UNIVERSITY OF SOUTHAMPTON

Lewis acid mediated cyclisations of methylenecyclopropyl imines

by

Suvi Henna Maria Rajamäki

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DEPARTMENT OF CHEMISTRY

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ABSTRACT

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LEWIS ACID MEDIATED CYCLISATIONS OF METHYLENECYCLOPROPYL IMINES

By Suvi Henna Maria Rajamäki

This thesis is concerned with intramolecular cyclisation reactions of methylenecyclopropyl imines mediated by Lewis acids in the formation of novel heterocyclic compounds.

Chapter 1 contains background information on synthetic chemistry involving methylenecyclopropanes. Background information on allylsilane chemistry involving Lewis acids is also described.

Chapter 2 describes synthesis and cyclisation studies of simple methylenecyclopropyl imines with different Lewis acids. These imines were found to be too unreactive for cyclisation to occur.

Chapter 3 describes the synthesis and cyclisation studies of methylenecyclopropyl imines with silyl substitution on the methylenecyclopropyl ring. Imines derived from methylenecyclopropane butyl amine were found to have the chain length required for cyclisation reactions. Various different Lewis acids and reaction conditions were studied for optimisation of the cyclisation reaction.

Chapter 4 discusses the synthesis and cyclisation studies of silylated methylenecyclopropyl imines derived from methylenecyclopropyl butyl amines with substitution on the linking alkyl chain. Effect of substitution patterns on the cyclisation reaction was studied, and was found to have an effect on the cyclisation reaction.

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Preface

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Thank you also for Sandra for keeping me more or less sane and normal during these three years, I don't think I would have made it amongst the 'natives' without you and Antonio!

Abbreviations

AIBN	2,2-azobisisobutyronitrile
Ac	acetyl
Ar	aryl
aq.	aqueous
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
b.p.	boiling point
Bu	butyl
Bz	benzoyl
°C	degrees centigrade
CAN	ceric ammonium nitrate
cat.	catalytic
CI	chemical ionisation
$(COD)_2$	Bis(1,5-cyclooctadiene)
Δ	heat
d	doublet
dba	*trans,trans*-dibenzylidene acetone
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCM	dichloromethane
DCE	1,2-dichloroethane
DEED	diethyl ethylenediamine
DHP	3,4-dihydro-2-*H*-pyran
DMAP	dimethylaminopyridine
DME	diglyme
DMF	dimethylformamide
DMPS	dimethylphenylsilyl
DMSO	dimethyl sulphoxide
EI	electron impact
ES	electrospray
Et	ethyl
eq.	equivalent(s)

GC	gas chromatography
GOESY	1D-gradient nuclear Overhauser spectroscopy
h	hour(s)
HRMS	high resolution mass spectroscopy
Hz	hertz
i	iso
IR	infrared spectroscopy
J	coupling constant
kbar	kilobar
LA	Lewis acid
LRMS	low resolution mass spectroscopy
m	multiplet
m-	meta
MCP	methylenecyclopropane
Me	methyl
mol.	molecular
m.p.	melting point
Ms	methanesulphonyl, mesyl
n-	normal
NCS	N-chlorosuccimide
NMO	N-methyl morpholine *N*-oxide
NMR	nuclear magnetic reasonance
o-	ortho
OTf	triflate
p-	para
Ph	phenyl
Phth	phthalimido
PMB	*p*-methoxybenzyl
ppm	parts per million
Pr	propyl
q	quartet
quint.	quintuplet
rt	room temperature
s	singlet

sat.	saturated
SDS	sodium dodecyl sulphate
t	triplet
t-	tertiary
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TDA-1	tris[2-(2-methoxyethoxy)ethyl]amine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	tri-isopropylsilyl
TLC	thin layer chromatography
TMM	trimethylene methane
TMS	trimethylsilyl
TOPP	tris(o-phenyl-phenyl)phosphite
Tr	trityl
Ts	toluenesulphonyl, tosyl
Å	Ångström

Chapter 1

Introduction

1.1 Methylenecyclopropane

1.1.1 General properties of methylenecyclopropane

Methylenecyclopropane (MCP) is a highly strained molecule. In addition to the ring strain on a three-membered carbon cycle, the exocyclic double bond imposes steric strain on the cyclopropane ring. This can be appreciated by comparing the bond lengths and bond angles of cyclopropane (**1**) and methylenecyclopropane (**2**). The strain in methylenecyclopropane can be seen in the increase of the length of the C-CH_2 bonds and difference in bond angles (Figure 1).[1,2]

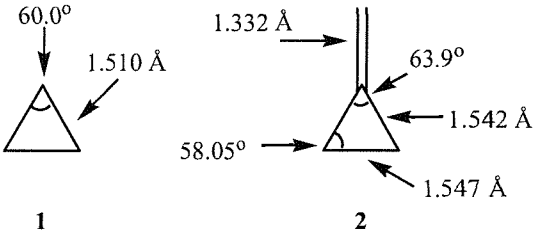


Figure 1

Comparison of cyclopropane (**1**) and methylenecyclopropane (**2**) bond lengths and bond angles.

