1 Hz, 1H, C*H*HO), 4.56 (t, *J*=9.0 Hz, 1H, CH*H*O); ^{13}C NMR (75 MHz, D_2O): δ 53.8 (CH), 62.6 (CH_2), 68.1 (CH_2), 159.9 (C=O); MS (EI) *m/z* (%) 118 (MH^+, 45), 106 (12), 97 (25), 91 (7), 86 (100); HRMS: $[M]^+$, found 117.04312, $C_4H_7O_3N$ requires 117.04259.

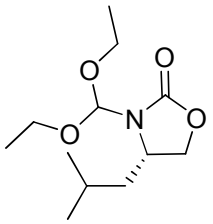
(*S*)-3-Diethoxymethyl-4-isopropyloxazolidin-2-one 201



A mixture of the oxazolidinone **199** (195 mg, 1.51 mmol, 1 eq.) and triethyl orthoformate (2.5 ml, 15 mmol, 10 eq.) was heated at 160 °C for 48 hours. The reaction mixture was cooled to room temperature before being quenched with a saturated aqueous solution of sodium bicarbonate (5 ml). The separated aqueous phase was extracted with diethyl ether (2 × 5 ml) and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether:ethyl acetate 4:1) to give **201** as a pale yellow oil (192 mg, 55%).

$[\alpha]_D^{19}$ +35.9 (*c* 1.18, $CHCl_3$); IR (film): ν_{max} 3493, 2976, 2878, 1755 (s), 1634 (s), 1487, 1414, 1234, 1063 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO): δ 0.86 (d, *J*=7.0 Hz, 3H, CH_3CHCH_3), 0.89 (d, *J*=7.0 Hz, 3H, CH_3CHCH_3), 1.19 (t, *J*=7.0 Hz, 3H, CH_3CH_2), 1.22 (t, *J*=7.0 Hz, 3H, CH_3CH_2), 2.16-2.24 (m, 1H, $CHMe_2$), 3.52-3.73 (m, 4H, 2 × OCH_2CH_3), 3.97 (ddd, *J*=9.0, 4.8, 3.3 Hz, 1H, $CHCH_2O$) 4.20 (dd, *J*=9.0, 4.8 Hz, 1H, CHHO), 4.31 (t, *J*=9.0 Hz, 1H, CHHO), 5.71 (s, 1H, $CH(OEt)_2$); ^{13}C NMR (125 MHz, DMSO): δ 14.1 (CH_3), 14.7 (CH_3), 14.7 (CH_3), 17.6 (CH_3), 29.0 (CH), 55.8 (CH), 61.9 (CH_2), 62.2 (CH_2), 63.1 (CH_2), 102.1 (CH), 157.1 (C=O); MS (EI) *m/z* (%): 254 (MNa^+, 100), 186 (68), 184 (10), 172 (79); HRMS: $[MNa]^+$, found 254.13712, $C_{11}H_{21}O_4NNa$ requires 254.13712.

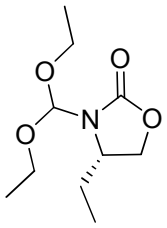
(*S*)-3-Diethoxymethyl-4-isobutyloxazolidin-2-one 228



A mixture of the oxazolidinone **221** (1.38 g, 9.64 mmol, 1 eq.), aluminium chloride (182 mg, 1.36 mmol, 0.14 eq.) and triethyl orthoformate (55.0 ml, 330 mmol, 34 eq.) was heated at 155 °C for 18 hours. The reaction mixture was cooled to room temperature before being quenched with a saturated aqueous solution of sodium bicarbonate (15 ml). The separated aqueous phase was extracted with diethyl ether (2 × 25 ml) and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether:ethyl acetate 9:1) to give **228** as a yellow oil (1.48 g, 63%).

$[\alpha]_D^{15}$ +38.1 (*c* 1.05, $CHCl_3$); IR (film): ν_{max} 2960 (s), 1743 (s), 1533 (w), 1470, 1410 (s), 1248 (s), 1067 (s), 899 (w) cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 0.91 (d, *J*=6.6 Hz, 3H, CH_3CHCH_3), 0.93 (d, *J*=6.6 Hz, 3H, CH_3CHCH_3), 1.20 (q, *J*=7.1 Hz, 6H, 2 × CH_3CH_2), 1.37-1.46 (m, 1H, $CHHCHMe_2$), 1.56-1.69 (m, 1H, $CHMe_2$), 1.82-1.90 (m, 1H, $CHHCHMe_2$), 3.50-3.69 (m, 4H, 2 × CH_2CH_3), 3.97-4.06 (m, 2H, CHHO, $CHCH_2O$), 4.48-4.52 (m, 1H, CHHO), 5.70 (s, 1H, $CH(OEt)_2$); ^{13}C NMR (75 MHz, DMSO): δ14.6 (CH_3), 14.6 (CH_3), 21.5 (CH_3), 23.4 (CH_3), 24.1 (CH), 42.2 (CH_2), 50.3 (CH), 61.4 (CH_2), 61.9 (CH_2), 68.0 (CH_2), 101.9 (CH), 156.9 (C=O); MS (FAB) *m/z* (%): 268 (MNa^+, 100), 166 (56); HRMS: $[MNa]^+$, found 268.15269, $C_{12}H_{23}O_4NNa$ requires 268.15247.

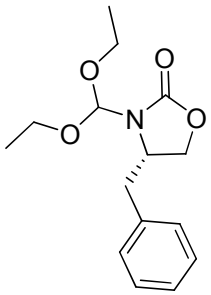
(*S*)-3-Diethoxymethyl-4-ethyloxazolidin-2-one 230



A mixture of the oxazolidinone **223** (908 mg, 7.89 mmol, 1 eq.) and triethyl orthoformate (13 ml, 78 mmol, 10 eq.) was heated at 160 °C for 48 hours. The reaction mixture was cooled to room temperature before being quenched with a saturated aqueous solution of sodium bicarbonate (15 ml). The separated aqueous phase was extracted with diethyl ether (2 × 25 ml) and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether:ethyl acetate 4:1) to give **230** as a pale yellow oil (932 mg, 55%).

$[\alpha]_D^{19}$ +27.7 (*c* 1.18, EtOAc); IR (film): ν_{max} 2976 (s), 1757 (s), 1412 (s), 1223, 1063 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO): δ 0.87 (d, *J*=7.5 Hz, 3H, CH_3CH_2), 1.19 (t, *J*=7.0 Hz, 3H, CH_3CH_2O), 1.21 (t, *J*=7.0 Hz, 3H, CH_3CH_2O), 1.53-1.64 (m, 1H, C*H*HCH_3), 1.82-1.91 (m, 1H, CH*H*CH_3) 3.52-3.69 (m, 4H, 2 × OCH_2CH_3), 3.93-3.99 (m, 1H, C*H*CH_2O), 4.06 (dd, *J*=8.6, 6.0 Hz, 1H, C*H*HO), 4.44 (t, *J*=8.6, 1H, CH*H*O), 5.70 (s, 1H, $CH(OEt)_2$); ^{13} NMR (125 MHz, DMSO): δ8.1 (CH_3), 14.7 (CH_3), 14.7 (CH_3), 25.8 (CH_2), 52.4 (CH), 61.8 (CH_2), 62.0 (CH_2), 67.0 (CH_2), 102.0 (CH), 157.0 (C=O); MS (EI) *m/z* (%): 240 (MNa^+, 100), 172 (30); HRMS: $[MNa]^+$, found 240.12164, $C_{10}H_{19}O_4NNa$ requires 240.12063.

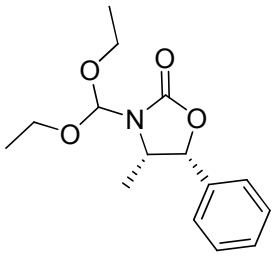
(*S*)-4-Benzyl-3-diethoxymethyloxazolidin-2-one 200



A mixture of the oxazolidinone **198** (1.00 g, 5.65 mmol, 1 eq.), aluminium chloride (112 mg, 0.84 mmol, 0.15 eq.) and triethyl orthoformate (28.0 ml, 168 mmol, 30 eq.) was heated at 155 °C for 18 hours. The reaction mixture was cooled to room temperature before being quenched with a saturated aqueous solution of sodium bicarbonate (20 ml). The separated aqueous phase was extracted with ethyl acetate (3 × 25 ml) and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether:ethyl acetate 9:1) to give **200** as a pale yellow oil (833 mg, 53%).

$[\alpha]_D^{20}$ +51.5 (*c* 1.22, CH_2Cl_2); IR (film): ν_{max} 2978 (w), 1753 (s), 1404, 1233, 1058 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 1.20 (t, *J*=7.0 Hz, 3H, CH_2CH_3), 1.21 (t, *J*=7.0 Hz, 3H, CH_2CH_3), 2.78 (dd, *J*=13.6, 8.6 Hz, 1H, C*H*HPh), 3.25 (dd, *J*=13.6, 2.6 Hz, 1H, CH*H*Ph), 3.52-3.71 (m, 4H, 2 × CH_2CH_3), 4.00-4.05 (m, 1H, C*H*HO), 4.17-4.22 (m, 2H, CH*H*O, C*H*CH_2Ph), 5.74 (br s, 1H, $CH(OEt)_2$), 7.23-7.28 (m, 3H, H-Ar), 7.32 (t, *J*=7.6 Hz, 2H, H-Ar); ^{13}C NMR (150 MHz, DMSO): δ 15.2 (CH_3), 15.3 (CH_3), 52.7 (CH), 62.4 (CH_2), 62.4 (CH_2), 67.2 (CH_2), 102.5 (CH), 127.1 (CH-Ar), 129.0 (CH-Ar), 129.7 (CH-Ar), 136.9 (C-Ar), 157.1 (C=O); MS (FAB) *m/z* (%): 302 (MNa^+, 74), 234 (100), 200 (23), 176 (21), 154 (25); HRMS: $[MNa]^+$, found 302.13687, $C_{15}H_{21}O_4NNa$ requires 302.13682.

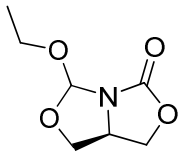
(4*S*,5*R*)-3-(Diethoxymethyl)-4-methyl-5-phenyloxazolidin-2-one 231



A mixture of the oxazolidinone **222** (1.00 g, 5.65 mmol, 1 eq.), aluminium chloride (113 mg, 0.85 mmol, 0.15 eq.) and triethyl orthoformate (28.0 ml, 168 mmol, 30 eq.) was heated at 155 °C for 18 hours. The reaction mixture was cooled to room temperature before being quenched with a saturated aqueous solution of sodium bicarbonate (20 ml). The separated aqueous phase was extracted with ethyl acetate (3 × 25 ml) and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether:ethyl acetate 9:1) to give **231** as a pale yellow oil (843 mg, 53%).

$[\alpha]_D^{20}$ −38.03 (*c* 1.02, DCM); IR (film): ν_{max} 2979 (w), 1750 (s), 1386, 1244, 1223, 1059 (s) cm^{-1}; ^{1}H NMR (600 MHz, DMSO): δ 0.74 (d, *J*=6.4 Hz, 3H, CH_3), 1.24 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.37 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 3.51 (dq, *J*=9.6, 7.1 Hz, 1H, $CHHCH_3$), 3.57-3.67 (m, 3H, $CHHCH_3$, CH_2CH_3), 4.31-4.36 (m, 1H, $CHCH_3$), 5.73-5.75 (m, 2H, CHPh, $CH(OEt)_2$), 7.31-7.33 (m, 2H, H-Ar), 7.35-7.39 (m, 1H, H-Ar), 7.41-7.45 (m, 2H, H-Ar); ^{13} NMR (150 MHz, DMSO): δ 15.2 (CH_3), 15.2 (CH_3), 16.7 (CH_3), 51.7 (CH), 62.2 (CH_2), 62.5 (CH_2), 79.0 (CH), 102.3 (CH), 126.7 (CH-Ar), 128.8 (CH-Ar), 128.9 (CH-Ar), 135.8 (C-Ar), 156.6 (C=O); MS (FAB) *m/z* (%): 302 (MNa^+, 100), 234 (77), 200 (31), 190 (27), 176 (18); HRMS: $[MNa]^+$, found 302.13635, $C_{15}H_{21}O_4NNa$ requires 302.13682.

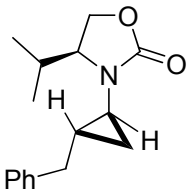
(7a*R*)-5-Ethoxy-dihydro-1H-oxazolo[3,4-*c*]oxazol-3(5H)-one 232



para-Toluenesulfonic acid monohydrate (162 mg, 0.85 mmol, 0.15 eq.) was added to a solution of the alcohol **226** (650 mg, 5.55 mmol, 1 eq.) in triethyl orthoformate (11 ml). The reaction mixture was heated at reflux (150 °C) for 6 hours. The triethyl orthoformate was evaporated and the resulting mixture purified by column chromatography (ethyl acetate:petroleum ether 1:1) to give **232** as an unstable pale yellow liquid (205 mg, 22%).

$[\alpha]_D^{20}$ +61.85 (*c* 1.24, $CHCl_3$); IR (film): ν_{max} 2925 (w), 1732 (s), 1410, 1242, 1033 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 1.19 (t, *J*=7.1 Hz, 3H, *CH*$_3$CH$_2$), *3*.62 (q, *J*=7.1 Hz, 2H, *CH*$_2$CH$_3$), 3.76 (br t, *J*=7.8 Hz, 1H, C*H*HOCH), 4.26 (dd, *J*=8.3, 7.1 Hz, 1H, CH*H*OCH), 4.31-4.41 (m, 2H, C*H*HOCO, CHNCO), 4.63 (dd, *J*=9.1, 7.5 Hz, 1H, CH*H*OCO), 6.02 (s, 1H, EtOCHN); ^{13}C NMR (75 MHz, DMSO): δ 14.6 (CH_3), 54.8 (CH), 60.4 (CH_2), 67.7 (CH_2), 69.8 (CH_2), 107.1 (CH), 159.5 (C=O); MS (CI^+) *m/z* (%): 174 (MH^+, 28), 146 (30), 128 (100), 118 (93), 100 (17); HRMS: $[MH]^+$, found 174.07685, $C_7H_{12}O_4N$ requires 174.07663.

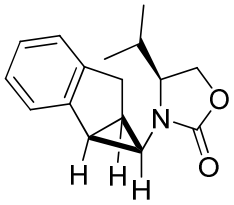
(*S*)-3-((1*S*,2*S*)-2-Benzylcyclopropyl)-4-isopropyloxazolidin-2-one 244



A solution of (S)-3-diethoxymethyl-4-isopropyloxazolidin-2-one **201** (142 mg, 0.61 mmol, 1.4 eq.) in diethyl ether (1.5 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (400 mg, 6.12 mmol, 13.6 eq.), copper(I) chloride (40 mg, 0.4 mmol, 1.1 eq.), zinc chloride (1.0 M solution in diethyl ether, 0.6 ml, 0.6 mmol, 1.3 eq.), chlorotrimethylsilane (0.40 ml, 3.13 mmol, 7 eq.) and allylbenzene **153** (0.06 ml, 0.45 mmol, 1 eq.) in diethyl ether (6 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (5 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 7 ml) and the combined organic extracts washed with brine (7 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product (**244** and undefined minor diastereoisomers) was purified by column chromatography (diethyl ether:petroleum ether 1:1) to give the *N*-cyclopropyl oxazolidinone **244** as a beige oil (49 mg, 42%).

$[\alpha]_D^{20}$ −42.1 (*c* 0.95, $CHCl_3$); IR (*trans*, film): υ_{max} 2962, 1755 (s), 1420 (s), 1227, 1051 cm^{-1}; ^{1}H NMR (*trans*, 500 MHz, $CDCl_3$) : δ 0.62 (d, *J*=7.0 Hz, 3H, C*H*$_3$CCH$_3$), 0.76 (d, *J*=7.0 Hz, 3H, CH$_3$CC*H*$_3$), 0.96-1.02 (m, 1H, C*H*HCHN), 1.17-1.24 (m, 2H, CH*H*CHN, C*H*CHN), 1.49-1.59 (m, 1H, $CHMe_2$), 2.23 (dt, *J*=7.0, 3.5 Hz, 1H, CHN), 2.28-2.34 (m, 1H, C*H*HPh), 2.86 (dd, *J*=14.5, 5.4 Hz, 1H, CH*H*Ph), 3.32 (dt, *J*=8.9, 3.9 Hz, 1H, C*H*CH$_2$O), 3.96 (dd, *J*=8.9, 3.9 Hz, 1H, C*H*HO), 4.03 (t, *J*=8.9 Hz, 1H, CH*H*O), 7.18-7.24 (m, 3H, Ar-H), 7.27-7.32 (m, 2H, Ar-H); ^{13}C NMR (*trans*, 125 MHz, $CDCl_3$): δ 14.1 (CH_3), 15.6 (CH_2), 17.6 (CH_3), 20.5 (CH), 27.5 (CH), 29.6 (CH), 38.2 (CH_2), 60.9 (CH), 62.4 (CH_2), 126.3 (CH-Ar), 128.3 (CH-Ar), 128.5 (CH-Ar), 140.7 (C-Ar), 158.0 (C=O); MS (EI) *m/z* (%) : 260 (MH^+, 100); HRMS: $[MH]^+$, found 260.16466, $C_{16}H_{22}O_2N$ requires 260.16451.

(4*S*)-3-((1*S*,2*R*)-1,1a,6,6a-Tetrahydrocyclopropa[*a*]inden-1-yl)-4-isopropyloxazolidin-2-one 245

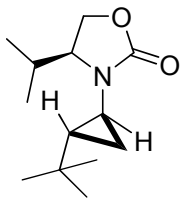


A solution of (S)-3-diethoxymethyl-4-isopropyloxazolidin-2-one **201** (426 mg, 1.84 mmol, 1.3 eq.) in diethyl ether (2.5 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (1.20 g, 18.4 mmol, 13.4 eq.), copper(I) chloride (120 mg, 1.21 mmol, 0.9 eq.), zinc chloride (1.0 M solution in diethyl ether, 1.8 ml, 1.8 mmol, 1.3 eq.), chlorotrimethylsilane (1.20 ml, 9.39 mmol, 6.9 eq.) and indene **165** (157 mg, 1.37 mmol, 1 eq.) in diethyl ether (8 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (8 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 10 ml) and the combined organic extracts washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product (**245** and minor undetermined diastereoisomers) was purified by column chromatography (diethyl ether:petroleum ether 1:1) to give the *N*-cyclopropyl oxazolidinone **245** as a colourless solid (140 mg, 40%).

M.p. 87-89 °C (Et_2O); $[\alpha]_D^{20}$ −13.5 (*c* 1.02, $CHCl_3$); IR(*cis*, film): υ_{max} 2964 (w), 1744 (s), 1412, 1227, 1047 cm^{-1}; ^1H NMR (*endo*, 500 MHz, $CDCl_3$): δ 0.76 (d, *J*=7.0 Hz, 3H, C*H*$_3$CCH$_3$), 0.89 (d, *J*=7.0 Hz, 3H, CH$_3$CC*H*$_3$), 2.00-2.07 (m, 1H, CHMe$_2$), 2.34 (qd, *J*=6.8, 1.2 Hz, 1H, C*H*CH$_2$Ar), 2.41 (dt, *J*=8.6, 3.1 Hz, 1H, C*H*CH$_2$O), 2.78 (td, *J*=6.8, 1.4 Hz, 1H, CHAr), 2.83 (t, *J*=6.8 Hz, 1H, CHN), 3.11 (br d, *J*=17.8 Hz, 1H, C*H*HAr), 3.19 (dd, *J*=17.8, 6.8 Hz, 1H, CH*H*Ar) 3.48 (t, *J*=8.8 Hz, 1H, C*H*HO), 3.77 (dd, *J*=8.8, 2.8 Hz, 1H, CH*H*O), 7.10-7.20 (m, 3H, Ar-H), 7.31 (d, *J*=6.6 Hz, 1H, Ar-H); ^{13}C NMR (*endo*, 125 MHz, $CDCl_3$): δ 15.3 (CH_3), 17.5 (CH_3), 23.3 (CH), 29.0 (CH), 29.2 (CH), 31.7 (CH_2), 32.9 (CH), 58.8 (CH), 63.4 (CH_2), 124.2 (CH-Ar), 124.5

(CH-Ar), 126.0 (CH-Ar), 126.7 (CH-Ar), 139.4 (C-Ar), 144.2 (C-Ar), 159.2 (C=O). MS (CI^+) *m/z* (%) : 258 (MH^+, 100), 142 (34), 129 (47), 85 (68); HRMS: $[MH]^+$, found 258.14954, $C_{16}H_{20}O_2N$ requires 258.14886. Anal. Calcd for $C_{16}H_{19}O_2N.H_2O$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.89; H, 7.13; N, 4.78.

(*S*)-3-((1*S*,2*R*)-2-*tert*-Butylcyclopropyl)-4-isopropyloxazolidin-2-one 246

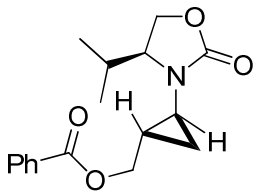


A solution of (S)-3-diethoxymethyl-4-isopropyloxazolidin-2-one **201** (448 mg, 1.94 mmol, 1.25 eq.) in diethyl ether (2.5 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (1.27 g, 19.4 mmol, 12.5 eq.), copper(I) chloride (127mg, 1.3 mmol, 0.8 eq.), zinc chloride (1.0 M solution in diethyl ether, 1.6 ml, 1.6 mmol, 1 eq.), chlorotrimethylsilane (1.24 ml, 9.70 mmol, 6.25 eq.) and 3,3-dimethylbut-1-ene **164** (0.20 ml, 1.55 mmol, 1 eq.) in diethyl ether (8 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (8 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 10 ml) and the combined organic extracts washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product (**246**, **227** and undefined minor diastereoisomers) was purified by column chromatography (diethyl ether:petroleum ether 3:2) to give a mixture of *N*-cyclopropyl oxazolidinone **246** and (*S*)-4-isopropyl-*N*-formyloxazolidin-2-one **227** (92 mg, **246**:**227** 2:1 as determined by ^{1}H NMR spectrum) and the *N*-cyclopropyl oxazolidinone **246** as a colourless solid (31 mg). The yield of **246** (102 mg, 29%) was calculated from ^{1}H NMR spectrum.

M.p. 53-55 °C (petroleum ether); $[\alpha]_D^{19}$ −49.3 (*c* 0.73, $CHCl_3$); IR(*trans*, film): υ_{max} 2961, 1728 (s), 1423, 1236, 1055 (w) cm^{-1}; ^{1}H NMR (*trans*, 500 MHz, $CDCl_3$): δ 0.86 (br s, 9H, 3 × CCH_3), 0.87-0.92 (m, 9H, 2 × $CHCH_3$, CH_2CHN, $CHCHN$), 2.20-2.25 (m, 1H, $CHMe_2$), 2.27 (dt, *J*=7.3, 3.6 Hz, 1H, CHN), 3.51-3.56 (m, 1H, $CHCH_2O$), 4.02-4.11 (m, 2H, CH_2OCO); ^{13}C NMR (*trans*, 125 MHz, $CDCl_3$): δ 10.9 (CH_2), 14.0 (CH_3), 17.7 (CH_3), 26.6 (CH), 27.9 (CH), 28.4 (CH_3), 29.0 (C), 30.7 (CH), 61.2 (CH),

62.2 (CH_2), 158.0 (C=O); MS (CI^+) *m/z* (%) : 226 (MH^+, 56), 170(100), 149 (46), 85 (81); HRMS: $[MH]^+$, found 226.17987, $C_{13}H_{24}O_2N$ requires 226.18070.

((1*S*,2*S*)-2-((S)-4-isopropyl-2-oxooxazolidin-3-yl)cyclopropyl)methyl benzoate 247

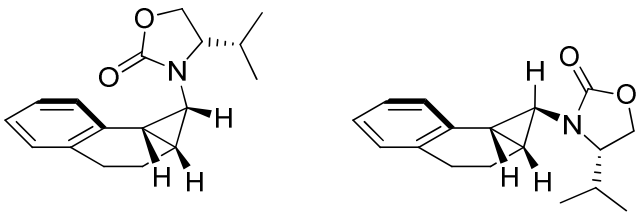


A solution of (S)-3-diethoxymethyl-4-isopropyloxazolidin-2-one **201** (448 mg, 1.94 mmol, 1.25 eq.) in diethyl ether (2.5 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (1.27 g, 19.4 mmol, 12.5 eq), copper(I) chloride (127 mg mg, 1.30 mmol, 0.8 eq.), zinc chloride (1.0 M solution in diethyl ether, 1.94 ml, 1.94 mmol, 1.25 eq.), chlorotrimethylsilane (1.24 ml, 9.70 mmol, 6.25 eq.) and alkene **243** (252 mg, 1.55 mmol, 1eq.) in diethyl ether (8 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (8 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 10 ml) and the combined organic extracts washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified twice by column chromatography (diethyl ether:petroleum ether 1:1 and petroleum:ethyl acetate 3:2) to give **247** as a colourless solid (60 mg, 13%).

M.p. 58-59 °C (Et_2O); $[\alpha]_D^{20}$ −9.6 (*c* 0.8, $CHCl_3$); IR (*trans*, film): υ_{max} 2885 (w), 1765 (s), 1726 (s), 1425, 1281, 1117 (w), 1049 (w) cm^{-1}; ^1H NMR (*trans*, 500 MHz, $CDCl_3$): δ 0.72 (d, *J*=7.0 Hz, 3H, C*H*$_3$CCH$_3$), 0.87 (d, *J*=7.0 Hz, 3H, CH$_3$CC*H*$_3$), 1.09-1.14 (m, 1H, C*H*HCHN), 1.31-1.35 (m, 1H, CH*H*CHN), 1.46-1.54 (m, 1H, C*H*CHN), 2.18-2.25 (m, 1H, CHMe$_2$), 2.47 (dt, *J*=7.2, 3.6 Hz, 1H, C*H*N), 3.56 (dt, *J*=8.9, 3.9 Hz, 1H, C*H*CH$_2$O), 3.88 (dd, *J*=11.7, 9.2 Hz, 1H, C*H*HOCOPh), 4.04 (dd, *J*=8.9, 3.9 Hz, 1H, C*H*HOCO), 4.12 (t, *J*=8.9 Hz, 1H, CH*H*OCO), 4.56 (dd, *J*=11.7, 5.5 Hz, 1H, CH*H*COOPh), 7.42-7.48 (m, 2H, Ar-H), 7.55-7.60 (m, 1H, Ar-H), 8.02-8.05 (m, 2H, Ar-H); ^{13}C NMR (*trans*, 125 MHz, $CDCl_3$): δ 13.2 (CH_2), 14.2 (CH_3), 17.6 (CH_3), 17.9 (CH), 27.8 (CH), 29.3 (CH), 61.1 (CH), 62.5 (CH_2), 66.5 (CH_2), 128.4 (CH-Ar), 129.5 (CH-Ar), 129.9 (C-Ar), 133.2 (CH-Ar), 157.8 (C=O), 166.4 (C=O); MS (EI) *m/z* (%) :

326 (MNa^+, 100), 301 (28), 247 (32), 212 (15), 182 (52), 166 (33); HRMS: $[MNa]^+$, found 326.13712, $C_{17}H_{21}O_4NNa$ requires 326.13683.

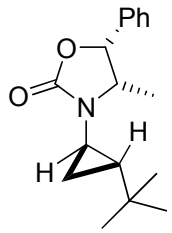
(*S*)-4-isopropyl-3-((1*R*,1a*R*,7b*R*)-1a,2,3,7b-tetrahydro-1H-cyclopropa[a]naphthalen-1-yl)oxazolidin-2-one 249 and (*S*)-4-isopropyl-3-((1*S*,1a*R*,7b*R*)-1a,2,3,7b-tetrahydro-1H-cyclopropa[a]naphthalen-1-yl)oxazolidin-2-one 250



A solution of (S)-3-diethoxymethyl-4-isopropyloxazolidin-2-one **201** (444 mg, 1.92 mmol, 1.25 eq.) in diethyl ether (2.5 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (1.26 g, 19.3 mmol, 12.5 eq.), copper(I) chloride (126 mg, 1.30 mmol, 0.8 eq.), zinc chloride (1.0 M solution in diethyl ether, 1.92 ml, 1.92 mmol, 1.25 eq.), chlorotrimethylsilane (1.23 ml, 9.62 mmol, 6.25 eq.) and alkene **166** (200 mg, 1.54 mmol, 1 eq.) in diethyl ether (8 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (8 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 10 ml) and the combined organic extracts washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (diethyl ether:petroleum ether 1:1) to give the *N*-cyclopropyl oxazolidinone **249** together with (*S*)-4-isopropyl-*N*-formyloxazolidin-2-one **227** (137 mg, **249**:**227** 1.1:1 as determined by ^{1}H NMR spectrum) as a colourless solid, a mixture of diastereoisomers (24 mg) as an orange oil and the *N*-cyclopropyl oxazolidinone **250** (57 mg) as a yellow-orange oil. The combined yield of diastereoisomers (169 mg, 40%) was calculated from ^{1}H NMR spectrum.

250: $[\alpha]_D^{17}$ −50.6 (*c* 0.8, $CHCl_3$); IR(film): υ_{max} 2483 (w), 2928, 1747 (s), 1418 (s), 1229, 1107, 1051 cm^{-1}; **249**: ^1H NMR (*endo*, 500 MHz, $CDCl_3$): δ 0.67 (d, *J*=7.0 Hz, 3H, C*H*$_3$CCH$_3$), 0.87 (d, *J*=7.0 Hz, 3H, CH$_3$CC*H*$_3$), 1.87-2.00 (m, 1H, C*H*CHN), 1.93-2.00 (m, 1H, C*H*HCH$_2$Ar), 2.00-2.08 (m, 1H, C*H*Me$_2$), 2.26 (br t, *J*=8.2 Hz, 1H, CHN), 2.42-2.52 (m, 2H, C*H*HAr, CH*H*CH$_2$Ar), 2.58 (dt, *J*=8.7, 3.0 Hz, 1H, C*H*CH$_2$O), 2.70-2.76 (m, 1H, CH*H*Ar), 2.81 (t, *J*=7.4 Hz, 1H, CHAr), 3.75 (t, *J*=8.8 Hz, 1H, C*H*HO), 3.86 (dd, *J*=9.0, 2.9 Hz, 1H, CH*H*O), 7.08 (d, *J*=7.3 Hz, 1H, Ar-H), 7.13-7.17 (m, 2H, Ar-H), 7.29-7.30 (m, 1H, Ar-H); **249**: ^{13}C NMR (*endo*, 125 MHz, $CDCl_3$): δ 15.0 (CH_3), 17.3 (CH_2), 17.4 (CH_3), 19.0 (CH), 19.5 (CH), 27.4 (CH_2), 28.4 (CH), 35.4 (CH), 58.7 (CH), 63.7 (CH_2), 126.0 (CH-Ar), 126.4 (CH-Ar), 129.0 (CH-Ar), 130.0 (CH-Ar), 132.6 (C-Ar), 135.6 (C-Ar), 159.2 (C=O); **250** : ^1H NMR (*exo*, 500 MHz, $CDCl_3$): δ 0.86 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CCH$_3$), 0.90 (d, *J*=7.0 Hz, 3H, CH$_3$CC*H*$_3$), 1.77 (tdd, *J*=13.4, 6.0, 3.0 Hz, 1H, C*H*HCH$_2$Ar), 2.04-2.11 (m, 3H, CHAr, C*H*CHN, C*H*Me$_2$), 2.42 (ddt, *J*=13.4, 6.6, 1.9 Hz, 1H, CH*H*CH$_2$Ar), 2.46-2.57 (m, 1H, C*H*HAr), 2.66 (t, *J*=3.0 Hz, 1H, CHN), 2.68-2.70 (m, 1H, CH*H*Ar), 3.74 (dt, *J*=8.8, 3.9 Hz, 1H, C*H*CH$_2$O), 4.08 (dd, *J*=9.0, 4.3 Hz, 1H, C*H*HO), 4.21 (t, *J*=8.9 Hz, 1H, CH*H*O), 7.02 (d, *J*=7.3 Hz, 1H, Ar-H), 7.11-7.18 (m, 2H, Ar-H), 7.25-7.28 (m, 1H, Ar-H); **250**: ^{13}C NMR (*exo*, 125 MHz, $CDCl_3$): δ 15.0 (CH_3), 17.6 (CH_3), 18.1 (CH_2), 22.7 (CH), 24.3 (CH), 26.0 (CH_2), 28.4 (CH), 32.6 (CH), 60.8 (CH), 63.0 (CH_2), 125.9 (CH-Ar), 126.2 (CH-Ar), 128.5 (CH-Ar), 128.9 (CH-Ar), 134.2 (C-Ar), 134.9 (C-Ar), 157.8 (C=O); MS (CI^+) *m/z* (%) : 272 (MH^+, 100), 179 (37), 142 (40), 136 (24); HRMS: $[MH]^+$, found 272.16374, $C_{17}H_{22}O_2N$ requires 272.16505.

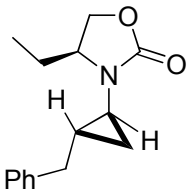
(4*S*,5*R*)-3-((1*S*,2*R*)-2-*tert*-Butylcyclopropyl)-4-methyl-5-phenyloxazolidin-2-one 251



A solution of (4S,5R)-3-diethoxymethyl-4-methyl-5-phenyloxazolidin-2-one **231** (386 mg, 1.38 mmol, 1.25 eq.) in diethyl ether (2 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (903 mg, 13.8 mmol, 12.5 eq.), copper(I) chloride (91.0 mg, 0.94 mmol; 0.9 eq.), zinc chloride (1.0 M solution in diethyl ether, 1.4 ml, 1.4 mmol, 1.3 eq.), chlorotrimethylsilane (0.88 ml, 6.93 mmol, 6.3 eq.) and 3,3-dimethyl-but-1-ene **164** (93 mg, 1.1 mmol, 1 eq.) in diethyl ether (6 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate solution (8 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 10 ml) and the combined organic extracts washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified twice by column chromatography (diethyl ether:petroleum ether 7:3) to give **251** together with **(4S,5R)-4-methyl-5-phenyl-*N*-formyloxazolidin-2-one** and **(4S,5R)-3-(diethoxymethyl)-4-methyl-5-phenyloxazolidin-2-one 231** (127 mg, **251**:**(4*S*,5*R*)-4-methyl-5-phenyl-*N*-formyloxazolidin-2-one**:**231** 1.3:1:1.6 as determined by ^{1}H NMR spectrum) and **251** together with **(4S,5R)-4-methyl-5-phenyl-*N*-formyloxazolidin-2-one** (21 mg, **251**:**(4*S*,5*R*)-4-methyl-5-phenyl-*N*-formyloxazolidin-2-one** 1.6:1 as determined by ^{1}H NMR spectrum). The yield of **251** (59 mg, 20%) was calculated from ^{1}H NMR spectrum.

IR (film): υ_{max} 2955, 1789, 1746, 1711, 1404, 1364, 1221, 1152, 1100 cm^{-1}; ^{1}H NMR (*trans*, 600 MHz, $CDCl_3$): δ 0.86 (d, *J*=6.7 Hz, 3H, CHC*H*$_3$), 0.91 (s, 9H, C(C*H*$_3$)$_3$), 0.95-1.00 (m, 3H, C*H*$_2$CHN, C*H*CHN), 2.39 (dt, *J*=6.8, 3.8 Hz, 1H, CHN), 3.91-3.94 (m, 1H, C*H*CH_3), 5.51 (d, *J*=7.5 Hz, 1H, CHO), 7.30-7.47 (m, 5H, Ar-H); ^{13}C NMR (*trans*, 150 MHz, $CDCl_3$): δ 11.2 (CH_2), 14.2 (CH_3), 26.7 (CH), 28.5 (CH_3), 30.7 (CH), 57.4 (CH), 78.3 (CH), 125.9 (C-Ar), 128.6 (C-Ar), 134.9 (C-Ar), 157.7 (C=O); MS (CI^+) m/z (%) : 274 (MH^+, 100), 230 (30), 178 (57), 134 (70); HRMS: $[MH]^+$, found 274.17962, $C_{17}H_{24}O_2N$ requires 274.18070.

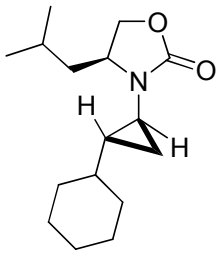
(*S*)-3-((1*S*,2*S*)-2-benzylcyclopropyl)-4-ethyloxazolidin-2-one 254



A solution of (S)-3-diethoxymethyl-4-ethyloxazolidin-2-one **230** (345 mg, 1.59 mmol, 1.25 eq.) in diethyl ether (2.5 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (1.04 g, 15.9 mmol,12.5 eq.), copper(I) chloride (104mg, 1.10 mmol, 0.9 eq.), zinc chloride (1.0 M solution in diethyl ether, 1.6 ml, 1.6 mmol, 1.25 eq.), chlorotrimethylsilane (1.0 ml, 7.8 mmol, 6.2 eq.) and allylbenzene **153** (150 mg, 1.27 mmol, 1 eq.) in diethyl ether (8 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (8 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 10 ml) and the combined organic extracts washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product (**254** and minor undetermined diastereoisomers) was purified by column chromatography (diethyl ether:petroleum ether 1:1) to give **254** as a pale yellow oil (136 mg, 44%).

$[\alpha]_D^{22}$ −34.2 (*c* 1.0, $CHCl_3$); IR (*trans*, film): υ_{max} 2966 (w), 1755 (s), 1420, 1219 (w), 1061 cm^{-1}; ^1H NMR (*trans*, 500 MHz, $CDCl_3$): δ 0.71 (t, *J*=7.5 Hz, 3H, CH_3), 0.94-1.00 (m, 1H, C*H*HCHN), 1.17-1.30 (m, 3H, CH*H*CHN, C*H*CHN, C*H*HCH_3), 1.33-1.41 (m, 1H, CH*H*CH_3), 2.25 (dt, *J*=7.0, 3.5 Hz, 1H, CHN), 2.38 (dd, *J*=14.4, 7.8 Hz, 1H, C*H*HPh), 2.83 (dd, *J*=14.4, 6.0 Hz, 1H, CH*H*Ph), 3.34-3.40 (m, 1H, C*H*CH_2O), 3.88 (dd, *J*=8.6, 4.6 Hz, 1H, C*H*HO), 4.17 (t, *J*=8.6 Hz, 1H, CH*H*O), 7.19-7.25 (m, 3H, Ar-H), 7.28-7.33 (m, 2H, Ar-H); ^{13}C NMR (*trans*, 125 MHz, $CDCl_3$): δ 8.0 (CH_3), 15.4 (CH_2), 20.4 (CH), 24.3 (CH_2), 29.6 (CH), 38.2 (CH_2), 57.6 (CH), 66.3 (CH_2), 126.3 (CH-Ar), 128.3 (CH-Ar), 128.5 (CH-Ar), 140.7 (C-Ar), 157.8 (C=O); MS (EI) *m/z* (%): 268 (MNa^+, 100), 246 (19); HRMS: $[MNa]^+$, found 268.13074, $C_{15}H_{19}O_2Na$ requires 268.13080.

(*S*)-3-((1*S*,2*R*)-2-cyclohexylcyclopropyl)-4-isobutyloxazolidin-2-one 255

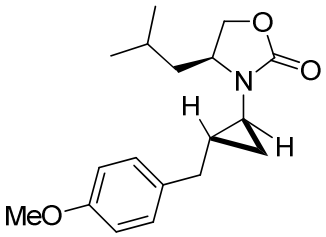


A solution of (S)-3-diethoxymethyl-4-isobutyloxazolidin-2-one **228** (200 mg, 0.82 mmol, 1.25 eq.) in diethyl ether (0.5 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred mixture of zinc amalgam (534 mg, 8.20 mmol, 12.5 eq.), zinc chloride (1.0 M solution in diethyl ether, 0.82 ml, 0.82 mmol, 1.25 eq.), vinylcyclohexane **252** (0.09 ml, 0.66 mmol, 1 eq.), trimethylsilyl chloride (0.52 ml, 4.08 mmol, 6.25 eq.), in diethyl ether (4 ml) at reflux. The resulting mixture was left to stir at reflux for 16 hours, cooled to room temperature and treated with a saturated aqueous solution of sodium bicarbonate (3 ml). The resulting mixture was stirred for 10 min, filtered and the separated zinc washed with ethyl acetate. The resulting aqueous phase was extracted with ethyl acetate (2 × 3 ml) and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (diethyl ether:petroleum ether 1:1) to give the *N*-cyclopropyl oxazolidinone **255** as a pale yellow semi-solid (80 mg, 46%).

$[\alpha]_D^{20}$ −74.0 (*c* 1.71, $CHCl_3$); IR (film): ν_{max} 2928, 1751, 1418, 1261, 1070, 1018 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.55-0.64 (m, 1H, C*H*CHCHN), 0.70-0.77 (m, 2H, C*H*CHN, C*H*HCHN), 0.90 (d, *J*=6.6 Hz, 3H, CH_3CCH$_3$), 0.94 (d, *J*=6.6 Hz, 3H, CH$_3$CCH_3), 0.95-0.97 (m, 1H, CH*H*CHN), 1.00-1.05 (m, 1H, C*H*HCHCH$_2$), 1.08-1.20 (m, 4H, C*H*HCH$_2$CH, C*H*HCH$_2$CH, C*H*HCH$_2$CH$_2$, C*H*HCHCH$_2$), 1.41 (ddd, *J*=13.3, 11.0, 4.3 Hz, 1H, C*H*HCHMe$_2$), 1.50-1.58 (m, 1H, CHMe$_2$), 1.58-1.63 (m, 1H, CH*H*CH$_2$CH$_2$), 1.65-1.72 (m, 3H, CH*H*CH$_2$CH, CH*H*CH$_2$CH, CH*H*CHCH$_2$), 1.76 (ddd, *J*=13.3, 9.8, 2.9 Hz, 1H, CH*H*CHMe$_2$), 1.80-1.88 (m, 1H, CH*H*CHCH$_2$), 2.15 (dt, *J*=6.5, 3.6 Hz, 1H, CHN), 3.56-3.66 (m, 1H, C*H*CH$_2$O), 3.91 (dd, *J*=8.6, 4.6 Hz, 1H, CH*H*O), 4.19 (dd, *J*=8.7, 8.3 Hz, 1H, C*H*HO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7

(CH_2), 21.7 (CH_3), 23.8 (CH_3), 24.7 (CH), 25.5 (CH), 25.9 (CH_2), 26.0 (CH_2), 26.3 (CH_2), 28.8 (CH), 32.2 (CH_2), 33.0 (CH_2), 40.7 (CH), 40.8 (CH_2), 55.5 (CH), 67.1 (CH_2), 157.7 (C=O); MS (EI) *m/z* (%): 266 (MH^+, 26), 182 (100), 126 (31), 113 (23); HRMS: $[M]^+$, found 265.20434, $C_{16}H_{27}O_2N$ requires 265.20417.

(*S*)-3-((1*S*,2*S*)-2-(4-methoxybenzyl)cyclopropyl)-4-isobutyloxazolidin-2-one 256

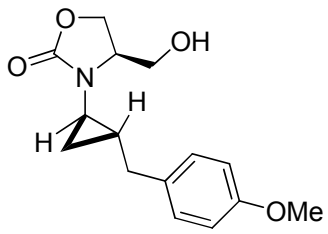


A solution of (S)-3-diethoxymethyl-4-isobutyloxazolidin-2-one **228** (328 mg, 1.34 mmol, 1.02 eq.) in diethyl ether (5 ml) was added dropwise *via* syringe pump (0.6 ml.h^{-1}) to a vigorously stirred mixture of zinc amalgam (1.07 g, 16.4 mmol, 12.5 eq.), zinc chloride (1.0 M solution in diethyl ether, 1.63 ml, 1.63 mmol, 1.25 eq.), 4-allylanisole **253** (193 mg, 1.31 mmol, 1 eq.), trimethylsilyl chloride (1.05 ml, 8.22 mmol, 6.28 eq.) in diethyl ether (10 ml) at reflux. The resulting mixture was heated at reflux for 16 hours, cooled to room temperature and treated with a saturated aqueous solution of sodium bicarbonate (8 ml). The resulting mixture was stirred for 10 min, filtered and the separated zinc washed with ethyl acetate. The separated aqueous phase was extracted with ethyl acetate (2 × 7 ml) and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (diethyl ether:petroleum ether 1:1) to give **256** as a pale orange oil (173 mg, 44%).

$[\alpha]_D^{10}$ +10.68 (*c* 1.46, $CHCl_3$); IR (film): ν_{max} 2959, 1755 (s), 1512, 1417 (w), 1248, 1038 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ0.67 (d, *J*=6.5 Hz, 3H, CH_3CHCH_3), 0.82 (d, *J*=6.5 Hz, 3H, CH_3CHCH_3), 0.90-1.00 (m, 2H, CH_2CHN), 1.1-1.35 (m, 4H, $CHMe_2$, CH_2CHMe_2, CHCHN), 2.29 (dt, *J*=6.9, 3.4 Hz, 1H, CHN), 2.31 (dd, *J*=14.4, 7.4 Hz, 1H, CHHAr), 2.77 (dd, *J*=14.4, 5.8 Hz, 1H, CHHAr), 3.42-3.51 (m, 1H, $CHCH_2O$), 3.79 (s, 3H, OCH_3), 3.89 (dd, *J*=8.5, 5.2 Hz, 1H, CHHO), 4.19 (t, *J*=8.5 Hz, 1H, CHHO), 6.85 (d, *J*=8.7 Hz, 2H, Ar-H), 7.13 (d, *J*=8.7 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ15.4 (CH_2), 21.0 (CH_3), 21.2 (CH_3), 23.6 (CH), 24.3 (CH), 29.2 (CH), 37.6 (CH_2), 40.5 (CH_2), 55.2 (CH), 55.2 (CH_3), 67.8 (CH_2), 114.1 (CH-Ar), 129.4 (CH-Ar), 132.7 (C-Ar), 157.7 (C-Ar), 158.1 (C=O); MS (CI^+) *m/z* (%): 304 (MH^+, 75), 182

(22), 134 (58), 121 (100); HRMS: $[MH]^+$, found 304.19154, $C_{18}H_{26}O_3N$ requires 304.19126.