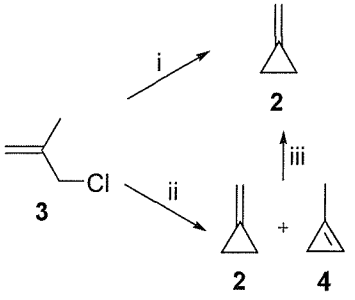
Despite the high ring strain, methylenecyclopropane is a stable structure, and can be stored in a sealed container for years.[3] Methylenecyclopropane is also a part of several natural products, which gives a further indication of its stability.[4-6] Methylenecyclopropane has been used extensively in organic synthesis because of its high reactivity and easy functionalisation.[7]

1.1.2 Synthesis of methylenecyclopropanes

1.1.2.1 Synthesis of methylenecyclopropane

Methylenecyclopropane can be synthesised in various different ways, the earliest synthesis dating as far back as 1953.[8] Many syntheses for both unsubstituted MCP and substituted methylenecyclopropanes have been developed after this date, and in 1998 Brandi and Goti wrote an extensive review on the subject.[7] The most commonly used methods have been widely reported in the literature, among them the ones described below.

Methylenecyclopropane can be easily prepared from methallyl chloride **3**,[9,10] either in one or two steps, depending on the base used in the synthesis (Scheme 1). In the one-step synthesis, methallyl chloride is deprotonated with KNH_2. The chloride then leaves to give a carbene, which inserts into a CH bond to give methylenecyclopropane.



i) KNH_2, THF, Δ ii) $NaNH_2$, *n*-Bu_2O, Δ iii) *t*-BuOK, *t*-BuOH, DMSO

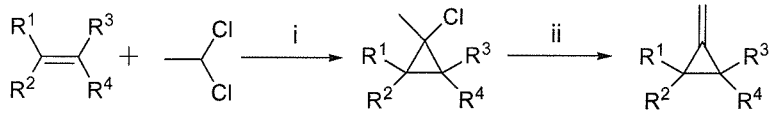
Scheme 1

In the two-step synthesis the base used to deprotonate methallyl chloride is $NaNH_2$. In this case the carbene can insert into either CH bond present in the molecule, giving a mixture of methylcyclopropene **4** and methylenecyclopropane **2**. The mixture is then fully isomerised to methylenecyclopropane in presence of *t*-BuOK in *t*-BuOH and DMSO. This method gives good yields of methylenecyclopropane, and can be used in large-scale synthesis.[9,11] Binger[12] has later introduced modifications to the original synthetic procedure to avoid difficulties in the purification of the product.

1.1.2.2 Synthesis of functionalised methylenecyclopropanes

Functionalised methylenecyclopropanes can be synthesized either by formation of the cyclopropane moiety from already substituted starting materials, or by substituting methylenecyclopropane and its derivatives with the cyclopropane ring already in place.

Methylenecyclopropane substituted on the cyclopropane ring can be synthesized conveniently by reacting an alkene of choice with a methylchlorocarbene to give a substituted chlorocyclopropane **7**. Dehydrohalogenation gives a substituted methylenecyclopropane **8** (Scheme 2).[13]