(*R*)-3-((1*R*,2*R*)-2-(4-methoxybenzyl)cyclopropyl)-4-(hydroxymethyl)oxazolidin-2-one 257

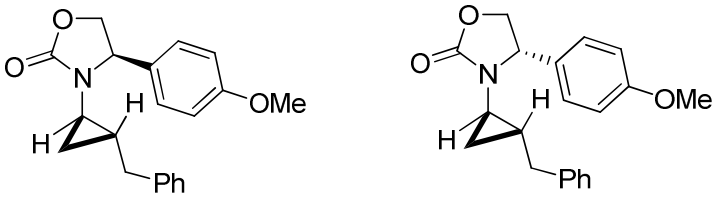


A solution of (7a*R*)-5-ethoxy-dihydro-1H-oxazolo[3,4-*c*]oxazol-3(5H)-one **232** (80.0 mg, 0.46 mmol, 1.25 eq.) in diethyl ether (2 ml) was added dropwise *via* syringe pump (0.6 ml.h^{-1}) to a vigorously stirred mixture of zinc (303 mg, 4.63 mmol, 12.5 eq.), zinc chloride (1.0 M solution in diethyl ether, 0.46 ml, 0.46 mmol, 1.25 eq.), 4-allylanisole **253** (0.06 ml, 0.37 mmol, 1 eq.), trimethylsilyl chloride (0.30 ml, 2.36 mmol, 6.4 eq.) in diethyl ether (3 ml) at reflux. The resulting mixture was heated at reflux for 36 hours, cooled to room temperature and treated with a saturated aqueous solution of sodium bicarbonate (3 ml). The resulting mixture was stirred for 10 min, filtered and the separated zinc washed with ethyl acetate. The separated aqueous phase was extracted with ethyl acetate (2 × 5 ml) and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate) to give the *N*-cyclopropyl oxazolidinone **257** as a yellow oil (24 mg, 23%).

$[\alpha]_D^{20}$ +13.0 (*c* 0.55, $CHCl_3$); IR (film): ν_{max} 3408, 3057, 2924, 1736 (s), 1612 (w), 1512, 1427, 1267, 1244, 1092 (w), 1036 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91-0.96 (m, 1H, CH*H*CHN), 1.12-1.17 (m, 1H, CH*H*CHN), 1.19-1.23 (m, 1H, C*H*CHN), 2.25 (dt, *J*=6.7, 3.5 Hz, 1H, CHN), 2.38 (dd, *J*=14.6, 7.6 Hz, 1H, CH*H*Ph), 2.72 (dd, *J*=14.6, 6.4 Hz, 1H, C*H*HPh), 3.33 (dd, *J*=10.7, 3.2 Hz, 1H, C*H*HOH). 3.36 (dd, *J*=10.7, 5.0 Hz, 1H, CH*H*OH), 3.47-3.53 (m, 1H, C*H*CH_2O), 3.79 (s, 3H, OCH_3), 4.10 (dd, *J*=8.6, 4.2 Hz, 1H, C*H*HOCO), 4.16 (t, *J*=8.6 Hz, 1H, CH*H*OCO), 6.84 (d, *J*=8.7 Hz, 2H, Ar-H), 7.12 (d, *J*=8.7 Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.4 (CH_2), 20.4 (CH), 29.6 (CH), 37.3 (CH_2), 55.2 (CH_3), 57.5 (CH), 60.7 (CH_2), 64.6 (CH_2), 113.9 (CH-Ar),

129.3 (CH-Ar), 132.6 (C-Ar), 158.1 (C-Ar), 158.2 (C=O); MS (CI^+) *m/z* (%): 278 (MH^+, 33), 161 (40), 134 (20), 121 (100); HRMS: $[MH]^+$, found 278.13742, $C_{15}H_{20}O_4N$ requires 278.13868.

(*R*)-3-((1*R*,2*R*)-2-benzylcyclopropyl)-4-(4-methoxyphenyl)oxazolidin-2-one 258 and (*S*)-3-((1*R*,2*R*)-2-benzylcyclopropyl)-4-(4-methoxyphenyl)oxazolidin-2-one 259

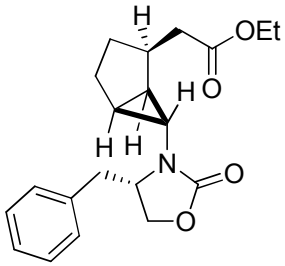


A solution of (*R*)-3-diethoxymethyl-4-(4-methoxyphenyl)-oxazolidin-2-one (300 mg, 1.01 mmol, 1.25 eq.) in diethyl ether (2 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (664 mg, 10.2 mmol, 12.5 eq.), copper(I) chloride (66.0 mg, 0.67 mmol, 0.8 eq.), zinc chloride (1.0 M solution in diethyl ether, 1.0 ml, 1.0 mmol, 1.25 eq.), chlorotrimethylsilane (0.65 ml, 5.12 mmol, 6.4 eq.) and allylbenzene **153** (96 mg, 0.8 mmol, 1 eq.) in diethyl ether (4ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (5 ml), filtered and the solids washed with diethyl ether (5 ml). The biphasic mixture was extracted with diethyl ether (2 × 3 mL) and the combined organic extracts washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (diethyl ether:petroleum ether 1:1) to give an inseparable mixture of **258** and **259** (70 mg, 29%, **258**:**259** 5.9:1 as determined by ^{1}H NMR spectrum) as a yellow oil.

IR(mixture cyclopropanes, film): υ_{max} 2917 (w), 1747 (s), 1612, 1513, 1407, 1245 (s), 1176, 1028 (s) cm^{-1}; **258**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.71-0.8 (m, 1H, C*H*HCHN), 1.10-1.28 (m, 2H, CH*H*CHN, C*H*CH_2Ph), 2.09 (dt, *J*=7.1, 3.5 Hz, 1H, C*H*N), 2.35 (dd, *J*=14.5, 6.2 Hz, 1H, C*H*HPh), 2.46 (dd, *J*=14.5, 6.4 Hz, 1H, CH*H*Ph), 3.82 (s, 3H, OCH_3), 4.02-4.08 (m, 1H, C*H*HO), 4.42-4.48 (m, 2H, CH*H*O, C*H*CH_2O), 6.81-6.92 (m, 2H, Ar-H), 6.96-7.08 (m, 3H, Ar-H), 7.09-7.30 (m, 4H, Ar-H); **258**: ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.7 (CH_2), 20.1 (CH), 30.6 (CH), 37.8 (CH_2), 55.4 (CH_3), 60.8 (CH), 69.7 (CH_2), 114.5 (C-Ar), 126.1 (C-Ar), 128.0 (C-Ar), 128.4 (C-Ar), 128.5 (C-Ar), 130.6 (C-Ar), 140.2 (C-Ar), 157.9 (C-Ar), 159.9 (C=O); **259**: ^{1}H NMR (500 MHz,

$CDCl_3$): δ 0.50-0.56 (m, 1H, C*H*HCHN), 0.80-0.89 (m, 1H, CH*H*CHN), 1.31-1.39 (m, 1H, C*H*CH_2Ph), 2.14 (dt, *J*=7.1, 3.5 Hz, 1H, C*H*N), 2.23 (dd, *J*=14.7, 8.0 Hz, 1H, C*H*HPh), 2.78 (dd, *J*=14.7, 5.6 Hz, 1H, CH*H*Ph), 3.81 (s, 3H, OCH_3), 4.08-4.12 (m, 1H, C*H*HO), 4.50-4.60 (m, 2H, CH*H*O, C*H*CH_2O), 6.81-6.92 (m, 2H, Ar-H), 6.96-7.08 (m, 3H, Ar-H), 7.09-7.30 (m, 4H, Ar-H); **259**: ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.1 (CH_2), 20.6 (CH), 31.3 (CH), 38.0 (CH_2), 55.4 (CH_3), 61.0 (CH), 69.8 (CH_2), 114.5 (C-Ar), 126.1 (C-Ar), 128.1 (C-Ar), 128.2 (C-Ar), 128.3 (C-Ar), 130.7 (C-Ar), 140.3 (C-Ar), 158.3 (C-Ar), 160.0 (C=O); MS (EI) *m/z* (%) : 323 (M^+, 8), 232 (55), 134 (100), 121 (50), 91 (25); HRMS: $[M]^+$, found 323.15083, $C_{20}H_{21}O_3N$ requires 323.15083.

Ethyl 2-((1*S*,2*S*,5*R*)-6-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)bicyclo[3.1.0]hexan-2-yl)acetate 260

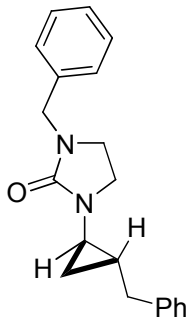


A solution of (*S*)-4-benzyl-3-diethoxymethyloxazolidin-2-one **200** (384 mg, 1.38 mmol, 1.25 eq.) in diethyl ether (2 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (900 mg, 13.8 mmol, 12.5 eq.), copper(I) chloride (90 mg, 0.9 mmol, 0.8 eq.), zinc chloride (1.0 M solution in diethyl ether, 1.4 ml, 1.4 mmol, 1.3 eq.), chlorotrimethylsilane (0.88 ml, 6.93 mmol, 6.25 eq.) and ethyl 2-(cyclopent-2-enyl)acetate **163** (170 mg, 1.10 mmol, 1 eq.) in diethyl ether (6 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (8 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 10 ml) and the combined organic extracts washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified twice by column chromatography (diethyl ether:petroleum ether 7:3) to give the cyclopropane **260** (12 mg) as a pale yellow oil and a mixture of isomers containing the cyclopropane **260** as a pale yellow semi solid (85 mg). The total yield of isomers was 26%.

$[\alpha]_D^{22}$ +33.7 (*c* 0.35, $CHCl_3$); IR(*trans*, film): υ_{max} 2939 (w), 1754 (s), 1729 (s), 1414, 1258, 1181, 1096, 1030 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.73-0.81 (m, 1H, C*H*HCHCH$_2$CO), 1.24 (t, *J*=7.1 Hz, 3H, CH_3), 1.74 (ddd, *J*=6.6, 4.4, 1.9 Hz, 1H, C*H*CHCH$_2$CO), 1.76-1.81 (m, 1H, CH*H*CHCH$_2$CO), 1.86-1.93 (m, 2H, C*H*CHN, C*H*HCHCHN), 2.06-2.10 (m, 1H, CH*H*CHCHN), 2.34 (t, *J*=1.9 Hz, 1H, CHN), 2.37 (dd, *J*=15.4, 9.1 Hz, 1H, C*H*HCO), 2.49 (dd, *J*=15.4, 5.7 Hz, 1H, CH*H*CO), 2.63-2.70

(m, 2H, C*H*HPh, C*H*CH_2CO), 3.24 (dd, *J*=13.4, 4.0 Hz, 1H, CH*H*Ph), 3.78-3.83 (m, 1H, C*H*CH_2O), 3.99-4.04 (m, 2H, CH_2O), 4.11-4.22 (m, 2H, OCH_2CH_3), 7.20-7.23 (m, 2H, Ar-H), 7.26-7.29 (m, 1H, Ar-H), 7.33-7.36 (m, 2H, Ar-H); ^{13}C NMR (*trans*, 150 MHz, $CDCl_3$): δ 14.3 (CH_3), 27.1 (CH_2), 27.8 (CH_2), 27.9 (CH), 28.5 (CH), 28.6 (CH), 36.8 (CH), 38.0 (CH_2), 38.1 (CH_2), 57.6 (CH), 60.5 (CH_2), 65.9 (CH_2), 127.2 (CH-Ar), 128.9 (CH-Ar), 129.3 (CH-Ar), 135.7 (C-Ar), 157.8 (C=O), 172.9 (C=O); MS (CI^+) m/z (%) : 344 (MH^+, 100), 298 (64); HRMS: $[MH]^+$, found 344.18531, $C_{20}H_{25}O_4N$ requires 344.18618.

1-Benzyl-3-((1*R*,2*R*)-2-benzylcyclopropyl)imidazolidin-2-one 269

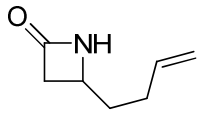


Zinc chloride (1.0 M solution in diethyl ether, 2.8 ml, 2.8 mmol, 2 eq.) and chlorotrimethylsilane (2.50 ml, 19.6 mmol, 14 eq.) were added to a solution of 1-benzylimidazolidin-2-one **268** (492 mg, 2.79 mmol, 2 eq.) in diethyl ether (5 ml) and the resulting mixture was heated at reflux for 10 min. The flask was removed from the oil bath, and zinc dust (1.37 g, 21.0 mmol, 15 eq.), copper(I) chloride (137 mg, 1.38 mmol, 1 eq.) and allylbenzene **153** (165 mg, 1.39 mmol, 1 eq.) in diethyl ether (5 ml) were added to the mixture which was then heated at reflux. A solution of triethyl orthoformate (2.30 ml, 13.8 mmol, 10 eq.) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to the vigorously stirred refluxing mixture. After heating at reflux for 16 hours, the mixture was quenched by the addition of a saturated aqueous solution of sodium bicarbonate (10 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 10 ml) and the combined organic extracts washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography twice (ethyl acetate:petroleum ether 6:4 then diethyl ether) to obtain **269** (90% pure by ^{1}H NMR spectrum) as a yellow oil (84 mg, 20%).

IR (film): ν_{max} 3026, 2858, 1699 (s), 1489 (s), 1439 (s), 1356, 1263 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.70-0.75 (m, 1H, C*H*HCHN), 0.97 (ddd, *J*=9.2, 5.6, 3.6 Hz, 1H, CH*H*CHN), 1.25-1.33 (m, 1H, C*H*CHN), 2.32 (dt, *J*=6.9, 3.6 Hz, 1H, CHN), 2.53 (dd, *J*=14.7, 7.4 Hz, 1H, C*H*HPh), 2.79 (dd, *J*=14.7, 6.6 Hz, 1H, CH*H*Ph), 3.10-3.15 (m, 2H, CH_2N), 3.05-3.10 (m, 2H, CH_2N), 4.31 (d, *J*=14.9 Hz, 1H, NC*H*HPh), 4.35 (d, *J*=14.9 Hz, 1H, NCH*H*Ph), 7.23-7.33 (m, 10H, H-Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.8

(CH_2), 19.9 (CH), 33.0 (CH), 38.1 (CH_2), 42.2 (CH_2), 43.6 (CH_2), 48.2 (CH_2), 126.0 (CH-Ar), 127.3 (CH-Ar), 128.2 (CH-Ar), 128.3 (CH-Ar), 128.4 (CH-Ar), 128.5 (CH-Ar), 129.0 (CH-Ar), 137.3 (C-Ar), 141.0 (C-Ar), 161.5 (C=O); MS (EI) *m/z* (%): 329 (MNa^+, 100); HRMS: $[MNa]^+$, found 329.16199, $C_{20}H_{22}ON_2Na$ requires 329.16243.

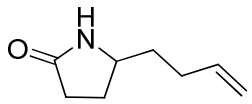
4-(But-3-enyl)azetidin-2-one 279 [134]



A mixture of hexa-1,5-diene **278** (3.65 ml, 30.8mmol, 1 eq.) and chlorosulfonyl isocyanate (2.70 ml, 31.0 mmol., 1 eq.) was stirred at room temperature for 7 days. The reaction mixture was dissolved in dichloromethane (10 ml) and added to a solution of sodium sulphite (5.25 g, 41.7 mmol, 1.6 eq.) in water (25 ml) and dichloromethane (12.5 ml). The pH was maintained between 7 and 9 by the addition of a solution of 10% KOH (approx. 50 ml). Ethyl acetate (50 ml) was added, and the organic layer separated. The aqueous phase was extracted with ethyl acetate (3 × 25 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (diethyl ether) to give **279** as an orange oil (1.406 g, 37%).

IR (film): ν_{max} 3258, 3258, 2934, 1744 (s), 1641, 1416, 1188 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.70-1.77 (m, 2H, C*H*$_2$CHNH), 2.09-2.15 (m, 2H, C*H*$_2$CH=CH$_2$), 2.29 (ddd, *J*=14.8, 2.4, 1.3 Hz, 1H, C*H*HCO), 3.06 (ddd, *J*=14.8, 5.0, 2.3 Hz, 1H, CH*H*CO), 3.61-3.66 (m, 1H, CHNH), 5.00 (ddd, *J*=10.2, 3.0, 1.3 Hz, 1H, C*H*H=CH), 5.05 (dq, *J*=17.1, 1.7 Hz, 1H, CH*H*=CH), 5.75-5.84 (m, 1H, C*H*=CH$_2$), 5.99 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.7 (CH_2), 34.5 (CH_2), 43.6 (CH_2), 47.8 (CH), 115.6 (*C*H$_2$=CH), 137.2 (*C*H=CH$_2$), 167.8 (C=O); MS (CI^+) m/z (%) : 126 (MH^+, 100), 83 (99); HRMS: $[MH]^+$ found 126.09147, $C_7H_{11}ON$ requires 126.09188.

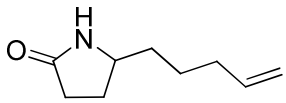
5-(But-3-enyl)pyrrolidin-2-one 280 [171]



Magnesium (3.92 g, 161 mmol, 5.3 eq.) was stirred at room temperature for 1 hour before being suspended in tetrahydrofuran (40 ml). A solution of 1-bromobut-3-ene (12.3 ml, 121 mmol, 4 eq.) in tetrahydrofuran (40 ml) was added dropwise and the resulting mixture heated at reflux for 30 min. After cooling to room temperature, the mixture was added dropwise *via* cannula to a solution of succinimide (3.00 g, 30.3 mmol, 1 eq.) in tetrahydrofuran (60 ml) at 0 °C. The mixture was allowed to warm to room temperature, stirred for 16 hours before sodium cyanoborohydride (1.90 g, 30.2 mmol,1 eq.) and a few drops of methyl orange were added. The mixture was acidified with acetic acid until the indicator changed from yellow to pink and stirred for 1.5 hours. Neutralisation (5% aq. NaOH) and removal of the solvents *in vacuo* gave a solid residue that was dissolved in a saturated aqueous solution of sodium bicarbonate (150 ml) and extracted with ethyl acetate (3 × 100 ml). The combined extracts were washed with water (100 ml), brine (100 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (1% methanol in ethyl acetate) to give the title product **280** as a yellow oil (2.7g, 64%).

IR (film): ν_{max} 3219 (w), 2928 (w), 1692 (s), 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.55-1.66 (m, 2H, C*H*$_2$CHNH), 1.70-1.77 (m, 1H, C*H*HCH$_2$CO), 2.07-2.17 (m, 2H, C*H*$_2$CH=CH$_2$), 2.29-2.36 (m, 3H, CH$_2$CO, CH*H*CH$_2$CO), 3.60-3.70 (m, 1H, CHNH), 5.0 (dd, *J*=10.6, 1.5 Hz, 1H, C*H*H=CH), 5.05 (dd, *J*=19.0, 1.5 Hz, 1H, CH*H*=CH), 5.71-5.87 (m, 1H, C*H*=CH$_2$), 6.14 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.3 (CH$_2$), 30.0 (CH$_2$), 30.4 (CH$_2$), 35.8 (CH$_2$), 54.0 (CH), 115.6 (*C*H$_2$=CH), 137.5 (*C*H=CH$_2$), 179.5 (C=O); MS (CI^+) m/z (%) : 140 (MH^+, 100), 138 (93), 100 (10); HRMS: $[MH]^+$ found 140.10761, $C_8H_{14}ON$ requires 140.10753.

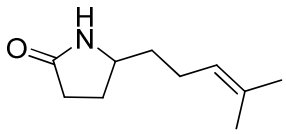
5-(Pent-4-enyl)pyrrolidin-2-one 281 [171]



Magnesium (1.72 g, 70.8 mmol, 7 eq.) was stirred at room temperature for 40 min before being suspended in tetrahydrofuran (60 ml). A solution of 5-bromopent-1-ene (6.00 ml, 50.6 mmol, 5 eq.) in tetrahydrofuran (20 ml) was added dropwise and the resulting mixture heated at reflux for 30 min. After cooling to room temperature, the mixture was added dropwise *via* cannula to a solution of succinimide (1.00 g, 10.0 mmol, 1 eq.) in tetrahydrofuran (20 ml) at 0 °C. The mixture was allowed to warm to room temperature, stirred for 16 hours before sodium cyanoborohydride (634 mg, 10.09 mmol, 1 eq.) and a few drops of methyl orange were added. The mixture was acidified with acetic acid until the indicator changed from yellow to pink and stirred for another 1 hour. Neutralisation (5% aq. NaOH) and removal of the solvents *in vacuo* gave a solid residue that was dissolved in a saturated aqueous solution of sodium bicarbonate (80 ml) and extracted with ethyl acetate (3 × 60 ml). The combined extracts were washed with water (60 ml), brine (60 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (1% methanol in ethyl acetate) to give **281** as a yellow oil (1.126 g, 73%).

IR (film): ν_{max} 3227, 2930, 1693 (s), 1460, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.34-1.57 (m, 4H, C*H*$_2$CHNH, C*H*$_2$CH$_2$CHNH), 1.65-1.73 (m, 1H, C*H*HCH$_2$CO), 2.04-2.10 (m, 2H, C*H*$_2$CH=CH$_2$), 2.20-2.27 (m, 1H, CH*H*CH$_2$CO), 2.28-2.35 (m, 2H, CH$_2$CO), 3.59-3.66 (m, 1H, CHNH), 4.90 (dd, *J*=10.2, 1.5 Hz, 1H, C*H*H=CH), 5.00 (dd, *J*=17.1, 1.5 Hz, 1H, CH*H*=CH), 5.72-5.82 (m, 1H, C*H*=CH$_2$), 6.55 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.1 (CH$_2$), 27.2 (CH$_2$), 30.2 (CH$_2$), 33.5 (CH$_2$), 36.1 (CH$_2$), 54.5 (CH), 115.0 (*C*H$_2$=CH), 138.1 (*C*H=CH$_2$), 178.4 (C=O); MS (EI) m/z (%) : 154 (MH^+, 7), 124 (9), 110 (73), 97 (34), 84 (100), 56 (24); HRMS: $[M]^+$ found 153.11421, $C_9H_{15}ON$ requires 153.11482.

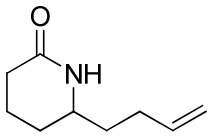
5-(4-Methylpent-3-enyl)pyrrolidin-2-one 282



Magnesium (894 mg, 36.8 mmol, 6 eq.) was stirred at room temperature for 16 hours before being suspended in tetrahydrofuran (30 ml). A solution of 5-bromo-2-methyl-pent-2-ene (4.00 g, 24.5 mmol, 4 eq.) in tetrahydrofuran (5 ml) was added dropwise and the resulting mixture heated at reflux for 45 min. After cooling to room temperature, the mixture was added dropwise *via* cannula to a solution of succinimide (607 mg, 6.13 mmol, 1 eq.) in tetrahydrofuran (15 ml) at 0 °C. The mixture was allowed to warm to room temperature, stirred for 16 hours before sodium cyanoborohydride (385 mg, 6.13 mmol, 1 eq.) and a few drops of methyl orange were added. The mixture was acidified with acetic acid until the indicator changed from yellow to pink and stirred for another 1.5 hours. Neutralisation (5% aq. NaOH) and removal of the solvents under vacuum gave a solid residue that was dissolved in a saturated aqueous solution of sodium bicarbonate (40 ml) and extracted with ethyl acetate (3 × 30 ml). The combined extracts were washed with water (60 ml), brine (60 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (5% methanol in ethyl acetate) to give the product **282** as a pale yellow oil (481 mg, 47%).

IR (film): ν_{max} 3209, 2918, 2359, 1693 (s), 1423, 1263 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.50-1.59 (m, 2H, C*H*$_2$CHNH), 1.61 (s, 3H, C*H*$_3$CCH$_3$), 1.70 (s, 3H, CH$_3$CC*H*$_3$), 1.72 (m, 1H, C*H*HCH$_2$CO), 2.00-2.07 (m, 2H, C*H*$_2$CH=C), 2.20-2.38 (m, 3H, C*H*$_2$CO, CH*H*CH$_2$CO), 3.60-3.68 (m, 1H, CHNH), 5.05-5.12 (m, 1H, C*H*=C), 5.76 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ24.7 (CH_3), 25.7 (CH_2), 27.4 (CH_2), 30.0 (CH_2), 36.7 (CH_2), 54.1 (CH), 123.0 (*C*H=C), 136.9 (*C*=CH), 169.1 (C=O); MS (EI) m/z (%) : 167 (M^+, 13), 124 (14), 110 (45), 97 (22), 24(100); HRMS: $[M]^+$ found 167.13060, $C_{10}H_{17}ON$ requires 167.13101.

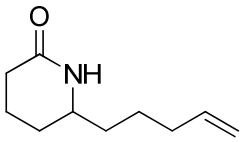
6-(But-3-enyl)-piperidin-2-one 283[171]



Magnesium (1.72 g, 70.8 mmol, 7 eq.) was stirred at room temperature for 1 hour before being suspended in diethyl ether (50 ml). A solution of 4-bromobut-1-ene (5.10 ml, 50.2 mmol, 5 eq.) in diethyl ether (10 ml) was added dropwise and the resulting mixture heated at reflux for 45 min. After cooling to room temperature, the mixture was added dropwise *via* cannula to a solution of glutarimide (1.01 g, 10.1 mmol, 1 eq.) in tetrahydrofuran (30 ml) at 0 °C. The mixture was allowed to warm to room temperature, stirred for 16 hours before sodium cyanoborohydride (634 mg, 10.1 mmol, 1 eq.) and a few drops of methyl orange were added. The mixture was acidified with acetic acid until the indicator changed from yellow to pink and stirred for another 1 hour. Neutralisation (5% aq. NaOH) and removal of the solvents *in vacuo* gave a solid residue that was dissolved in a saturated aqueous solution of sodium bicarbonate (80 ml) and extracted with ethyl acetate (3 × 60 ml). The combined extracts were washed with water (60 ml), brine (60 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (1% methanol in ethyl acetate) to give the product **283** as a yellow oil (1.01 g, 66%).

IR (film): ν_{max} 3209 (s), 2943 (s), 1663 (s), 1408, 1346 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.32-1.40 (m, 1H, C*H*HCH$_2$CH$_2$CO), 1.54-1.61 (m, 2H, C*H*$_2$CH$_2$CH=CH$_2$), 1.62-1.74 (m, 1H, C*H*HCH$_2$CO), 1.84-1.95 (m, 2H, CH*H*CH$_2$CH$_2$CO, CH*H*CH$_2$CO), 2.08-2.15 (m, 2H, C*H*$_2$CH=CH$_2$), 2.27 (ddd, *J*=17.8, 10.6, 5.9 Hz, 1H, C*H*HCO), 2.34-2.42 (m, 1H, CH*H*CO), 3.34-3.42 (m, 1H, CHN), 5.00 (d, *J*=10.1 Hz, 1H, C*H*H=CH), 5.05 (dd, *J*=17.2, 1.3 Hz, 1H, CH*H*=CH), 5.73-5.83 (m, 1H, C*H*=CH$_2$), 5.95 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.7 (CH_2), 28.3 (CH_2), 29.6 (CH_2), 31.3 (CH_2), 35.9 (CH_2), 52.6 (CH), 115.6 (*C*H$_2$=CH), 137.2 (*C*H=CH$_2$), 172.3 (C=O); MS (EI) m/z (%) : 154 (MH^+, 100), 98 (8); HRMS: $[MH]^+$ found 154.12271, $C_9H_{16}ON$ requires 154.12319.

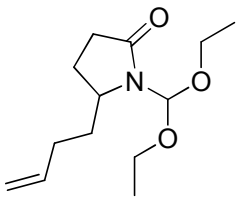
6-(Pent-4-enyl)piperidin-2-one 284[171]



Magnesium (1.72 g, 70.8 mmol, 7 eq.) was stirred at room temperature for 1 hour before being suspended in diethyl ether (50 ml). A solution of 5-bromopent-1-ene (5.95 ml, 50.2 mmol, 5 eq.) in diethyl ether (10 ml) was added dropwise and the resulting mixture heated at reflux for 45 min. After cooling to room temperature, the mixture was added dropwise *via* cannula to a solution of glutarimide (1.14 g, 10.1 mmol, 1 eq.) in tetrahydrofuran (30 ml) at 0 °C. The mixture was allowed to warm to room temperature, stirred for 16 hours before sodium cyanoborohydride (634 mg, 10.1 mmol, 1 eq.) and a few drops of methyl orange were added. The mixture was acidified with acetic acid until the indicator changed from yellow to pink and stirred for another 1.5 hours. Neutralisation (5% aq. NaOH, 60 ml) and removal of the solvents *in vacuo* gave a solid residue that was dissolved in a saturated aqueous solution of sodium bicarbonate (80 ml) and extracted with ethyl acetate (3 × 60 ml). The combined extracts were washed with water (60 ml), brine (60 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (1% methanol in ethyl acetate) to give the product **284** as a pale yellow oil (1.0 g, 68%).

IR (film): ν_{max} 2937 (s), 2943 (s), 2360, 1666 (s), 1408, 1182 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.30-1.39 (m, 1H, C*H*HCH$_2$CH$_2$CO), 1.40-1.52 (m, 4H, C*H*$_2$CH$_2$CH=CH$_2$, C*H*$_2$CHNH), 1.62-1.73 (m, 1H, C*H*HCH$_2$CO), 1.84-1.95 (m, 2H, CH*H*CH$_2$CH$_2$CO, CH*H*CH$_2$CO), 2.04-2.1 (m, 2H, C*H*$_2$CH=CH$_2$), 2.27 (ddd, *J*=17.8, 10.8, 6.0 Hz, 1H, C*H*HCO), 2.35-2.42 (m, 1H, CH*H*CO), 3.32-3.39 (m, 1H, CHN), 4.95-5.04 (m, 2H, C*H*$_2$=CH), 5.73-5.82 (m, 1H, C*H*=CH$_2$), 5.85 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.8 (CH_2), 24.5 (CH_2), 28.4 (CH_2), 31.3 (CH_2), 33.4 (CH_2), 36.3 (CH_2), 53.1 (CH), 115.1 (*C*H$_2$=CH), 138.0 (CH=CH$_2$), 172.3 (C=O); MS (EI) m/z (%) : 168 (MH^+, 100), 97 (5); HRMS: $[MH]^+$ found 168.13890, $C_{10}H_{18}ON$ requires 168.13884.

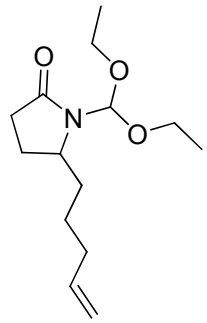
5-(But-3-enyl)-1-(diethoxymethyl)pyrrolidin-2-one 285



A stirred mixture of the amide **280** (713 mg, 5.13 mmol, 1 eq.), aluminium chloride (103 mg, 0.77 mmol, 0.15 eq.) and triethyl orthoformate (25.0 ml, 150 mmol, 29 eq.) was heated at 155 °C for 18 hours. The reaction mixture was cooled to room temperature before being quenched with a saturated aqueous solution of sodium bicarbonate (15 ml). The separated aqueous phase was extracted with ethyl acetate (4 × 20 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The triethyl orthoformate was evaporated under high vacuum and as analysis by NMR, the residue indicated only 50% conversion, the reaction was restarted by mixing the residue with $AlCl_3$ (0.15 eq) in triethyl orthoformate (36 ml), and heating at 155 °C for 18 hours. After a similar work-up, the residue was purified by column chromatography (diethyl ether:petroleum ether 3:1) to give **285** as a yellow oil (565 mg, 46%).

IR (film): ν_{max} 2980, 1694 (s), 1418, 1262 (s), 1063 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 1.13-1.24 (m, 6H, 2 × CH_2CH_3), 1.49-1.62 (m, 1H, C*H*HCHN), 1.65-1.75 (m, 1H, CH*H*CHN), 1.99-2.18 (m, 4H, CH_2CH_2CO, $CH_2CH{=}CH_2$), 2.26-2.36 (m, 1H, C*H*HCO), 2.39-2.47 (m, 1H, CH*H*CO), 3.43-3.67 (m, 4H, 2 × CH_2CH_3), 3.75-3.80 (m, 1H, CHN), 5.10 (dd, *J*=10.2, 1.6 Hz, 1H, C*H*H=CH), 5.20 (dd, *J*=17.2, 1.6 Hz, 1H, CH*H*=CH), 5.82-5.92 (m, 2H, $CH(OEt)_2$, $CH{=}CH_2$); ^{13}C NMR (75 MHz, DMSO): δ 14.7 (CH_3), 23.5 (CH_2), 28.8 (CH_2), 29.9 (CH_2), 33.1 (CH_2), 53.8 (CH), 61.6 (CH_2), 61.7 (CH_2), 99.1 (CH), 114.7 ($CH_2{=}CH$), 138.2 ($CH{=}CH_2$), 174.8 (C=O); MS (CI^+) m/z (%) : 264(MNa^+, 34), 196 (100), 182 (19), 168 (55); HRMS: $[MNa]^+$ found 264.15684, $C_{13}H_{23}O_3NNa$ requires 264.15701.

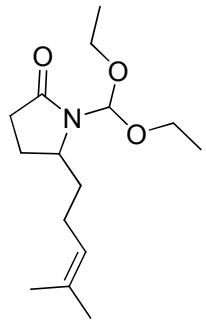
1-(Diethoxymethyl)-5-(pent-4-enyl)pyrrolidin-2-one 286



A mixture of the amide **281** (894 mg, 5.84 mmol, 1 eq.), aluminium chloride (116 mg, 0.87 mmol, 0.15 eq.) and triethyl orthoformate (42.0 ml, 253 mmol, 43 eq.) was heated at 155 °C for 18 hours. The reaction mixture was cooled to room temperature before being quenched with a saturated aqueous solution of sodium bicarbonate (30 ml). The separated aqueous phase was extracted with ethyl acetate (3 × 40 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The triethyl orthoformate was evaporated under high vacuum and the residue was purified by column chromatography (diethyl ether:petroleum ether 3:1) to give **286** as a yellow-orange oil (875 mg, 59%).

IR (film): ν_{max} 3076, 2976, 1705 (s), 1414 (s), 1105 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 1.17 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.19 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.33-1.50 (m, 3H, $CH_2CH_2CH=CH_2$, CHHCHN), 1.64-1.72 (m, 1H, CHHCH$_2$CO), 1.88-1.96 (m, 1H, CHHCHN), 2.04-2.15 (m, 3H, $CH_2CH=CH_2$, CHHCH$_2$CO), 2.29 (ddd, *J*=16.9, 9.7, 5.8 Hz, 1H, CHHCO), 2.40 (ddd, *J*=16.9, 9.4, 7.3 Hz, 1H, CHHCO), 3.45-3.64 (m, 4H, 2 × OCH_2), 3.73-3.80 (m, 1H, CHN), 4.99-5.03 (m, 1H, CHH=CH), 5.04-5.10 (m, 1H, CHH=CH), 5.80-5.90 (m, 2H, $CH(OEt)_2$, CH=CH_2); ^{13}C NMR (125 MHz, DMSO): δ 14.7 (CH_3), 14.8 (CH_3), 23.7 (CH_2), 30.1 (CH_2), 33.2 (CH_2), 33.7 (CH_2), 54.2 (CH), 61.6 (CH_2), 61.8 (CH_2), 100.0 (CH), 114.8 (CH_2=CH), 138.6 (CH=CH_2), 175.2 (C=O); MS (FAB) m/z (%) : 278 (MNa^+, 100), 248 (7), 199 (7), 173 (19); HRMS: $[MNa]^+$,found 278.17284, $C_{14}H_{25}O_3NNa$ requires 278.17320.

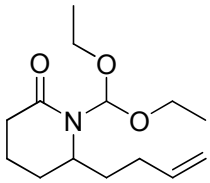
1-(Diethoxymethyl)-5-(4-methylpent-3-enyl)pyrrolidin-2-one 287



A mixture of the amide **282** (130 mg, 0.78 mmol, 1 eq.), aluminium chloride (20.0 mg, 0.15 mmol, 0.19 eq.) and triethyl orthoformate (15 ml, 30 mmol, 38.5 eq.) was heated at 155 °C for 18 hours. The reaction mixture was cooled to room temperature before being quenched with a saturated aqueous solution of sodium bicarbonate (15 ml). The separated aqueous phase was extracted with ethyl acetate (4 × 20 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The triethyl orthoformate was evaporated under high vacuum and the residue was purified by column chromatography (diethyl ether:petroleum ether 3:1) to give **287** as a yellow-orange oil (189 mg, 90%).

IR (film): ν_{max} 2976, 1705 (s), 1413, 1263 (s), 1062 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 1.17 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 1.19 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 1.41-1.51 (m, 1H, $CHHCH_2CO$), 1.63 (s, 3H, CH_3CCH_3), 1.71 (s, 3H, CH_3CCH_3), 1.72-1.76 (m, 1H, $CHHCH_2CO$), 1.88-2.06 (m, 3H, $CHHCH=C$, CH_2CHN), 2.09-2.16 (m, 1H, $CHHCH=C$), 2.30 (ddd, *J*=16.9, 9.6, 6.0 Hz, 1H, $CHHCO$), 2.41 (ddd, *J*=16.9, 9.5, 7.1 Hz, 1H, $CHHCO$), 3.42-3.65 (m, 4H, 2 × CH_2CH_3), 3.69-3.78 (m, 1H, CHN), 5.10-5.17 (m, 1H, CH=C), 5.85 (s, 1H, $CH(OEt)_2$); ^{13}C NMR (125 MHz, DMSO): δ 14.7 (CH_3), 14.8 (CH_3), 17.5 (CH_3), 23.4 (CH_2), 23.7 (CH_2), 25.5 (CH_3), 30.1 (CH_2), 34.3 (CH_2), 54.1 (CH), 61.7 (CH_2), 61.8 (CH_2), 100.0 (CH), 123.9 ($CH=C$), 131.6 ($C=CH$), 175.2 (C=O); MS (FAB) m/z (%) : 292 (MNa^+, 100), 190 (12), 173 (27); HRMS: $[MNa]^+$, found 292.18933, $C_{15}H_{27}O_3N$ requires 292.18885.

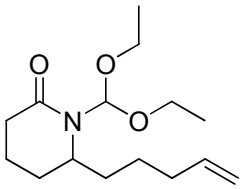
6-(But-3-enyl)-1-(diethoxymethyl)piperidin-2-one 288



A mixture of the amide **283** (965 mg, 6.30 mmol, 1 eq.), aluminium chloride (126 mg, 0.95 mmol, 0.15 eq.) and triethyl orthoformate (46.0 ml, 276 mmol, 44 eq.) was heated at 155 °C for 18 hours. The reaction mixture was cooled to room temperature before being quenched with Et_3N (0.2 ml) and a saturated aqueous solution of sodium bicarbonate (30 ml). The separated aqueous phase was extracted with ethyl acetate (3 × 40 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The triethyl orthoformate was evaporated under high vacuum and the residue was purified by column chromatography (diethyl ether:petroleum ether 4:1) to give **288** as a pale yellow oil (671 mg, 42%).

IR (film): ν_{max} 2976 (s), 2359 (w), 1655 (s), 1439 (s), 1412, 1292, 1103 (s), 1063 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ 1.17 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.18 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.55-1.73 (m, 3H, C*H*HCH_2CO, C*H*HCHN, C*H*HCH_2CH_2CO), 1.80-1.95 (m, 3H, CH*H*CH_2CO, CH*H*CHN, CH*H*CH_2CH_2CO), 1.96-2.06 (m, 1H, C*H*$HCH=CH_2$), 2.07-2.16 (m, 1H, CH*H*$CH=CH_2$), 2.26-2.43 (m, 2H, CH_2CO), 3.40-3.47 (m, 1H, OC*H*HCH_3), 3.49-3.57 (m, 2H, OC*H*HCH_3, OCH*H*CH_3), 3.62-3.68 (m. 1H, OCH*H*CH_3), 3.68-3.74 (m, 1H, CHN), 5.01 (dd, *J*=10.4, 1.3 Hz, 1H, C*H*H=CH), 5.10 (dq, *J*=17.2, 1.7 Hz, 1H, CH*H*=CH), 5.80-5.88 (m, 1H, C*H*=CH_2), 6.25 (s, 1H, $CH(OEt)_2$); ^{13}C NMR (125 MHz, DMSO): δ 14.8 (CH_3), 15.4 (CH_2), 24.6 (CH_2), 30.0 (CH_2), 30.8 (CH_2), 32.0 (CH_2), 48.7 (CH), 61.6 (CH_2), 62.0 (CH_2), 100.2 (CH), 114.9 (*C*H_2=CH), 138.2 (*C*H=CH_2), 170.1 (C=O); MS (CI^+) m/z (%) : 278 (MNa^+, 100), 232 (17), 176 (31); HRMS: $[MNa]^+$, found 278.17413, $C_{14}H_{25}O_3NNa$ requires 278.17321.

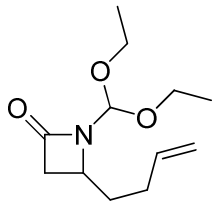
1-(Diethoxymethyl)-6-(pent-4-enyl)piperidin-2-one 289



A mixture of the amide **284** (975 mg, 5.83 mmol, 1 eq.), aluminium chloride (117 mg, 0.88 mmol, 0.15 eq.) and triethyl orthoformate (43.0 ml, 258 mmol, 44 eq.) was heated at 155 °C for 18 hours. The reaction mixture was cooled to room temperature before being quenched with Et_3N (0.2 ml) and a saturated aqueous solution of sodium bicarbonate (30 ml). The separated aqueous phase was extracted with ethyl acetate (3 × 40 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The triethyl orthoformate was evaporated under high vacuum and the residue was purified by column chromatography (diethyl ether:petroleum ether 4:1) to give **289** as a pale yellow oil (859 mg, 55%).

IR (film): ν_{max} 3481 (w), 3076, 2976 (s), 2930 (s), 2359, 1659 (s), 1439 (s), 1414 (s), 1292 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ 1.17 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.18 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.28-1.36 (m, 1H, $CHHCH_2CH=CH_2$), 1.36-1.45 (m, 1H, $CHHCH_2CH=CH_2$), 1.51-1.63 (m, 2H, CHHCHN, $CHHCH_2CH_2CO$), 1.63-171 (m, 1H, $CHHCH_2CO$), 1.77-1.90 (m, 3H, CHHCHN, $CHHCH_2CH_2CO$, $CHHCH_2CO$), 2.03-2.09 (m, 2H, $CH_2CH=CH_2$), 2.28-2.44 (m, 2H, CH_2CO), 3.40-3.47 (m, 1H, $OCHHCH_3$), 3.47-3.55 (m, 2H, $OCHHCH_3$, $OCHHCH_3$), 3.60-3.67 (m, 1H, $OCHHCH_3$), 3.67-3.75 (m, 1H, CHN), 4.95-5.02 (m, 1H, CHH=CH), 5.07 (ddd, *J*=17.2, 3.6, 1.7 Hz, 1H, CH*H*=CH), 5.81-5.90 (m, 1H, $CH=CH_2$), 6.25 (s, 1H, $CH(OEt)_2$); ^{13}C NMR (125 MHz, DMSO): δ 14.8 (CH_3), 15.4 (CH_2), 24.8 (CH_2), 25.0 (CH_2), 30.8 (CH_2), 32.6 (CH_2), 33.1 (CH_2), 49.0 (CH), 61.5 (CH_2), 61.9 (CH_2), 100.1 (CH), 114.9 (CH_2=CH), 138.5 ($CH=CH_2$), 170.0 (C=O); MS (EI) m/z (%) : 292 (MNa^+, 100), 278 (12), 246 (22), 190 (22); HRMS: $[MNa]^+$, found 292.18912, $C_{15}H_{27}O_3NNa$ requires 292.18886

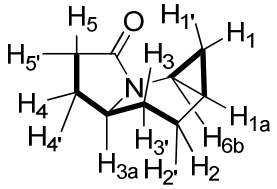
4-(But-3-enyl)-1-(diethoxymethyl)azetidin-2-one 290



A mixture of the amide **279** (1.0g, 8.0 mmol, 1 eq.), aluminium chloride (168 mg, 1.26 mmol, 0.16 eq.) and triethyl orthoformate (59.0 ml, 355 mmol, 44 eq.) was heated at 155 °C for 36 hours. The reaction mixture was cooled to room temperature before being quenched with a saturated aqueous solution of sodium bicarbonate (30 ml). The separated aqueous phase was extracted with ethyl acetate (3 × 40 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The triethyl orthoformate was evaporated under high vacuum and the residue was purified by column chromatography (diethyl ether:petroleum ether 1:1) to give **290** as a pale yellow oil (580 mg, 32%).

IR (film): ν_{max} 2978, 1765 (s), 1641, 1381, 1063 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ 1.18 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.19 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.57-1.66 (m, 1H, C*H*HCHN), 1.90-1.98 (m, 1H, CH*H*CHN), 2.08-2.20 (m, 2H, $CH_2CH{=}CH_2$), 2.63 (dd, *J*=14.9, 2.7 Hz, 1H, C*H*HCO), 3.04 (dd, *J*=14.9, 5.4 Hz, 1H, CH*H*CO), 3.52-3.65 (m, 4H, 2 × OCH_2CH_3), 3.71-3.76 (m, 1H, CHN), 5.0-5.04 (m, 1H, C*H*H=CH), 5.09 (ddd, *J*=17.2, 3.6, 1.7 Hz, 1H, CH*H*=CH), 5.59 (s, 1H, $CH(OEt)_2$), 5.83-5.92 (m, 1H, C*H*=CH_2); ^{13}C NMR (125 MHz, DMSO): δ 14.8 (CH_3), 29.4 (CH_2), 33.0 (CH_2), 41.2 (CH_2), 49.0 (CH), 61.2 (CH_2), 61.4 (CH_2), 97.4 (CH), 115.0 (*C*H_2=CH), 138.0 (*C*H=CH_2), 166.2 (C=O); MS (CI^+) m/z (%) : 228 (MH^+, 10), 182 (10), 155 (10), 103 (10); HRMS: $[MH]^+$ found 228.15915, $C_{12}H_{22}O_3N$ requires 228.15996.

Hexahydro-1*H*-cyclopropa[e]indolizin-6(7aH)-8-one 291

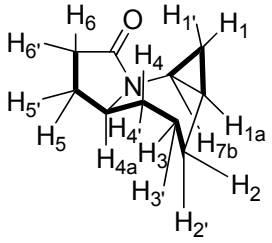


A solution of **285** (142 mg, 0.59 mmol, 1 eq.) in diethyl ether (2 ml) was added dropwise *via* syringe pump (0.6 ml.h^{-1}) to a vigorously stirred mixture of zinc amalgam (481 mg, 7.36 mmol, 12.5 eq.), zinc chloride (1.0 M solution in diethyl ether, 0.74 ml, 0.74 mmol, 1.25 eq.), trimethylsilyl chloride (0.47 ml, 3.68 mmol, 6.2 eq.) in diethyl ether (2 ml) at reflux. The resulting mixture was stirred at reflux for 16 hours. A mixture of zinc dust (481 mg) and copper(I) chloride (50 mg) was then added and the resulting mixture was stirred for an additional 4 hours, cooled to room temperature, treated with Et_3N (1 ml) and was stirred for a further 30 min. The resulting mixture was treated with a saturated aqueous solution of sodium bicarbonate (5 ml), stirred for a further 10 min, filtered and the separated zinc washed with ethyl acetate. The separated aqueous phase was extracted with ethyl acetate (2 × 7 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (2% methanol in ethyl acetate) to give **291** (36 mg, >95 % purity, 41%)**,** contaminated by trace of **5-(but-3-enyl)pyrrolidin-2-one 280** (<5%), as a colourless oil.

IR (film): ν_{max} 3441, 2928, 2858, 1666 (s), 1444, 1279, 1014 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.29 (ddd, *J*=6.7, 5.6, 3.3 Hz, 1H, H-1'), 0.90 (ddd, *J*=9.5, 6.8, 5.6 Hz, 1H, H-1), 1.02 (dddd, *J*=13.4, 12.8, 11.5, 4.5 Hz, 1H, H-3), 1.23 (dddd, *J*=9.5, 7.8, 6.7, 1.2 Hz, 1H, H-1a), 1.45 (dddd, *J*=12.7, 10.9, 9.7, 8.8 Hz, 1H, H-4), 1.75 (dddd, *J*=13.4, 5.4, 2.6, 2.2 Hz, 1H, H-3'), 1.82 (ddd, *J*=13.9, 12.8, 5.4 Hz, 1H, H-2), 1.99 (dddd, *J*=13.9, 4.5, 2.2, 1.2 Hz, 1H, H-2'), 2.13 (dddd, *J*=12.7, 9.2, 6.7, 2.2 Hz, 1H, H-4'), 2.24 (ddd, *J*=16.8, 9.7, 2.2 Hz, 1H, H-5), 2.33 (ddd, *J*=16.8, 10.9, 9.2 Hz, 1H, H-5'), 2.92 (ddd, *J*=7.8, 6.8, 3.3 Hz, 1H, H-6b), 3.24 (dddd, *J*=11.5, 8.8, 6.7, 2.6 Hz, 1H, H-3a); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.1 (CH), 11.2 (CH_2), 20.7 (CH_2), 26.0 (CH), 26.3 (CH_2),

29.2 (CH_2), 30.2 (CH_2), 55.2 (CH), 176.1 (C=O); MS (CI^+) m/z (%) : 151 (M^+, 100), 136 (38), 96 (63); HRMS: $[M]^+$, found 151.09928, $C_9H_{13}ON$ requires 151.09971.

Octahydro-7a-aza cyclopropa[e]azulen-7-one 292

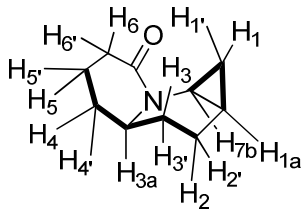


A solution of **286** (239 mg, 0.94 mmol, 1 eq.) in diethyl ether (2 ml) was added dropwise *via* syringe pump (0.6 ml.h^{-1}) to a vigorously stirred mixture of zinc amalgam (765 mg, 11.5 mmol, 12.2 eq.), zinc chloride (1.0 M solution in diethyl ether, 1.17 ml, 1.17 mmol, 1.25 eq.), trimethylsilyl chloride (0.75 ml, 5.87 mmol, 6.24 eq.) in diethyl ether (4 ml) at reflux. The resulting mixture was stirred at reflux for 16 hours, cooled to room temperature, treated with Et_3N (1 ml) and stirred for a further 30 min. The resulting mixture was treated with a saturated aqueous solution of sodium bicarbonate (5 ml), stirred for a further 20 min, filtered and the separated zinc washed with ethyl acetate (5 ml). The aqueous phase was separated and extracted with ethyl acetate (3 × 10 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane:acetone 4:1) to give a mixture of the cyclopropane **292** and **1-methyl-5-(pent-4-enyl)pyrrolidin-2-one** (73 mg, **292**:**1-methyl-5-(pent-4-enyl)pyrrolidin-2-one** 8:1 as determined by ^{1}H NMR spectrum) as a yellow solid. The yield of **292** (65 mg, 41%) was calculated from ^{1}H NMR spectrum.

IR (film): ν_{max} 2922, 1782 (s), 1425, 1325, 1242 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (ddd, *J*=6.1, 5.5, 4.1 Hz, 1H, H-1'), 0.91 (dddd, *J*=14.2, 11.3, 10.0, 1.4 Hz, 1H, H-2), 0.94 (ddddd, *J*=10.8, 7.2, 6.5, 6.1 Hz, 1H, H-1a), 1.13 (ddd, *J*=8.0, 7.6, 5.5 Hz, 1H, H-1), 1.38 (dddd, *J*=13.4, 12.3, 11.4, 3.1 Hz, 1H, H-4) 1.49 (ddddd, *J*=14.0, 12.3, 11.3, 2.6, 1.3 Hz, 1H, H-3), 1.56 (dddd, *J*=12.7, 10.1, 2.9, 2.8 Hz, 1H, H-5), 1.74 (ddddd, *J*=14.0, 6.5, 4.7, 3.1, 1.4 Hz, 1H, H-3'), 1.87 (dddd, *J*=13.4, 4.7, 2.9, 2.6 Hz, 1H, H-4'), 2.21 (dddd, *J*=12.7, 9.9, 9.6, 8.5 Hz, 1H, H-5'), 2.24 (ddd, *J*=16.7, 9.9, 2.8 Hz, 1H, H-6'), 2.29 (dddd, *J*=14.2, 6.5, 6.5, 1.3 Hz, 1H, H-2'), 2.34 (ddd, *J*=7.6, 7.2, 4.1 Hz, 1H, H-7b), 2.48 (ddd, *J*=16.7, 10.1, 9.6 Hz, 1H, H-6), 3.65 (dddd, *J*=11.4, 8.5, 2.9, 2.9 Hz,

1H, H-4a); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.7 (CH_2), 17.3 (CH), 26.2 (CH_2), 26.7 (CH_2), 29.3 (CH), 30.7 (CH_2), 31.2 (CH_2), 39.0 (CH_2), 62.4 (CH), 177.2 (C=O); MS (EI) m/z (%) : 165 (M^+, 55), 150 (86), 98 (97), 84 (100); HRMS: $[M]^+$, found 165.11536, $C_{10}H_{15}ON$ requires 165.11482.

Octahydro-7a-aza cyclopropa[α]naphtalene-7-ene 293

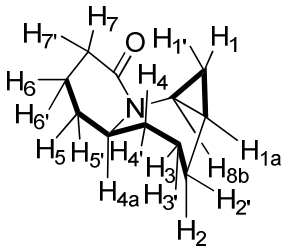


A solution of the **288** (503 mg, 1.97 mmol, 1 eq.) in diethyl ether (2 ml) was added dropwise *via* syringe pump (0.6 ml.h^{-1}) to a vigorously stirred mixture of zinc (1.61 g, 24.6 mmol, 12.5 eq.), copper(I) chloride (161 mg, 1.63 mmol, 0.8 eq.), zinc chloride (1.0 M solution in diethyl ether, 2.46 ml, 2.46 mmol, 1.25 eq.), trimethylsilyl chloride (1.57 ml, 12.4 mmol, 6.3 eq.) in diethyl ether (5 ml) at reflux. The resulting mixture was stirred at reflux for 16 hours, cooled to room temperature, treated with Et_3N (1.7ml) and stirred for a further 30 min. The resulting mixture was treated with a saturated aqueous solution of sodium bicarbonate (5 ml), stirred for a further 20 min. The solution was filtered and the separated zinc washed with ethyl acetate. The aqueous phase was separated, extracted with ethyl acetate (3 × 10 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (methanol:acetone:ethyl acetate :1:1:50) to give a mixture of the cyclopropane **293** and **6-(but-3-enyl)-piperidin-2-one 283** (300 mg, **293**: **283** 1:3.7 as determined by ^{1}H NMR spectrum) as a yellow oil. The yield of **293** (68 mg, 21%) was calculated from ^{1}NMR spectrum. 4 mg of **293** were also isolated (77% purity).

IR (film): ν_{max} 3458, 2939 (s), 1671 (s), 1447, 1416, 1344, 1180 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ0.31 (ddd, *J*=6.9, 5.5, 3.7 Hz, 1H, H-1'), 0.94 (ddd, *J*=9.4, 7.3, 5.5 Hz, 1H, H-1), 1.13 (dddd, *J*=13.8, 13.2, 11.4, 5.0 Hz, 1H, H-3), 1.26 (ddddd, *J*=9.4, 7.8, 6.9, 5.4, 1.2 Hz, 1H, H-1a), 1.32 (dddd, *J*=13.4, 12.7, 10.7, 3.1 Hz, 1H, H-4), 1.60 (dddd, *J*=13.8, 5.4, 2.1, 2.0 Hz, 1H, H-3'), 1.66 (ddddd, *J*=13.0, 12.7, 12.2, 5.4, 2.6 Hz, 1H, H-5), 1.80 (ddddd, *J*=13.0, 6.2, 4.6, 3.1, 2.6 Hz, 1H, H-5'), 1.84 (dddd, *J*=13.6, 13.2, 5.4, 5.4 Hz, 1H, H-2), 1.85 (dddd, *J*=13.4, 4.6, 2.6, 2.1 Hz, 1H, H-4'), 1.96 (dddd, *J*=13.6, 5.0, 2.1, 1.2 Hz, 1H, H-2'), 2.32 (ddd, *J*=17.7, 12.2, 6.2 Hz, 1H, H-6), 2.50 (dddd,

J=17.7, 5.4, 2.6, 2.1 Hz, 1H, H-6'), 3.08 (ddd, *J*=7.8, 7.3, 3.7 Hz, 1H, H-7b), 3.11 (dddd, *J*=11.4, 10.7, 4.6, 2.0 Hz, 1H, H-3a); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.4 (CH_2), 11.4 (CH), 20.0 (CH_2), 21.0 (CH_2), 29.3 (CH_2), 29.4 (CH), 30.7 (CH_2), 33.7 (CH_2), 55.3 (CH), 171.2 (C=O); MS (CI^+) m/z (%) : 166 (MH^+, 100); HRMS: $[MH]^+$ found 166.12275, $C_{10}H_{16}ON$ requires 166.12319.

Decahydro-8a-aza benzo[α]cyclopropa[c]cyclohepten-8-one 294

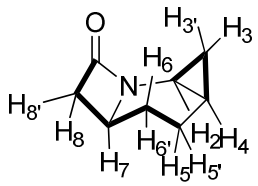


A solution of **289** (400 mg, 1.49 mmol, 1 eq.) in diethyl ether (2 ml) was added dropwise *via* syringe pump (0.6 ml.h^{-1}) to a vigorously stirred mixture of zinc (1.94 g, 29.7 mmol, 20 eq.), copper(I) chloride (194 mg, 1.96 mmol, 1.3 eq.), zinc chloride (1.0 M solution in diethyl ether, 2.97 ml, 2.97 mmol, 2 eq.), trimethylsilyl chloride (1.88 ml, 14.8 mmol, 10 eq.) in diethyl ether (5 ml) at reflux. The resulting mixture was stirred at reflux for 16 hours, cooled to room temperature, then treated with a saturated aqueous solution of sodium bicarbonate (5 ml), stirred for a further 20 min, filtered and the separated zinc washed with ethyl acetate (5 ml). The aqueous phase was separated, extracted with ethyl acetate (3 × 10 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (methanol:acetone:ethylacetate :1:1:50) to give the cyclopropane **294** together with **6-(pent-4-enyl)piperidin-2-one 284** (70 mg, **294**: **284** 2.7:1 as determined by ^{1}H NMR spectrum) and pure **294** (34 mg) as a yellow solid. The yield of **294** (70 mg, 26%) was calculated from ^{1}H NMR spectrum.

M.p. 54-58 °C (MeOH); IR (film): ν_{max} 2930, 1663 (s), 1411, 1331, 1186 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.74 (ddd, *J*=6.1, 5.8, 4.3 Hz, 1H, H-1'), 0.97 (m, 1H, H-1a), 1.01 (dddd, *J*=14.3, 11.5, 9.4, 1.9 Hz, 1H, H-2), 1.14 (ddd, *J*=8.3, 7.8, 6.1 Hz, 1H, H-1), 1.51 (m, 1H, H-3), 1.64 (m, 1H, H-4), 1.66 (m, 1H, H-5'), 1.69 (m, 1H, H-4'), 1.70 (m, 1H, H-6'), 1.73 (m, 1H, H-3'), 1.80 (m, 1H, H-5), 1.85 (m, 1H, H-6), 2.22 (m, 1H, H-2'), 2.35 (dd, *J*=18.3, 10.0, 1.1 Hz, 1H, H-7), 2.40 (m, 1H, H-8b), 2.41 (m, 1H, H-7'), 3.58 (m, 1H, H-4a); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.4 (CH_2), 17.2 (CH_2), 17.5 (CH), 26.4 (CH_2), 30.0 (CH_2), 30.1 (CH_2), 32.3 (CH_2), 34.4 (CH), 36.5 (CH_2), 60.5

(CH), 172.6 (C=O); MS (CI^+) m/z (%) : 180 (MH^+, 14), 168 (100), 98 (5); HRMS: $[MH]^+$ found 180.13868, $C_{11}H_{18}ON$ requires 180.13884.

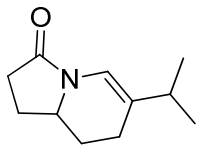
1-Azatricyclo[5.2.0.0^{2,4}]nonan-9-one 295



A solution of **290** (256 mg, 1.13 mmol, 1 eq.) in diethyl ether (2.5 ml) was added dropwise *via* syringe pump (0.6 ml.h^{-1}) to a vigorously stirred mixture of zinc (921 mg, 14.1 mmol, 12.5 eq.), copper(I) chloride (92.0 mg, 0.83 mmol, 0.8 eq.), zinc chloride (1.0 M solution in diethyl ether, 1.4 ml, 1.4 mmol), trimethylsilyl chloride (0.9 ml, 7.0 mmol, 6.2 eq.) in diethyl ether (7 ml) at reflux. The resulting mixture was stirred at reflux for 16 hours, then cooled to room temperature, treated with Et_3N (1 ml) and stirred for a further 30 min. The resulting mixture was treated with a saturated aqueous solution of sodium bicarbonate (5 ml), stirred for a further 20 min, filtered and the separated zinc washed with ethyl acetate. The aqueous phase was separated, extracted with ethyl acetate (3 × 10 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (diethyl ether:petroleum ether 1:1) to give the cyclopropane **295** as a yellow oil (32 mg, > 90% purity, 21%) contaminated by trace of 4-(but-3-enyl)azetidin-2-one **279**(<10 %).

IR (film): ν_{max} 2932, 1747 (s), 1394, 1192 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.52 (ddd, *J*=6.7, 5.8, 3.1 Hz, 1H, H-3'), 0.85 (ddd, *J*=9.3, 6.2, 5.8 Hz, 1H, H-3), 1.07 (dddd, *J*=13.2, 12.9, 11.1, 4.6 Hz, 1H, H-6), 1.12 (ddddd, *J*=9.3, 7.9, 6.7, 4.8, 1.7 Hz, 1H, H-4), 1.87 (dddd, *J*=14.1, 12.9, 4.8, 4.7 Hz, 1H, H-5), 1.90 (dddd, *J*=12.3, 4.7, 3.3, 3.2 Hz, 1H, H-6'), 2.03 (dddd, *J*=14.1, 4.6, 3.2, 1.7 Hz, 1H, H-5'), 2.34 (dd, *J*=14.8, 1.8 Hz, 1H, H-8'), 2.64 (dddd, *J*=7.9, 6.2, 3.1, 1.7 Hz, 1H, H-2), 3.00 (ddd, *J*=14.8, 4.6, 1.7 Hz, 1H, H-8), 3.10 (dddd, *J*=11.1, 4.6, 3.3, 1.8 Hz, 1H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.4 (CH), 12.3 (CH_2), 19.7 (CH_2), 24.0 (CH), 26.4 (CH_2), 43.5 (CH_2), 45.7 (CH), 170.9 (C=O); MS (CI$^+$) m/z (%) : 138 (MH^+, 100), 126 (13), 112 (8), 89 (94); HRMS: $[MH]^+$ found 138.09216, $C_8H_{12}ON$ requires 138.09188.

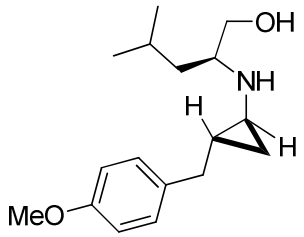
6-Isopropyl-1,7,8,8a-tetrahydro-2*H*-indolizin-3-one 296



A solution of **287** (150 mg, 0.56 mmol, 1 eq.) in diethyl ether (2 ml) was added dropwise *via* syringe pump (0.6 ml.h^{-1}) to a vigorously stirred mixture of zinc amalgam (455 mg, 6.96 mmol, 12.5 eq.), zinc chloride (1.0 M solution in diethyl ether, 0.7 ml, 0.7 mmol, 1.25 eq.), trimethylsilyl chloride (0.45 ml, 3.52mmol, 6.3 eq.) in diethyl ether (5 ml) at reflux. The resulting mixture was stirred at reflux for 16 hours, cooled to room temperature, treated with Et_3N (0.6 ml) and was stirred for a further 30 min. The resulting mixture was treated with a saturated aqueous solution of sodium bicarbonate (5 ml), stirred for a further 20 min, filtered and the separated zinc washed with ethyl acetate (5 ml). The separated aqueous phase was extracted with ethyl acetate (3 × 10 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give **296** as a yellow oil (< 5%).

IR (film): ν_{max} 2928, 1693 (s), 1410, 1315 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ1.03 (d, *J*=6.5 Hz, 3H, C*H*$_3$CCH$_3$), 1.04 (d, *J*=6.5 Hz, 3H, CH$_3$CC*H*$_3$), 1.46-1.52 (m, 1H, C*H*HCHN), 1.57-1.66 (m, 2H, C*H*HCH$_2$CO, CH*H*CHN), 2.08-2.11 (m, 1H, C*H*HC=CH), 2.16-2.29 (m, 3H, CHMe$_2$, CH*H*C=CH, CH*H*CH$_2$CO), 2.37-2.51 (m, 2H, CH$_2$CO), 3.59-3.66 (m, 1H, CHN), 6.64 (s, 1H, NCH=C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.0 (CH$_3$), 21.6 (CH$_3$), 24.2 (CH$_2$), 26.4 (CH$_2$), 29.0 (CH$_2$), 31.5 (CH$_2$), 32.7 (CH), 55.8 (CH), 114.9 (*C*H=C), 127.9 (*C*=CH), 170.8 (C=O); MS (EI) m/z (%) : 178 (M-H, 77), 164 (100), 138 (79), 127(25); HRMS: [M]$^+$, found 179.13122, $C_{11}H_{17}ON$ requires 179.13047.

(*S*)-2-((1*S*,2*S*)-2-(4-Methoxybenzyl)cyclopropylamino)-4-methylpentan-1-ol 304

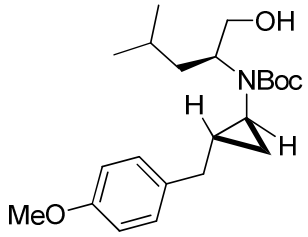


Lithium hydroxide monohydrate (789 mg, 18.8 mmol, 33 eq.) was added in one portion to a suspension of the *N*-cyclopropyl oxazolidinone **256** (190 mg, 0.57 mmol, 1 eq.) in a mixture of ethanol (8.55 ml) and water (3.8 ml). The reaction was heated at 84 °C for 36 hours and then allowed to cool to room temperature. The solution was concentrated to *ca.* one third of its volume and an aqueous saturated solution of ammonium chloride (6 ml) was added. The separated aqueous phase was extracted with dichloromethane (3 × 5 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (2% triethylamine in ethyl acetate) to give the aminocyclopropane **304** as a yellow solid (106 mg, 67%);

M.p. 56-59 °C (EtOAc); $[\alpha]_D^{20}$ +31.3 (*c* 1.01, $CHCl_3$); IR (film): ν_{max} 3364 (w), 2959, 1612 (w), 1512, 1468 (w), 1265, 1246, 1177 (w), 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ0.41-0.48 (m, 1H, C*H*HCHN), 0.62 (ddd, *J*=8.8, 4.9, 3.8 Hz, 1H, CH*H*CHN), 0.85 (d, *J* = 6.6 Hz, 3H, C*H*$_3$CHCH$_3$), 0.87 (d, *J*=6.6 Hz, 3H, CH$_3$CHC*H*$_3$), 0.92-1.00 (m, 1H, C*H*CHN), 1.16 (dt, *J*=13.9, 7.0 Hz, 1H, CH*H*CHMe$_2$), 1.36 (ddd, *J*=13.9, 7.6, 6.6 Hz, 1H, C*H*HCHMe$_2$), 153-1.63 (m, 1H, CHMe$_2$), 2.04 (dt, *J*=6.7, 3.3 Hz, 1H, CHN), 2.10 (br s, 2H, NH, OH), 2.41-2.53 (m, 2H, C*H*$_2$Ar), 2.62-2.70 (m, 1H, C*H*CH$_2$OH), 3.11 (dd, *J*=10.5, 6.7 Hz, 1H, CH*H*OH), 3.50 (dd, *J*=10.5, 4.2 Hz, 1H, C*H*HOH), 3.79 (s, 3H, OCH$_3$), 6.82 (d, *J*=8.7 Hz, 2H, Ar-H), 7.12 (d, *J*=8.7 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ13.7 (CH_2), 22.6 (CH_3), 23.0 (CH_3), 22.4 (CH), 24.9 (CH), 35.2 (CH), 37.5 (CH_2), 41.5 (CH_2), 55.3 (CH_3), 57.4 (CH), 63.2 (CH_2), 113.8 (CH-Ar), 129.3 (CH-Ar), 133.5 (C-Ar), 157.9 (C-Ar), MS (CI^+) *m/z* (%): 278 (MH^+,

100), 260 (18), 220 (12), 170 (14), 156 (90); HRMS: $[MH]^+$, found 278.21125, $C_{17}H_{28}O_2N$ requires 278.21199.

_N_-*tert*-Butoxycarbonyl-(*S*)-2-((1*S*,2*S*)-2-(4-methoxybenzyl)cyclopropylamino)-4-methylpentan-1-ol 305

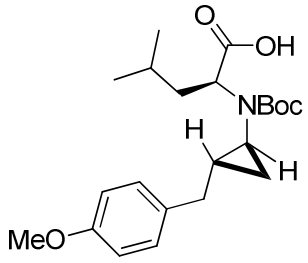


A solution of di-*tert*-butyl dicarbonate (96.0 mg, 0.44 mmol, 1.2 eq.) in dichloromethane (2.5 ml) was added to a solution of aminocyclopropane **304** (104 mg, 0.37 mmol, 1 eq.) in dichloromethane (2.5 ml). The resulting mixture was stirred at reflux for 24 hours. The cooled reaction mixture was treated with a saturated aqueous solution of sodium bicarbonate (3 ml) and the separated aqueous phase was extracted with dichloromethane (2 × 4 ml). The combined organic extracts were washed with water (8 ml), brine (8 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether:ethyl acetate 3:1) to give the boc-protected aminocyclopropane **305** as a pale yellow oil (111 mg, 80%).

$[\alpha]_D^{27}$ −48.11 (*c* 0.846, $CHCl_3$); IR (film): ν_{max} 3019, 1685 (w), 1653 (w), 1513, 1216 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.68-0.74 (m, 1H, C*H*HCHN), 0.85 (d, *J*=6.6 Hz, 3H, CH_3CCH_3), 0.87 (d, *J*=6.6 Hz, 3H, CH_3CCH_3), 0.86-0.89 (m, 1H, CH*H*CHN), 1.19-1.28 (m, 1H, C*H*CHN), 1.47 (s, 9H, 3 × CCH_3), 1.48-1.55 (m, 2H, $CHMe_2$, C*H*HCHMe_2), 1.61 (ddd, *J*=13.8, 8.7, 5.8 Hz, 1H, CH*H*CHMe_2), 2.30 (dt, *J*=6.9, 3.4 Hz, 1H, CHN), 2.35 (dd, *J*=14.5, 8.2 Hz, 1H, CH*H*Ar), 2.81 (dd, *J*=14.5, 5.6 Hz, 1H, C*H*HAr), 3.45-3.58 (m, 2H, C*H*CH_2OH, C*H*HOH), 3.59-3.67 (m, 1H, CH*H*OH), 3.78 (s, 3H, OCH_3), 6.83 (d, *J*=8.7 Hz, 2H, Ar-H), 7.11 (d, *J*=8.7 Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.2 (CH_2), 22.6 (CH_3), 22.9 (CH_3), 25.0 (CH), 28.3 (CH), 28.5 (CH_3), 36.4 (CH), 37.0 (CH_2), 37.1 (CH_2), 55.2 (CH_3), 60.1 (CH), 65.6 (CH_2), 80.0 (C), 113.8 (CH-Ar), 129.7 (CH-Ar), 132.6 (C-Ar), 157.9 (C-Ar), 158.0 (C=O); MS (CI^+) *m/z*

(%): 378 (MH^+, 97), 322 (99), 306 (65), 278 (100), 156 (54), 121 (27); HRMS: $[MH]^+$, found 378.26454, $C_{22}H_{36}O_4N$ requires 378.26442.

***N*-*tert*-Butoxycarbonyl-((*S*)-2-((1*R*,2*S*)-2-(4-methoxybenzyl)cyclopropylamino)-4-methylpentanoic acid 306**

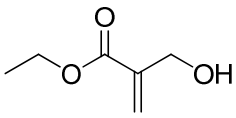


Sodium (*meta*)periodate (250 mg, 1.17 mmol, 4 eq.) was added portionwise to a mixture of aminocyclopropane **305** (110 mg, 0.29 mmol, 1 eq.), ruthenium (IV) oxide hydrate (2.2 mol%) in carbon tetrachloride (0.58 ml), acetonitrile (0.58 ml) and water (0.87 ml). The resulting mixture was stirred vigorously for 45 min at room temperature. Then dichloromethane (3 ml) was added, and the phases separated. The aqueous phase was extracted with dichloromethane (3 × 3 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was diluted with diethyl ether (6 ml), filtered through a celite pad and concentrated under reduced pressure. The crude product was purified by column chromatography (acetic acid:ethanol:dichloromethane 1:19:380) to give the cyclopropyl amino acid **306** as a pale brown oil (74 mg, 65%).

$[\alpha]_D^{27}$ –38.08 (*c* 0.73, $CHCl_3$); IR (film): ν_{max} 3018, 1691 (w), 1512 (w),1215 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.69-0.75 (m, 1H, C*H*HCHN), 0.85 (d, *J*=6.6 Hz, 3H, CH_3CHCH_3), 0.89 (d, *J*=6.6 Hz, 3H, CH_3CHCH_3), 0.93-1.00 (m, 1H, CH*H*CHN), 1.33-1.41 (m, 1H, C*H*CHN), 1.47 (s, 9H, 3 × CH_3), 1.51-1.59 (m, 2H, $CHMe_2$, CH*H*CHMe_2), 1.71-1.81 (m, 1H, C*H*HCHMe_2), 2.33 (dd, *J*=14.6, 8.5 Hz, 1H, C*H*HAr), 2.36-2.41 (m, 1H, CHN), 2.86 (dd, *J*=14.6, 5.3 Hz, 1H, CH*H*Ar), 3.79 (s, 3H, OCH_3), 3.92-4.09 (m, 1H, C*H*CO_2H) 6.83 (d, *J*=8.5 Hz, 2H, Ar-H), 7.12 (d, *J*=8.5 Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.6 (CH_2), 21.8 (CH_3), 22.9 (CH_3), 25.1 (CH), 28.4 (CH_3), 29.7 (CH), 36.9 (CH_2), 36.9 (CH_2), 38.0 (CH), 55.2 (CH_3), 61.2 (CH), 81.1 (C), 113.8 (CH-Ar), 129.4 (CH-Ar), 132.9 (C-Ar), 158.0 (C-Ar), 179.6 (C=O); MS

(CI$^+$) *m/z* (%): 392 (MH^+, 5), 336 (32), 292 (72), 170 (52), 121 (37); HRMS: $[MH]^+$, found 392.24436, $C_{22}H_{34}O_5N$ requires 392.24369.

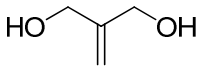
Ethyl 2-(hydroxymethyl)acrylate 315[146]



A saturated aqueous solution of potassium carbonate (5.39 g, 39.0 mmol, 1.7 eq.) was added dropwise over 1 hour to a mixture of triethylphosphonoacetate **314** (4.44 ml, 22.4 mmol, 1 eq.) and an aqueous solution of formaldehyde (37%, 7.24 ml, 89.2 mmol, 4 eq.). At the end of the addition the temperature reached 35 °C and stirring was continued for 1 hour. A saturated aqueous solution of ammonium chloride (20 ml) was then added and the mixture was extracted with diethyl ether (3 × 15 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (diethyl ether:petroleum ether 7:3) to give **315** as a pale yellow oil (2.04 g, 70%)

IR (film): ν_{max} 3437, 2983, 1718 (s), 1468, 1446, 1386, 1235 (s), 1149 (s), 1020 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.30 (t, *J*=7.1 Hz, 3H, CH_3), 2.21 (br s, 1H, OH), 4.22 (q, *J*=7.1 Hz, 2H, O*C*$H_2$$CH_3$), 4.30-4.31 (m, 2H, C$H_2$OH), 5.80-5.81 (m, 1H, C*H*H=C), 6.23-6.24 (m, 1H, CH*H*=C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (CH_3), 60.9 (CH_2), 62.6 (CH_2), 125.6 (CH_2), 139.5 (C), 166.3 (C=O); MS (CI^+) *m/z* (%): 131 (MH^+, 100), 133 (12), 85 (40); HRMS: $[MH]^+$, found 131.07043, $C_6H_{11}O_3$ requires 131.07082.

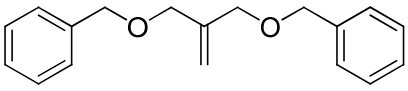
2-Methylenepropane-1,3-diol 316[172]



A solution of DIBAL-H (1.0 M in hexane, 33 ml, 33 mmol, 4.3 eq.) was added dropwise to a solution of **315** (1.0 g, 7.7 mmol, 1 eq.) in diethyl ether (30 ml) at –78 °C. The resulting mixture was allowed to warm to room temperature and was stirred for a further 1.5 hours. After cooling to 0 °C, the mixture was quenched by the addition of acetone (15 ml) followed by powdered sodium sulphate hexahydrate (ground with a pestle and mortar) until all reaction stopped. The resulting mixture was left to warm to room temperature and stirred for a further 16 hours. An excess of magnesium sulphate was added, the mixture was filtered, solids washed with ethyl acetate, and the resulting solution was evaporated under reduced pressure to give **316** as a yellow oil (602 mg, 89%).

IR (film): ν_{max} 3294 (br), 2970, 1709, 1658, 1454, 1011 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.16 (br s, 2H, 2 × OH), 4.20 (t, *J*=1.0 Hz, 4H, 2 × C*H*$_2$OH), 5.11 (t, *J*=1.0 Hz, 2H, CH_2=C); ^{13}C NMR (150 MHz, $CDCl_3$): δ 64.8 (CH_2), 112.4 (*C*H_2=C), 147.4 (*C*=CH_2).

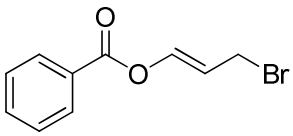
(2-Methylenepropane-1,3-diyl)bis(oxy)bis(methylene)dibenzene 317[147]



To a stirred solution of sodium hydride (60% in mineral oil, 382 mg, 9.55 mmol, 9.4 eq.) in *N*,*N* dimethylformamide (4 ml) were added a solution of diol **316** (300 mg, 3.41 mmol, 3.3 eq.) in *N*,*N* dimethylformamide (2ml), benzyl bromide (1.12 ml, 9.50 mmol, 9.3 eq.) and *n*-tetrabutylammonium iodide (377 mg, 1.02 mmol, 1 eq.). The resulting mixture was stirred at 40 °C for 16 hours and then quenched by the addition of brine and water. The separated organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified twice by column chromatography (petroleum ether: diethyl ether 3 :7 to 9 : 1) to give **317** as a yellow oil (663 mg, 72%).

IR (film): ν_{max} 3030, 2854, 1496, 1453, 1364, 1071 (s) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 4.09 (t, *J*=1.1 Hz, 4H, 2 × OCH_2C), 4.53 (br s, 4H, 2 × CH_2Ph), 5.29 (t, *J*=1.1 Hz, 2H, CH_2=C), 7.29-7.33 (m, 2H, H-Ar), 7.33-7.38 (m, 8H, H-Ar); ^{13}C NMR (150 MHz, $CDCl_3$): δ70.9 (CH_2), 72.2 (CH_2), 114.4 (CH_2), 127.7 (CH-Ar), 128.2 (CH-Ar), 128.4 (CH-Ar), 138.3 (C-Ar), 142.6 (C); MS (CI^+) *m/z* (%): 269 (MH^+, 100), 233 (28), 181 (15), 143 (17), 92 (11); HRMS: $[MH]^+$, found 269.15347, $C_{18}H_{21}O_2$ requires 269.15415.

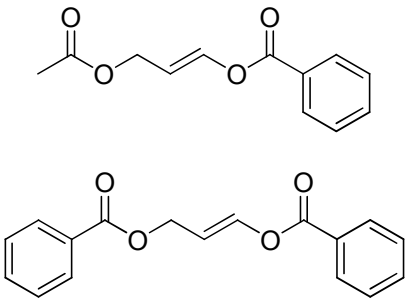
(*E*)-3-Bromoprop-1-enylbenzoate 321[149]



A solution of benzoyl bromide **319** (2.36 ml, 20.0 mmol, 1 eq.) was added to a solution of freshly distilled acrolein **318** (1.33 ml, 20.0 mmol, 1 eq.) in dichloromethane (20 ml) at 0 °C. The resulting mixture was allowed to warm to room temperature and was stirred for a further 72 hours. The reaction mixture was then cooled to 0 °C and quenched by the addition of a saturated aqueous solution of sodium bicarbonate (30 ml). The biphasic mixture was extracted with dichloromethane (15 ml), and the extract dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was recrystallised (hexane) to give **321** as a colourless solid (1.46 mg, 30%).

M.p. 64-70 °C (hexane), lit.,[149] 74-76 °C (pentane); IR (film): ν_{max} 2831 (w), 2555 (w), 1664, 1600, 1453, 1264 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 4.09 (dd, *J*=8.5, 1.0 Hz, 2H, CH_2Br), 5.9 (dt, *J*=12.4, 8.5 Hz, 1H, C*H*CH_2Br), 7.48-7.52 (m, 2H, H-Ar), 7.62-7.66 (m, 1H, H-Ar), 7.69 (dt, *J*=12.4, 1.0 Hz, 1H, CHO), 8.11 (dd, *J*=8.3, 1,4 Hz, 2H, H-Ar); ^{13}C NMR (150 MHz, $CDCl_3$): δ 28.7 (CH_2), 111.8 (CH), 128.5 (C-Ar), 128.7 (C-Ar), 130.1 (C-Ar), 133.9 (C-Ar), 139.4 (CH), 163.2 (C=O); MS (CI^+) *m/z* (%): 241 (M^+ ^{79}Br, 14), 243 (M^+ ^{81}Br, 14), 161 (36), 137 (29), 106 (100); HRMS: $[MH]^+$, found 240.098650, $C_{10}H_9O_2Br$ requires 240.98642.

(*E*)-3-Acetoxyprop-1-enyl benzoate 322 and (*E*)-prop-1-ene-1,3-diyl dibenzoate 323



Potassium acetate (210 mg, 2.14 mmol, 1.1 eq.), pulverised in a pestle and mortar, and aliquat (78.0 mg, 0.19 mmol, 0.2 eq.) were stirred for 10 min. A solution of (*E*)-3-bromoprop-1-enyl benzoate **321** (465 mg, 1.94 mmol, 1 eq.) in toluene (8 ml) was then added and the resulting mixture was left to stir for 16 hours followed by heating at 85 °C for 16 hours. After SiO_2 (1 g) was added, the mixture was filtered, the solids washed with diethyl ether (15 ml) and solvents evaporated under reduced pressure. The residue was purified by column chromatography (petroleum ether: diethyl ether 9 :1) to give **322** (223 mg, 52%) as a yellow solid and **323** (116 mg, 20%) as a yellow oil.

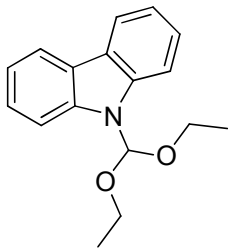
322

M.p. 51-53 °C (Et_2O); IR (film): ν_{max} 3086 (w), 2951 (w), 1734 (s), 1677, 1602, 1452, 1228 (s), 1124 (s), 1048 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 2.10 (s, 3H, CH_3), 4.66 (dd, *J*=7.4, 1.2 Hz, 2H, CH_2O), 5.78 (dt, *J*=12.5, 7.4 Hz, 1H, C*H*CH_2O), 7.48-7.52 (m, 2H, H-Ar), 7.62-7.64 (m, 1H, H-Ar), 7.65-7.68 (m, 1H, CHOCO), 8.11 (dd, *J* = 8.4, 1.2 Hz, 2H, H-Ar); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.1 (CH_3), 61.2 (CH_2), 109.1 (CH), 128.5 (CH-Ar), 128.6 (CH-Ar), 130.1 (CH-Ar), 133.8 (C-Ar), 140.3 (CH), 163.4 (C=O), 170.8 (C=O).

323[173]

IR (film): ν_{max} 2359, 1737 (s), 1453, 1256 (s), 1097 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.92 (d, *J*=7.6 Hz, 2H, CH_2O), 5.91 (dt, *J*=12.5, 7.6 Hz, 1H, C*H*CH_2O), 7.47 (t, *J*=7.7 Hz, 2H, H-Ar), 7.50 (t, *J*=7.7 Hz, 2H, H-Ar), 7.59 (t, *J*=7.6 Hz, 1H, H-Ar), 7.64 (t, *J*=7.6 Hz, 1H, H-Ar), 7.80 (d, *J*=12.5 Hz, 1H, CHOCO), 8.10 (d, *J*=7.8 Hz, 2H, H-Ar), 8.12 (d, *J*=7.8 Hz, 2H, H-Ar); ^{13}C NMR (150 MHz, $CDCl_3$): δ61.7 (CH_2), 109.2 (CH), 128.4 (CH-Ar), 128.6 (CH-Ar), 129.7 (CH-Ar), 130.0 (CH-Ar), 133.1 (C-Ar), 133.9 (C-Ar), 140.4 (C-H), 163.4 (C=O), 166.4 (C=O); MS (FAB) *m/z* (%): 283 (MH^+, 22), 176 (17); HRMS: $[MH]^+$, found 283.09652, $C_{17}H_{15}O_4$ requires 283.09703.

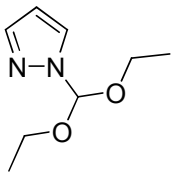
9-(Diethoxymethyl)-9*H*-carbazole 336[156]



A mixture of carbazole **329** (1.0 g, 6.0 mmol, 1 eq.), triethyl orthoformate (10 ml, 60 mmol, 10 eq.) and *p*-toluene sulfonic acid (100 mg, 0.60 mmol, 0.1 eq.) was heated at 85 °C for 36 hours. The cooled reaction mixture was poured into a mixture of a saturated aqueous solution of ammonium chloride and ice (ammonical ice/water), and then extracted with dichloromethane (4 × 8 ml). The combined organic extracts were concentrated under reduced pressure and the residue purified by column chromatography (petroleum ether:acetone 9:1) to give **336** as an orange oil (675mg, 42%).

IR (film): ν_{max} 2977, 1699 (w), 1599, 1484, 1449 (s), 1318 (s), 1227 (s) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 1.11 (t, *J*=7.1 Hz, 6H, 2 × OCH_2CH_3), 3.45 (dq, *J*=9.7, 7.1 Hz, 2H, CH_2CH_3), 3.70 (dq, *J*=9.7, 7.1 Hz, 2H, CH_2CH_3), 6.80 (s, 1H, $CH(OEt)_2$), 7.20-7.24 (m, 2H, H-Ar), 7.39-7.44 (m, 2H, H-Ar), 7.83 (d, 2H, *J*=8.3 Hz, H-Ar), 8.13 (d, 2H, *J*=7.8 Hz, H-Ar); ^{13}C NMR (125 MHz, DMSO): δ15.3 (CH_3), 62.1 (CH_2), 102.3 (CH), 111.9 (CH-Ar), 120.3 (CH-Ar), 120.6 (CH-Ar), 123.3 (C-Ar), 126.3 (CH-Ar), 139.0 (C-Ar); MS (EI) *m/z* (%): 269 (M^+, 22), 224 (38), 196 (33); 167 (90), 140 (28), 103 (100), 75 (36); HRMS: $[M]^+$, found 269.13643, $C_{17}H_{19}O_2N$ requires 269.13607.

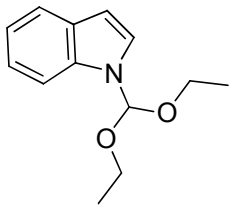
1-(Diethoxymethyl)-1*H*-pyrazole 337[157]



A mixture of pyrazole **330** (3.4 g, 50 mmol, 1 eq.) and triethyl orthoformate (8.3 ml, 50 mmol, 1 eq.) was heated at 140 °C and ethanol distilled from the reaction during 16 hours. The resulting product was distilled under vacuum and purified by column chromatography (petroleum ether: diethyl ether 1:1) to give **337** as a colourless oil (4.30 g, 50%).

IR (film): ν_{max} 2980 (w), 1513 (w), 1445.6 (w), 1373, 1316, 1066 (s) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 1.11 (t, *J*=7.1 Hz, 6H, 2 × OCH_2CH_3), 3.49 (dq, *J*=9.7, 7.1 Hz, 2H, CH_2CH_3), 3.59 (dq, *J*=9.7, 7.1 Hz, 2H, CH_2CH_3), 6.22 (s, 1H, $CH(OEt)_2$), 6.33 (t, *J*=2.0 Hz, 1H, CH=N), 7.50-7.52 (m, 1H, CH=CHN), 7.82 (d, *J*=2.40 Hz, 1H, CHN); ^{13}C NMR (125 MHz, DMSO): δ 14.6 (CH_3), 61.5 (CH_2), 104.4 (CH), 106.0 (CH-Ar), 126.6 (CH-Ar), 139.0 (CH-Ar).

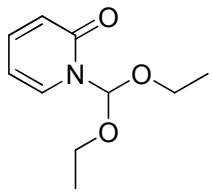
1-(Diethoxymethyl)-1*H*-indole 338[154]



A mixture of indole **331** (1.50 g, 12.8 mmol, 1 eq.) and triethyl orthoformate (21.2 ml, 128 mmol, 10 eq.) was heated at 160 °C for 48 hours. The resulting mixture was concentrated under reduced pressure and the residue purified by column chromatography (petroleum ether: diethyl ether 1:1) to give **338** as a pale pink oil (354 mg, 13%).

IR (film): ν_{max} 2978 (w), 1459, 1303, 1222, 1103 (s), 1052 (s), 1013 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 1.19 (t, *J*=7.1 Hz, 6H, 2 × OCH_2CH_3), 3.55 (dq, *J*=9.7, 7.1 Hz, 2H, CH_2CH_3), 3.66 (dq, *J*=9.7, 7.1 Hz, 2H, CH_2CH_3), 6.52 (s, 1H, $CH(OEt)_2$), 6.54 (dd, *J*=3.4, 0.7 Hz, 1H, C*H*=CHN), 7.12 (td, *J*=7.3, 1.1 Hz, 1H, H-Ar), 7.20 (ddd, *J*=8.2, 7.1, 1.2 Hz, 1H, H-Ar), 7.52 (d, *J*=3.4 Hz, 1H, CH=C*H*N), 7.61 (dt, *J*=7.8, 1.0 Hz, 1H, H-Ar), 7.69 (dd, *J*=8.3, 0.9 Hz, 1H, H-Ar); ^{13}C NMR (125 MHz, DMSO): δ 14.8 (CH_3), 61.1 (CH_2), 101.8 (CH), 101.9 (CH-Ar), 111.4 (CH-Ar), 119.9 (CH-Ar), 120.5 (CH-Ar), 121.6 (CH-Ar), 125.3 (CH-Ar), 128.7 (C-Ar), 134.4 (C-Ar).

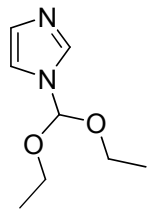
1-Diethoxymethyl-1*H*-pyridin-2-one 339



A mixture of 2-hydroxypyridine **332** (1.00 g, 10.5 mmol, 1 eq.) and triethyl orthoformate (27.0 ml, 162 mmol, 15.4 eq.) was heated at 155 °C for 24 hours. The cooled mixture was poured into a saturated aqueous solution of sodium bicarbonate (20 ml) and the resulting mixture was extracted with ethyl acetate (15 ml). The combined organic extracts were washed with brine (15 ml), concentrated under reduced pressure and the residue purified by column chromatography (petroleum ether:ethyl acetate 1:1) to give **339** as a pale yellow oil (950 mg, 46%).

IR (film): ν_{max} 2979 (w), 1738 (w), 1661 (s), 1594, 1538, 1376, 1250, 1059 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 1.13 (t, *J*=7.1 Hz, 6H, 2 × OCH_2CH_3), 3.51 (dq, *J*=9.7, 7.1 Hz, 2H, 2 × $CHHCH_3$), 3.66 (dq, *J*=9.7, 7.1 Hz, 2H, 2 × $CHHCH_3$), 6.27 (td, *J*=7.1, 1.1 Hz, 1H, C*H*=CH), 6.37 (dt, *J*=9.2, 1.1 Hz, 1H, CH=C*H*), 6.58 (s, 1H, $CH(OEt)_2$), 7.40-7.44 (m, 1H, C*H*=CH), 7.55 (dd, *J*=7.1, 2.1 Hz, 1H, C*H*=CH); ^{13}C NMR (125 MHz, DMSO): δ 15.1 (CH_3), 63.0 (CH_2), 99.8 (CH), 106.2 (CH-Ar), 120.4 (CH-Ar), 132.7 (CH-Ar), 141.0 (CH-Ar), 161.5 (C=0); MS (EI) *m/z* (%): 197 (M^+, 97), 152 (97), 124 (66); 103 (100), 95 (92), 75 (60), 67 (70); HRMS: $[M]^+$, found 197.09990, $C_{10}H_{15}O_3N$ requires 197.9969.

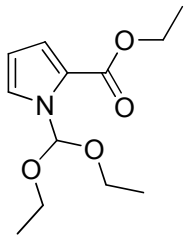
1-(Diethoxymethyl)-1*H*-imidazole 340[155]



A mixture of imidazole **333** (1.28 g, 18.8 mmol, 1 eq.), *p*-toluene sulfonic acid (100 mg, 0.58 mmol, 0.03 eq.) and triethyl orthoformate (13.3 ml, 80.0 mmol, 4.25 eq.) was heated at 130 °C until no more ethanol distilled from the reaction mixture and then heated at 160 °C for 16 hours. After excess triethyl orthoformate was removed under vacuum, sodium carbonate (100 mg) was added to the residue which was then fractionally distilled to give **340** as a colourless oil (1.45 g, 45%).

B.p 117-119 °C (0.7 mbar), lit.,[155] b.p 52 °C (0.02 Torr); IR (film): ν_{max} 2979 (w), 1739 (w), 1218, 1060 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.22 (t, *J*=7.2 Hz, 6H, 2 × OCH_2CH_3), 3.56 (q, *J*=7.2 Hz, 4H, OCH_2CH_3), 6.02 (s, 1H, $CH(OEt)_2$), 7.06 (dd, *J*=10.2, 1.1 Hz, 2H, C*H*=CH, CH=C*H*), 7.70 (s, 1H, NCHN); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.7 (CH_3), 60.9 (CH_2), 101.4 (CH), 116.1 (CH-Ar), 129.5 (CH-Ar), 135.1 (CH-Ar); MS (EI) *m/z* (%): 170 (M^+, 6), 125 (77), 103 (100), 75 (85); HRMS: $[M]^+$, found 170.10006, $C_8H_{14}O_2N_2$ requires 170.10002.

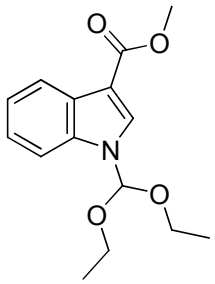
Ethyl 1-(diethoxymethyl)-1*H*-pyrrole-2-carboxylate 341[153]



A mixture of ethyl pyrrole-2-carboxylate **334** (2.00 g, 14.4 mmol, 1 eq.) and triethyl orthoformate (24.0 ml, 144 mmol, 10 eq.) was heated at 165 °C for 6 days. The resulting mixture was concentrated under reduced pressure and the residue purified by column chromatography (petroleum ether:ethyl acetate (9:1) to give **341** as a slightly yellow oil (2.54 g, 73%).

IR (film): ν_{max} 2979 (w), 1699 (s), 1419, 1285, 1232, 1207, 1089 (s), 1057 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 1.22 (t, *J*=7.1 Hz, 6H, 2 × OCH_2CH_3), 1.35 (t, *J*=7.1 Hz, 3H, CH_3), 3.55 (dq, *J*=9.5, 7.1 Hz, 2H, $CHOCH_2CH_3$), 3.67 (dq, *J*=9.5, 7.1 Hz, 2H, $CHOCH_2CH_3$), 4.28 (q, *J*=7.2 Hz, 2H, OCH_2CH_3), 6.19 (br t, *J*=3.2 Hz, 1H, H_4), 6.98 (dd, *J*=3.8, 1.8 Hz, 1H, H_3), 7.02 (s, 1H, $CH(OEt)_2$), 7.34 (dd, *J*=2.7, 1.8 Hz, 1H, H_2); ^{13}C NMR (150 MHz, DMSO): δ14.2 (CH_3), 14.7 (CH_3), 59.8 (CH_2), 62.0 (CH_2), 101.3 (CH), 108.7 (CH-Ar), 118.6 (CH-Ar), 121.4 (C), 124.3 (CH-Ar), 160.1 (C=O).; MS (EI) *m/z* (%): 264 (Mna^+, 29), 196 (74), 182 (100); HRMS: $[Mna]^+$, found 264.12174, $C_{12}H_{19}O_3Nna$ requires 264.12063.

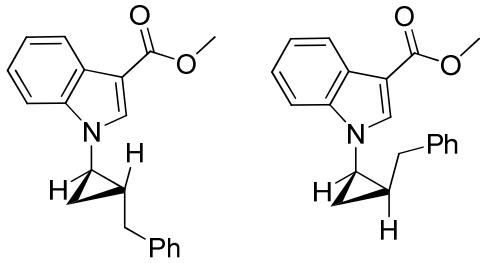
Methyl 1-(diethoxymethyl)-1*H*-indole-3-carboxylate 342[154]



A mixture of methyl indole-3-carboxylate **335** (5.00 g, 28.5 mmol, 1 eq.) and triethyl orthoformate (50.0 ml, 301 mmol, 10 eq.) was heated at 160 °C for 60 hours. The resulting mixture was concentrated under reduced pressure and the residue purified twice by column chromatography (petroleum ether:diethyl ether 1:1) to give **342** as a pale orange oil (6.74 g, 85%).

IR (film): ν_{max} 2980, 1709 (s), 11537, 1460, 1377, 1205 (s), 1072 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 1.23 (t, *J*=7.1 Hz, 6H, 2 × OCH_2CH_3), 3.55-3.63 (m, 4H, CH_2CH_3), 3.92 (s, 3H, OCH_3), 6.29 (s, 1H, $CH(OEt)_2$), 7.27-7.32 (m, 2H, H-Ar), 7.58-7.62 (m, 1H, H-Ar), 8.11 (s, 1H, CHN), 8.16-8.19 (m, 1H, H-Ar); ^{13}C NMR (75 MHz, DMSO): δ 14.6 (CH_3), 50.8 (CH_3), 61.4 (CH_2), 102.3 (CH), 106.5 (C-Ar), 112.5 (CH-Ar), 120.6 (CH-Ar), 122.2 (CH-Ar), 122.9 (CH-Ar), 126.4 (C-Ar), 131.7 (CH-Ar), 134.5 (C-Ar), 164.3 (C=O); MS (EI) *m/z* (%): 300 (Mna^+, 38), 232 (100), 218 (37), 204 (69), 198 (20), 176 (38); HRMS: $[MNa]^+$, found 300.12117, $C_{15}H_{19}O_4NNa$ requires 300.12063.

***trans*-Methyl 1-(2-benzylcyclopropyl)-1H-indole-3-carboxylate 343 and *cis*-methyl 1-(2-benzylcyclopropyl)-1H-indole-3-carboxylate 344**



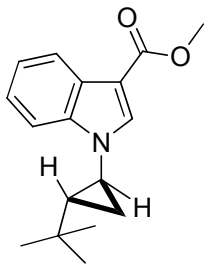
1.4:1

A solution of 1-diethoxymethyl-1*H*-indole-3-carboxylic acid methyl ester **342** (703 mg, 2.54 mmol, 2 eq.) in diethyl ether (3 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (1.66 g, 25.4 mmol, 20 eq.), copper(I) chloride (166 mg, 1.68 mmol, 1.3 eq.), zinc chloride (1.0 M solution in diethyl ether, 2.5 ml, 2.5 mmol, 2 eq.), chlorotrimethylsilane (1.62 ml, 12.7 mmol, 1.3 eq.) and allylbenzene **153** (150 mg, 1.27 mmol, 1 eq.) in diethyl ether (6 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (8 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 10 ml) and the combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by column chromatography (diethyl ether:petroleum ether 7:3) to give an inseparable mixture of **343** and **344** (70 mg, 18%, *trans*:*cis* 1.4:1 as determined by ^{1}H NMR spectrum) as a pale yellow oil.

IR (mixture of *trans* and *cis*, film): ν_{max} 3005, 2947, 1699 (s), 1605 (w), 1533 (s), 1464 (s), 1375, 1317, 1196 (s) cm^{-1}; **343**: ^{1}H NMR (*trans*, 500 MHz, $CDCl_3$): δ 1.07-1.13 (m, 1H, C*H*HCHN), 1.31 (ddd, *J*=9.6, 5.8, 3.8 Hz, 1H, CH*H*CHN), 1.60-1.68 (m, 1H, C*H*CHN), 2.77 (dd, *J*=14.4, 7.4 Hz, 1H, C*H*HPh), 2.90 (dd, *J*=14.4, 6.7, 1H, CH*H*Ph), 3.22 (dt, *J*=7.2, 3.6 Hz, 1H, CHN), 3.89 (s, 3H, OCH_3), 7.10-7.15 (m, 2H, H-Ar), 7.21-7.25 (m, 2H, H-Ar), 7.28-7.33 (m, 2H, H-Ar), 7.35-7.39 (m, 2H, H-Ar), 7.74 (s, 1H, CH=C), 8.11-8.13 (m, 1H, H-Ar); **343**: ^{13}C NMR (*trans*, 125 MHz, $CDCl_3$): δ 13.3

(CH), 21.5 (CH), 32.7 (CH_2), 33.5 (CH_2), 51.0 (CH_3), 107.0 (C-Ar), 110.8 (C-Ar), 121.6 (C-Ar), 122.1 (C-Ar), 122.7 (C-Ar), 126.2 (C-Ar), 126.7 (C-Ar), 128.6 (C-Ar), 128.8 (C-Ar), 134.3 (C-Ar), 137.7 (C-Ar), 139.8 (C-Ar), 165.5 (C=O); **344**: ^{1}H NMR (*cis*, 500 MHz, $CDCl_3$): δ 1.15 (td, *J*=6.2, 4.4 Hz, 1H, C*H*HCHN), 1.37-1.43 (m, 1H, CH*H*CHN), 1.67-1.72 (m, 1H, C*H*CHN), 1.90 (dd, *J*=15.1, 9.6 Hz, 1H, C*H*HPh), 2.79 (dd, *J*=15.1, 5.0, 1H, CH*H*Ph), 3.55 (td, *J*=7.3, 4.3 Hz, 1H, CHN), 3.92 (s, 3H, OCH_3), 7.05-7.07 (m, 2H, H-Ar), 7.16-7.19 (m, 1H, H-Ar), 7.28-7.33 (m, 4H, H-Ar), 7.52-7.55 (m, 1H, H-Ar), 7.84 (s, 1H, CH=C), 8.18-8.20 (m, 1H, H-Ar); **344**: ^{13}C NMR (*cis*, 125 MHz, $CDCl_3$): δ 11.1 (CH), 19.3 (CH), 32.7 (CH_2), 33.5 (CH_2), 51.0 (CH_3), 107.1 (C-Ar), 111.0 (C-Ar), 121.6 (C-Ar), 122.3 (C-Ar), 123.0 (C-Ar), 126.6 (C-Ar), 126.8 (C-Ar), 128.3 (C-Ar), 128.4 (C-Ar), 134.8 (C-Ar), 138.2 (C-Ar), 140.2 (C-Ar), 165.4 (C=O); MS (EI) *m/z* (%): 306 (MH^+, 100), 274 (17); HMRS: $[MH]^+$, found 306.14782, $C_{20}H_{20}O_2N$ requires 306.14886.

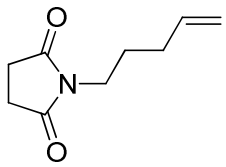
trans-Methyl 1-(2-_tert_-butylcyclopropyl)-1_H_-indole-3-carboxylate 345



A solution of 1-diethoxymethyl-1*H*-indole-3-carboxylic acid methyl ester **342** (687 mg, 2.48 mmol, 2 eq.) in diethyl ether (2 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (1.62 g, 24.8 mmol, 20 eq.), copper(I) chloride (162 mg, 1.64 mmol, 1.3 eq.), zinc chloride (1.0 M solution in diethyl ether, 2.5 ml, 2.5 mmol, 2 eq.), chlorotrimethylsilane (1.60 ml, 12.5 mmol, 10 eq.) and 3,3 dimethylbut-1-ene **164** (0.16 ml, 1.24 mmol, 1 eq.) in diethyl ether (6 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (8 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 10 ml) and the combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether: diethyl ether 1:1) to give **342** as a yellow solid (35 mg, 10%).

M.p. 65-70 °C (Et_2O); IR (film): ν_{max} 2948, 1691 (s), 1534, 1463, 1435, 1374, 1259, 1193 (s) cm^{-1}; ^1H NMR (*trans*, 600 MHz, $CDCl_3$): δ 1.06 (s, 9H, $C(CH_3)_3$), 1.07-1.14 (m, 2H, CH_2CHN), 1.38-1.42 (m, 1H, $CHC(CH_3)_3$), 3.29 (dt, *J*=7.6, 3.7 Hz, 1H, CHN), 3.92 (s, 3H, OCH_3), 7.29-7.31 (m, 2H, H-Ar), 7.61-7.63 (m, 1H, H-Ar), 7.81 (s, 1H, CH=C), 8.15-8.17 (m, 1H, H-Ar); ^{13}C NMR (*trans*, 150 MHz, $CDCl_3$): δ 9.7 (CH_2), 28.5 ($C(CH_3)_3$), 29.4 ($C(CH_3)_3$), 30.6 (CH), 31.4 (CH), 51.0 (CH_3), 106.8 (C-Ar), 110.8 (CH-Ar), 121.7 (CH-Ar), 122.1 (CH-Ar), 122.7 (CH-Ar), 126.7 (C-Ar), 134.5 (CH-Ar), 137.7 (C-Ar), 165.5 (C=O); MS (EI) *m/z* (%): 271 (M^+, 100), 240 (30), 214 (100), 201 (27), 182 (22), 170 (28), 154 (53); HMRS: $[M]^+$, found 271.15197, $C_{17}H_{21}O_2N$ requires 271.15172.

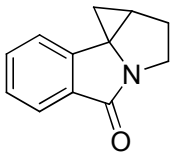
1-(Pent-4-enyl)pyrrolidine-2,5-dione 351[174]



Sodium hydride (60% in mineral oil, 2.24 g, 56.0 mmol, 1.1 eq.) was added portionwise to a solution of succinimide (5.00 g, 50.5 mmol, 1 eq.) in *N*,*N* dimethylformamide (30 ml) at 0 °C and stirred at 0 °C for 5 minutes before warming to room temperature and stirring for a further 1 hour. 5 Bromopentene (6.00 ml, 50.6 mmol, 1 eq.) was added dropwise to the mixture and the reaction mixture was stirred for 16 hours before being poured into water (50 ml) and a saturated aqueous solution of ammonium chloride (50 ml). The resulting mixture was extracted with diethyl ether (3 × 25 ml) and the combined organic extracts were washed with water (3 × 50 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (hexane:ethyl acetate 6:4) to give **351** as a yellow oil (7.18g, 85%).

IR (film): ν_{max} 2941 (w), 1773 (w), 1690 (s), 1438, 1399, 1341, 1250, 1162, 1131 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.66 (dt, *J*=15.0, 7.4 Hz, 2H, C*H*$_2$CH$_2$N), 2.02-2.07 (m, 2H, C*H*$_2$CH=CH), 2.67 (s, 4H, 2 × CH_2CO), 3.50 (t, *J*=7.4 Hz, 2H, CH_2N), 4.96 (ddd, *J*=10.2, 3.1, 1.3 Hz, 1H, C*H*H=CH), 5.02 (ddd, *J*=17.2, 3.4, 1.7 Hz, 1H, CH*H*=CH), 5.77 (ddt, *J*=17.2, 10.3, 6.6 Hz, 1H, C*H*=CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 26.7 (CH_2), 28.1 (CH_2), 31.0 (CH_2), 38.4 (CH_2), 115.3 (*C*H_2=CH), 137.4 (*C*H=CH_2), 177.3 (C=O); MS (CI^+) *m/z* (%): 168 (MH^+,59), 114 (19), 101 (100); HRMS: $[MH]^+$, found 168.10254, $C_9H_{14}O_2N$ requires 168.10245.

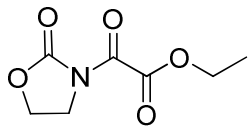
1,1a,2,3-Tetrahydro-3a-aza cyclopropa[1,5]cyclopenta[1,2-*a*]inden-4-one 354



A solution of 2-(but-3-enyl)isoindoline-1,3-dione **353** (200 mg, 1.00 mmol, 1 eq.) in dichloromethane (3 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred refluxing mixture of zinc dust (1.38 g, 21.1 mmol, 21.1 eq.), copper(I) chloride (138 mg, 1.39 mmol, 1.4 eq.), zinc chloride (1.0 M solution in diethyl ether, 2.0 ml, 2.0 mmol, 2 eq.) and chlorotrimethylsilane (1.90 ml, 14.9 mmol, 15 eq.) in diethyl ether (5 ml). The reaction mixture was heated at reflux for 16 hours, then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (15 ml), filtered and the solids washed with diethyl ether (10 ml). The biphasic mixture was extracted with diethyl ether (2 × 10 ml) and the combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (diethyl ether:petroleum ether 4:1) to give **354** as a orange oil (15 mg, 8%)

IR (film): ν_{max} 2956, 1679 (s), 1474, 1398, 1347, 1265, 1083 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.54 (dd, *J*=6.6, 5.6 Hz, 1H, C*H*HCN), 1.62 (dd, *J*=8.9, 6.6 Hz, 1H, CH*H*CN), 2.02 (dt, *J*=8.9, 5.3 Hz, 1H, CHCN); 2.22 (ddd, *J*=12.9, 7.8, 1.4 Hz, 1H, C*H*HCH_2N), 2.36-2.45 (m, 1H, CH*H*CH_2N), 3.04 (ddd, *J*=12.5, 9.9, 7.8 Hz, 1H, C*H*HN), 4.09 (ddd, *J*=12.5, 9.9, 1.4 Hz, 1H, CH*H*N), 7.14 (d, *J*=7.6 Hz, 1H, H-Ar), 7.41 (td, *J*=7.5, 1.0 Hz, 1H, H-Ar), 7.48 (td, *J*=7.5, 1.1 Hz, 1H, H-Ar), 7.82 (d, *J*=7.6 Hz, 1H, H-Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.6 (CH_2), 22.3 (CH), 31.4 (CH_2), 38.4 (CH_2), 54.7 (C), 119.0 (CH-Ar), 124.0 (CH-Ar), 125.5 (C-Ar), 127.6 (CH-Ar), 131.2 (CH-Ar), 144.8 (C-Ar), 168.6 (C=O); MS (CI^+) *m/z* (%): 186 (MH^+, 100); HRMS: $[MH]^+$, found 186.09093, $C_{12}H_{11}ON$ requires 186.09189.

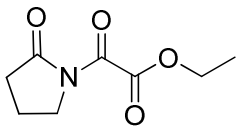
Ethyl 2-oxo-2-(2-oxooxazolidin-3-yl)acetate 361



A solution of oxazolidin-2-one **180** (3.00 g, 34.5 mmol, 1 eq.) in tetrahydrofuran (20 ml) was added dropwise to a solution of sodium hydride (60% in mineral oil, 4.13 g, 103 mmol, 3 eq.) in tetrahydrofuran (80 ml) at 0 °C. The reaction mixture was stirred for 1 hour at 0 °C. Ethyloxalyl chloride (5.75 ml, 51.6 mmol, 1.5 eq.) was then added dropwise at 0 °C and the resulting mixture allowed to warm to room temperature and stirred for 16 hours before being partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous phase was separated and extracted with ethyl acetate (50 ml). The combined organic extracts were washed with a saturated aqueous solution of sodium carbonate (3 × 50 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **361** together with 2-ethoxy-2-oxoacetic acid (1.9g, **361**: **2-ethoxy-2-oxoacetic acid** 1:3 as determined by ^{1}H NMR spectrum) as a yellow oil, which was used without further purification. The yield of **361** (1.60 g, 25%) was calculated from ^{1}H NMR spectrum.

IR (film): ν_{max} 2989 , 2925, 1792 (s), 1751 (s), 1705 (s), 1475, 1402 (s), 1236 (s), 1018 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, *J*=7.2 Hz, 3H, CH_3), 4.04 (t, *J*= 8.0 Hz, 2H, CH_2N), 4.40 (q, *J*= 7.2 Hz, 2H, CH_2CH_3), 4.56 (t, *J*=8.0 Hz, 2H, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6 (CH_3), 40.7 (CH_2), 62.9 (CH_2), 63.7 (CH_2), 152.8 (C=O), 160.0 (C=O), 160.3 (C=O); MS (CI$^+$) *m/z* (%): 188 (MH^+, 66), 160 (37), 142 (51), 114 (62), 88 (100); HRMS : $[MH]^+$, found 188.05586, $C_7H_{10}O_5N$ requires 188.05535.

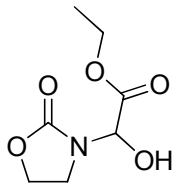
Ethyl 2-oxo-2-(2-oxopyrrolidin-1-yl)acetate 362



A solution of pyrrolidin-2-one **215** (3.00 g, 35.3 mmol, 1 eq.) in tetrahydrofuran (20 ml) was added dropwise to a solution of sodium hydride (60% in mineral oil, 4.23 g, 106 mmol, 3 eq.) in tetrahydrofuran (80 ml) at 0 °C. The reaction mixture was stirred for 1 hour at 0 °C. Ethyloxalyl chloride (5.90 ml, 52.9 mmol, 1.5 eq.) was then added dropwise at 0 °C and the resulting mixture allowed to warm to room temperature and stirred for 16 hours before being partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous phase was separated and extracted with ethyl acetate (50 ml). The combined organic extracts were washed with a saturated aqueous solution of sodium carbonate (3 × 50 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale brown semi-solid mixture of **362** and 2-ethoxy-2-oxoacetic acid (2.14 g, **362**:**2-ethoxy-2-oxoacetic acid** 5:1 as determined by ^{1}H NMR spectrum) which was used without further purification. The yield of **362** (1.87g, 29%) was calculated from the ^{1}H NMR spectrum.

IR (film): ν_{max} 2914, 1750 (s), 1699 (s), 1355 (s), 1220 (s), 1018 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, *J*=7.2 Hz, 3H, CH_3), 2.18 (tt, *J*=8.1, 7.3 Hz, 2H, C*H*$_2$CH$_2$N), 2.62 (t, *J*=8.1 Hz, 2H, CH_2CO), 3.82 (t, *J*=7.3 Hz, 2H, CH_2N), 4.39 (q, *J*=7.2 Hz, 2H, OC*H*$_2$CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6 (CH_3), 17.7 (CH_2), 31.7 (CH_2), 43.3 (CH_2), 62.4 (CH_2), 160.2 (C=O), 161.3 (C=O), 175.2 (C=O); MS (CI$^+$) *m/z* (%): 186 (MH^+, 8), 112 (26), 31 (100); HRMS : $[MH]^+$, found 186.07679, $C_8H_{12}O_4N$ requires 186.07608.

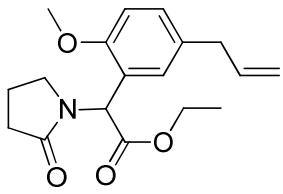
Ethyl 2-hydroxy-2-(2-oxooxazolidin-3-yl)acetate 365



Oxazolidin-2-one **180** (430 mg, 4.94 mmol, 1 eq.) was added to a solution of ethyl glyoxalate (55% in toluene, 1.00 g, 4.94 mmol, 1 eq.), acetic acid (0.28 ml, 4.94 mmol, 1 eq.) and toluene (10 ml). The resulting mixture was stirred at room temperature for 3 hours before being concentrated, diluted with toluene and evaporated under reduced pressure to give **365** as a colourless oil (778 mg, 83%).

IR (film): ν_{max} 3354 (br) , 2985, 1739 (s), 1485, 1425, 1252 (s), 1071, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (t, *J*=7.2 Hz, 3H, CH_3), 3.51 (dd, *J*= 8.4, 6.9 Hz, 1H, C*H*HN), 3.77 (dd, 1H, *J*=8.4, 7.6 Hz, 1H, CH*H*N), 4.30-4.38 (m, 2H, OCH_2CH_3), 4.39-4.43 (m, 2H, CH_2OCO), 5.64 (s, 1H, CHN); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 40.5 (CH_2), 62.5 (CH_2), 63.0 (CH_2), 74.9 (CH), 157.8 (C=O), 169.2 (C=O); MS (CI^+) *m/z* (%): 190 (MH^+, 69), 173 (68), 134 (95), 114 (41), 103 (77), 89 (100); HRMS : $[MH]^+$, found 190.07101, $C_7H_{12}O_5N$ requires 190.07154.

Ethyl 2-(5-allyl-2-methoxyphenyl)-2-(2-oxopyrrolidin-1-yl)acetate 366

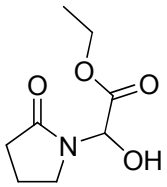


A solution of oxo-(2-oxo-pyrrolidin-1-yl)-acetic acid ethyl ester **362** (469 mg, 2.21 mmol, 1.3 eq.) in diethyl ether (5 ml) was added *via* syringe pump over 4 hours to a vigorously stirred mixture of zinc amalgam (1.38 g, 21.1 mmol, 12.5 eq.), zinc chloride (1.0 M solution in diethyl ether, 2.5 ml, 2.5 mmol, 1.5 eq.), 4-allylanisole **253** (250 mg, 1.69 mmol, 1 eq.), trimethylsilyl chloride (1.35 ml, 10.6 mmol, 6.25 eq.) in diethyl ether (8 ml) at reflux. Zinc dust (1.00 g, 15.3 mmol, 9 eq.) and copper(I) chloride (138 mg, 1.39 mmol, 0.8 eq.) were added and the resulting mixture heated at reflux for 16 hours. After cooling to room temperature, a saturated aqueous solution of sodium bicarbonate was added and the mixture stirred for 10 min. The solution was filtered and the separated zinc washed with ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate (3 × 5 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (diethyl ether:petroleum ether 4:1) to give **366** as a yellow oil (128 mg, 24%).

IR (film): ν_{max} 2968, 1739 (s), 1688 (s), 1502, 1420, 1263 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.80-1.91 (m, 1H, C*H*HCH_2N), 1.99-2.08 (m, 1H, CH*H*CH_2N), 2.32-2.51 (m, 2H, CH_2N), 2.89-3.00 (m, 1H, C*H*HCO), 3.31 (d, *J*=6.7 Hz, 2H, CH_2CH=CH_2), 3.54-3.59 (m, 1H, CH*H*CO), 3.78 (s, 3H, OCH_3), 4.14-4.25 (m, 2H, CH_2CH_3), 5.01-5.07 (m, 2H, CH_2=CH), 5.87-5.97 (m, 1H, C*H*=CH_2), 6.03 (s, 1H, CHN), 6.83 (d, *J*= 8.4 Hz, 1H, H-Ar), 7.0 (d, *J*= 2.2 Hz, 1H, H-Ar), 7.14 (dd, *J*= 8.4, 2.2 Hz, 1H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 17.9 (CH_2), 30.7 (CH_2), 39.1 (CH_2), 44.4 (CH_2), 54.1 (CH), 55.4 (CH_3), 61.0 (CH_2), 110.9 (CH-Ar), 115.7 (CH_2=CH), 122.7 (C-Ar), 129.8 (CH-Ar), 131.0 (CH-Ar), 132.3 (C-Ar), 137.2

(*C*H=CH_2), 155.7 (C=O), 170.2 (C-Ar), 175.1 (*C*=O); MS (EI) *m/z* (%): 317 (M^+, 2), 271 (15), 244 (100); HRMS : $[M]^+$, found 317.161128, $C_{18}H_{23}O_4N$ requires 317.16216.

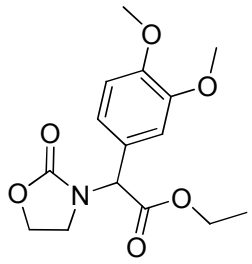
Ethyl 2-hydroxy-2-(2-oxopyrrolidin-1-yl)acetate 367[175]



Pyrrolidin-2-one **215** (420 mg, 4.94 mmol, 1 eq.) was added to a solution of ethyl glyoxalate (55% in toluene (1.00 g, 4.94 mmol, 1 eq.), acetic acid (0.28 ml, 4.94 mmol, 1 eq.) and toluene (10 ml). The resulting mixture was stirred at room temperature for 3 hours before being concentrated, diluted in toluene and evaporated under reduced pressure to give **367** as an orange semi-solid (787 mg, 85%).

IR (film): ν_{max} 3257 (br), 2983, 1751 (s), 1678 (s), 1421, 1271, 1099, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, *J*=7.1 Hz, 3H, CH_3), 2.02-2.11 (m, 2H, C*H*$_2$CH$_2$N), 2.43 (t, *J*=8.1 Hz, 2H, CH_2CO), 3.21-3.27 (m, 1H, C*H*HN), 3.52.3.58 (m, 1H, CH*H*N), 3.93 (s, 1H, OH), 4.30 (q, *J*=7.1 Hz, 2H, OC*H*$_2$CH$_3$), 5.74 (s, 1H, CHN); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3), 18.0 (CH_2), 30.9 (CH_2), 43.1 (CH_2), 62.8 (CH_2), 73.0 (CH), 170.1 (C=O), 175.8 (C=O); MS (EI) *m/z* (%): 188 (MH^+, 37), 170 (73), 142 (22), 114 (75), 86 (100); HRMS : $[M]^+$, found 187.08488, $C_8H_{13}O_4N$ requires 187.08445.

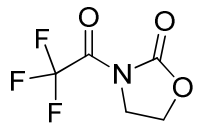
Ethyl 2-(3,4-dimethoxyphenyl)-2-(2-oxo-oxazolidin-3-yl)acetate 370



A solution of oxo-(2-oxo-oxazolidin-3-yl)-acetic acid ethyl ester **361** (230 mg, 0.98 mmol, 1.1 eq.) in diethyl ether (3 ml) was added dropwise *via* syringe pump (0.6 $ml.h^{-1}$) to a vigorously stirred mixture of zinc amalgam (0.69 mg, 10.6 mmol, 12.3 eq.), zinc chloride (1.0 M solution in diethyl ether, 1.25 ml, 1.25 mmol, 1.45 eq.), 1,2 dimethoxybenzene **369** (0.11 ml, 0.86 mmol, 1 eq.), trimethylsilyl chloride (0.68 ml, 5.32 mmol, 6.2 eq.) in diethyl ether (3 ml) at reflux. The resulting mixture was heated at reflux for 16 hours, cooled to room temperature and treated with a saturated aqueous solution of sodium bicarbonate. After stirring for 10 min, the reaction mixture was filtered and the separated zinc washed with ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate (2 × 7 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (diethyl ether:petroleum ether 4:1) to give **370** as a yellow oil (150 mg, 56%).

IR (film): ν_{max} 2912, 2837 (w), 1740 (s), 1737 (s), 1593, 1518, 1421, 1246, 1198, 1145, 1076, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 1.25 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 3.06-3.14 (m, 1H, C*H*HN), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.89-4.00 (m, 1H, CH*H*N), 4.19-4.28 (m, 3H, C*H*HOCO, OCH_2CH_3), 4.33.4.39 (m, 1H, CH*H*OCO), 5.64 (s, 1H, CHN), 6.77-6.80 (m, 2H, H-Ar), 6.84 (d, *J*=8.1 Hz, 1H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 41.7 (CH_2), 55.9 (CH_3), 59.4 (CH), 61.6 (CH_2), 62.4 (CH_2), 120.7 (CH-Ar), 111.8 (CH-Ar), 111.2 (CH-Ar), 125.6 (C-Ar), 149.3 (C-Ar), 158.2 (C=O), 170.1 (C=O); MS (EI) *m/z* (%): 309 (M^+, 7), 263 (13), 236 (36), 220 (19), 205 (49), 192 (7), 174(42), 129 (76), 100 (100); HRMS : $[M]^+$, found 309.12018, $C_{15}H_{19}O_6N$ requires 309.12123.

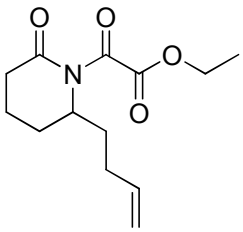
3-(2,2,2-Trifluoroacetyl)oxazolidin-2-one 359[176]



A mixture of 2-oxazolidinone **180** (1.00 g, 11.5 mmol, 1 eq.) and trifluoroacetic anhydride (539 ml, 276 mmol, 24 eq.) was heated at reflux for 24 hours. The resulting mixture was concentratred *in vacuo* and the residue was recrystallised from ethyl acetate to give **359** as a colourless solid (0.92 g, 80%).

M.p. 74-78 °C (EtOAc), lit.,[176] 90-93.5 °C; IR (film): ν_{max} 1716 (s), 1699, 1475, 1416 (s), 1169 (s) , 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (t, *J*=7.9 Hz, 2H, CH_2N), 4.55 (t, *J*=7.9 Hz, 2H, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.1 (CH_2), 62.8 (CH_2), 114.8 (q, J_{C-F} 284 Hz, CF_3), 149.8 (q, J_{C-F} 43 Hz, $C{=}OCF_3$), 155.9 (C=O); MS (EI) *m/z* (%): 183 (M^+, 32), 114 (93), 96 (13), 87 (17), 70 (100), 56 (37); HRMS: $[M]^+$, found 183.01480, $C_5H_4O_3NF_3$ requires 183.01433.

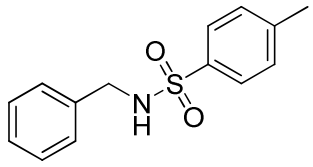
Ethyl 2-(2-(but-3-enyl)-6-oxopiperidin-1-yl)-2-oxoacetate 374



A solution of **283** (397 mg, 2.59 mmol, 1 eq.) in tetrahydrofuran (10 ml) was added to a mixture of sodium hydride (311 mg, 13.0 mmol, 5 eq.), which was washed with hexane three times, in tetrahydrofuran (3 ml) at 0 °C. The reaction mixture was stirred for 1 hour at 0 °C. Ethyl oxalyl chloride (0.44 ml, 5.20 mmol, 2 eq.) was added dropwise and the mixture was allowed to warm to room temperature then stirred for 16 hours before the addition of water (20 ml) and ethyl acetate (15 ml). The aqueous phase was separated and extracted with ethyl acetate (3 × 15 ml). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (20 ml), brine (20 ml), dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether:ethyl acetate 1:1) to give **374** as a yellow oil (429 mg, 65%).

IR (film): ν_{max} 2958, 1742, 1690 (s), 1389, 1371, 1328, 1267, 1185 (s), 1163 (s), 1018 (s) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.38 (t, *J*=7.2 Hz, 3H, CH_3), 1.63 (ddd, *J*=13.6, 9.7, 5.6, 1H, C*H*HCH$_2$CH=CH$_2$), 1.80-1.90 (m, 3H, C*H*HCH$_2$CH$_2$CO, C*H*HCH$_2$CO, CH*H*CH$_2$CH=CH$_2$), 1.93-2.03 (m, 2H, CH*H*CH$_2$CH$_2$CO, CH*H*CH$_2$CO), 2.07-2.19 (m, 2H, C*H*$_2$CH=CH$_2$), 2.55-2.66 (m, 2H, CH$_2$CO), 4.32-4.40 (m, 2H, OC*H*$_2$CH$_3$), 4.40-4.45 (m, 1H, CHN), 5.02 (ddd, *J*=10.3, 3.0, 1.3 Hz, 1H, C*H*H=CH), 5.08 (dq, *J*=17.2, 1.6 Hz, 1H, CH*H*=CH), 5.82 (ddt, *J*=17.2, 10.3, 6.6 Hz, 1H, C*H*=CH$_2$); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.8 (CH_3), 15.9 (CH_2), 24.3 (CH_2), 30.2 (CH_2), 31.6 (CH_2), 32.7 (CH_2), 52.6 (CH), 62.3 (CH_2), 115.6 (*C*H$_2$=CH), 136.9 (*C*H=CH$_2$), 161.6 (C=O), 163.2 (C=O), 173.0 (C=O); MS (CI^+) *m/z* (%): 254 (MH^+, 100), 208 (55), 180 (59), 139 (31), 99 (21); $[MH]^+$, found 254.13855, $C_{13}H_{20}O_4N$ requires 254.13923.

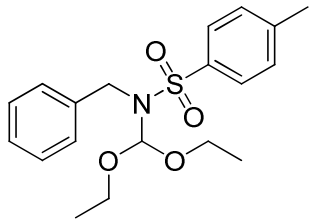
***N*-Benzyl-4-methylbenzenesulfonamide 381[160]**



Benzylamine **380** (2.2 ml, 20 mmol, 2 eq.) was added dropwise to a solution of tosyl chloride (1.9 g, 10 mmol, 1 eq.) in diethyl ether (50 ml) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 1 hour. An aqueous solution of HCl (0.5 M, 50 ml) was added to the reaction mixture to dissolve the amine salt, and the organic phase was separated and washed with an aqueous solution of HCl (0.5 M, 3 × 50 ml). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by column chromatography (petroleum ether: diethyl ether 3:2) to give **381** as a colourless solid (2.07 g, 79%).

M.p. 112-118 °C (Et_2O), lit.,[160] 111-113 °C (EtOH); IR (film): ν_{max} 3270, 1455, 1423, 1323 (s), 1178, 1165, 1060 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 4.10 (d, *J*=6.2 Hz, 2H, CH_2Ph), 4.65 (br t, *J*=5.8 Hz, 1H, NH), 7.16-7.19 (m, 2H, H-Ar), 7.21-7.27 (m, 3H, H-Ar), 7.29 (d, *J*=8.0 Hz, 2H, H-Ar), 7.74 (d, *J*=8.3 Hz, 2H, H-Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.5 (CH_3), 47.3 (CH_2), 127.2 (CH-Ar), 127.8 (CH-Ar), 127.9 (CH-Ar), 128.7 (CH-Ar), 129.7 (CH-Ar), 136.2 (C-Ar), 136.8 (C-Ar), 143.5 (C-Ar); MS (CI^+) *m/z* (%): 262 (MH^+, 10), 155 (26), 139 (31), 106 (100), 91 (94); HRMS: $[MH]^+$, found 262.08965, $C_{14}H_{16}O_2NS$ requires 262.09017.

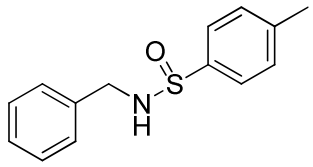
_N_-Benzyl-_N_-diethoxymethyl-4-methylbenzenesulfonamide 382



A mixture of _N_-benzyl-4-methyl-benzenesulfonamide **381** (1.0 g, 3.8 mmol, 1 eq.), triethyl orthoformate (30.0 ml, 180 mmol, 47 eq.) and aluminium chloride (77.0 mg, 0.58 mmol) was heated at 160 °C for 16 hours. After cooling the mixture was poured into a saturated aqueous solution of sodium bicarbonate (20 ml), and the resulting mixture was extracted with ethyl acetate (15 ml). The combined organic extracts were washed with brine (15 ml), concentrated under reduced pressure and the residue purified by column chromatography (petroleum ether: diethyl ether 9:1) to give **382** as a yellow oil (700 mg, 51%).

IR (film): ν_{max} 2978, 1496, 1455, 1340 (s), 1163 (s), 1055 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (t, _J_=7.0 Hz, 6H, 2 × CH_2CH_3), 2.46 (s, 3H, CH_3), 3.34-3.41 (m, 2H, 2 × $CHHCH_3$), 3.53 (dq, _J_=9.5, 7.0 Hz, 2H, 2 × $CHHCH_3$), 4.26 (s, 2H, CH_2Ph), 5.8 (s, 1H, $CH(OEt)_2$), 7.26-7.31 (m, 1H, H-Ar), 7.35 (t, _J_=7.5 Hz, 2H, H-Ar), 7.41 (d, _J_=8.0 Hz, 2H, H-Ar), 7.45 (d, _J_=8.1 Hz, 2H, H-Ar), 7.75 (d, _J_=8.4 Hz, 2H, H-Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2 (CH_3), 21.0 (CH_3), 45.0 (CH_2), 61.8 (CH_2), 104.3 (CH-Ar), 126.8 (CH-Ar), 127.4 (CH-Ar), 127.8 (CH-Ar), 128.0 (CH-Ar), 129.4 (CH-Ar), 136.3 (C-Ar), 138.3 (C-Ar), 143.4 (C-Ar); MS (EI) _m/z_ (%): 386 (MNa^+, 38), 325 (75), 318 (100), 295 (50); HRMS: $[MNa]^+$, found 386.14020, $C_{19}H_{25}O_4NSNa$ requires 386.14190.

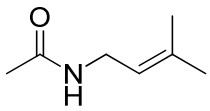
_N_-Benzyl-4-methylbenzenesulfinamide 384[162,163]



To a suspension of sodium *para*-toluenesulfinate **384** (2.92 g, 16.4 mmol, 1 eq.) in diethyl ether (15 ml) was added thionyl chloride (1.20 ml, 16.4 mmol, 1 eq.) at 0 °C over 15 min. The reaction mixture was allowed to warm to room temperature, stirred for 3 hours before being filtered and concentrated under vacuum. The residue (1.74 g, 10.0 mmol, 1 eq.) was dissolved in diethyl ether (50 ml) and cooled to 0 °C.[176] Benzylamine **380** (2.2 ml, 20 mmol, 2 eq.) was then added dropwise and the resulting mixture allowed to warm to room temperature. An aqueous solution of HCl (0.5 M, 50 ml) was added to dissolve the amine salt, and the organic phase was separated and washed with an aqueous solution of HCl (0.5 M, 2 × 50 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure and the residue was purified by column chromatography (petroleum ether:ethyl acetate 3:2) to give **386** as a pale yellow solid (1.32g, 33%).

M.p. 81-85 °C (petroleum ether) ,lit.,[163] 80-81 °C (MeOH); IR (film): ν_{max} 3213, 1597 (w), 1497, 1455, 1417, 1086, 1051 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H, CH_3), 3.90 (dd, *J*=14.7, 8.4 Hz, 1H, NH), 4.21-4.30 (m, 2H, CH_2Ph), 7.26-7.36 (m, 7H, H-Ar), 7.65 (d, *J*=8.0 Hz, 2H, H-Ar); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.4 (CH_3), 44.6 (CH_2), 126.0 (CH-Ar), 127.7 (CH-Ar), 128.3 (CH-Ar), 128.7 (CH-Ar), 129.7 (CH-Ar), 137.8 (C-Ar), 140.8 (C-Ar), 141.4 (C-Ar); MS (CI^+) *m/z* (%): 246 (MH^+, 32), 197 (68), 140 (53), 107 (100), 92 (52); HRMS: $[MH]^+$, found 246.09566, $C_{14}H_{16}ONS$ requires 246.09256.

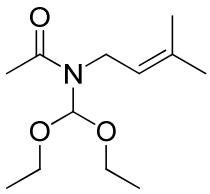
_N_-(3-Methylbut-2-enyl)acetamide 392[164]



2-Methyl but-3-ene-2 ol (861 mg, 10.0 mmol, 1 eq) and acetic anhydride (1.23 g,12.0 mmol, 1.2 eq.) were added to a solution of cobalt(II) chloride (65 mg, 0.5 mmol, 0.05 eq.) in acetonitrile (120 ml) and then heated at 80 °C for 48 hours. After removal of the solvent under reduced pressure, the residue was dissolved in ethyl acetate (50 ml), washed with a saturated aqueous solution of sodium bicarbonate (5 × 20 ml), water (3 × 20 ml) and brine (30 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated under vacuum. The residue was purified by column chromatography (petroleum ether:ethyl acetate 1:1) to give **392** as a yellow oil (220 mg, 17%).

IR (film): ν_{max} 3280, 1647 (s), 1546 (s), 1440, 1374, 1284 (s) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.69 (s, 3H, CCH_3), 1.74 (s, 3H, CCH_3), 2.00 (s, 3H, $COCH_3$), 3.84 (t, *J*= 5.9 Hz, 2H, CH_2N), 5.2 (tt, *J*=7.2, 1.4 Hz, 1H, CH=C), 5.47 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ17.9 (CH_3), 23.2 (CH_3), 25.7 (CH_3), 37.7 (CH_2), 119.9 (*C*H=C), 136.7 (*C*=CH), 170.0 (C=O).

_N_-(Diethoxymethyl)-_N_-(3-methylbut-2-enyl)acetamide 393



A mixture of **392** (217 mg, 1.70 mmol, 1 eq), triethyl orthoformate (15 ml, 90 mmol, 53 eq.) and aluminium chloride (34.0 mg, 0.25 mmol, 0.15 eq.) was heated at 165 °C for 16 hours. After cooling the resulting mixture was poured into a saturated aqueous solution of sodium bicarbonate (10 ml), and extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether: diethyl ether 1:1) to give a yellow oil which was a 1 : 1 mixture of amide rotamers **393** (163mg, 42%).

IR (mixture of rotamers 1:1, film): ν_{max} 3457 (w), 2971, 1739 (s), 1660, 1373 (s), 1217 (s), 1096, 1058 (s) cm^{-1}; ^1H NMR (mixture of rotamers 1:1, 600 MHz, $CDCl_3$): δ 1.09-1.15 (m, 6H, 2 × OCH_2CH_3), 1.61-1.69 (m, 6H, 2 × CCH_3), 1.99 (s, 1.5 H, $COCH_3$), 2.07 (s, 1.5 H, $COCH_3$), 3.38-3.46 (m, 2H, OCH_2CH_3), 3.48-3.59 (m, 2H, OCH_2CH_3), 3.75-3.83 (m, 2H, CH_2N), 5.07-5.11 (m, 1H, CH=C), 5.68 (s, 0.5 H, $CH(OEt)_2$), 6.20 (s, 0.5 H, $CH(OEt)_2$); ^{13}C NMR (mixture of rotamers 1:1, 150 MHz, $CDCl_3$): δ 15.0, 15.1, 15.2, 18.1, 22.3, 22.5, 25.9, 61.6, 61.8, 61.9, 99.8, 104.4, 105.0, 121.0, 122.4, 122.9, 132.6, 133.3, 134.0, 162.3, 169.5, 171.6; MS (FAB) *m/z* (%): 252 (MNa^+, 38), 230 (37), 185 (94), 177 (42), 155 (100); HRMS: $[MNa]^+$, found 252.15704, $C_{12}H_{23}O_3N$ requires 252.15755.

Chapter 5: References

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