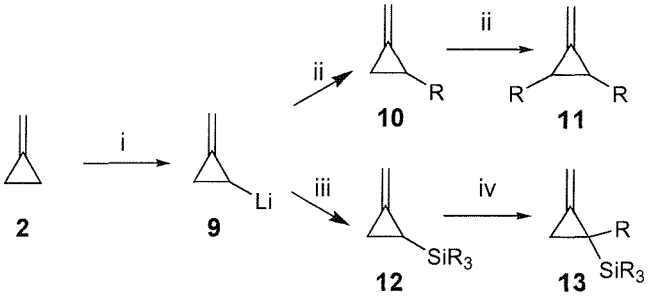


5 **6** **7** **8**

i) Et_2O, *n*-BuLi ii) t-BuOK, DMSO

Scheme 2

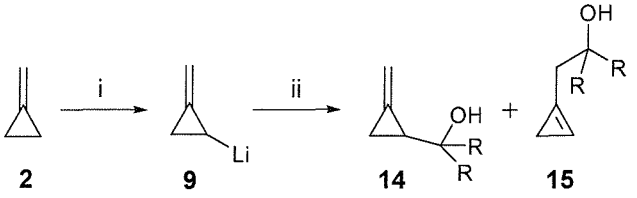
Methylenecyclopropane substituted on the cyclopropane ring can also be synthesized by reacting methylenecyclopropyl anion **9**, formed by deprotonation of methylenecyclopropane with *n*-butyllithium, with a choice of electrophile (Scheme 3).[14,15] When alkyl halides are used, substitution can be achieved exclusively on the cyclopropane ring. If a substituted methylenecyclopropane is alkylated with a second equivalent of electrophile, 1,2-substituted methylenecyclopropanes are obtained. Instead, when the first electrophile used is trialkylsilyl chloride, the second electrophile will go on the same carbon giving 1,1-substitution (Scheme 3).



i) *n*-BuLi, THF -78 °C to 0 °C, ii) R-X, THF, -78 °C, iii) R_3SiCl, THF, -78 °C, iv) 1. *n*-BuLi, THF, -78 °C to 0 °C, 2. R-X, THF, -78 °C.

Scheme 3

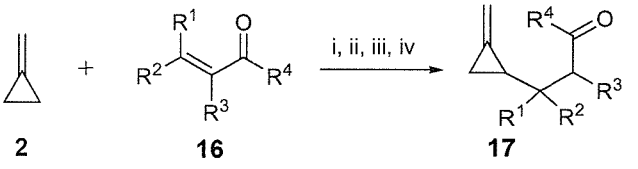
When aldehydes and ketones are used to alkylate methylenecyclopropyl anion, γ-alkylation is also possible leading to substituted methylcyclopropenes **15** and methylenecyclopropanes **14** (Scheme 4).[14,16]



i) n-BuLi, THF, -78 °C to 0 °C, ii) R_2CO, THF, -78 °C.

Scheme 4

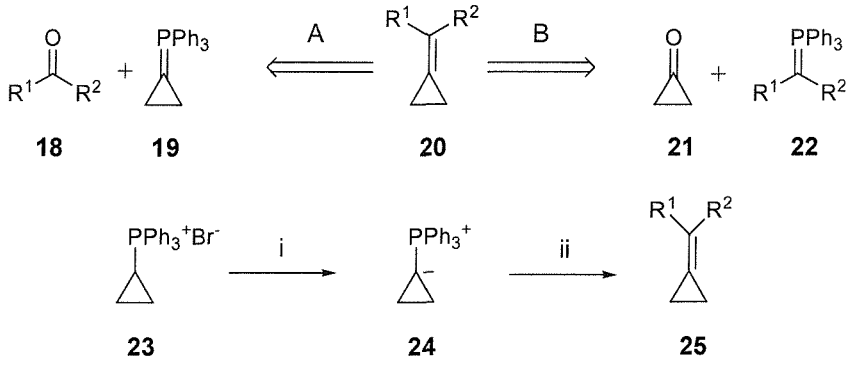
Peron[17,18] has shown that substituted methylenecyclopropanes can also be synthesised by 1,4-addition of lithium bis(methylenecyclopropyl) cuprate to various different α,β-unsaturated ketones to give different methylenecyclopropyl ketones in good yields (Scheme 5).



i) n-BuLi, THF, -30°C, ii) CuI, iii) **16**, iv) 2M HCl. yield 59-95%

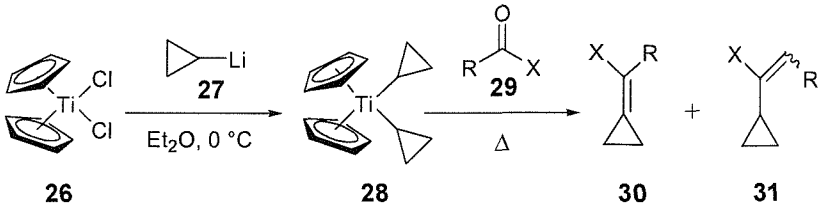
Scheme 5

The most widely used method for synthesis of alkylidene cyclopropanes is Wittig olefination. This reaction is normally carried out starting from commercially available cyclopropyltriphenylphosphonium bromide **23** and the carbonyl compound of choice (Scheme 6, route A).[19-22] An improvement on the original method was developed by McMurry by adding 10% TDA-1 (tris[2-(2-methoxyethoxy)ethyl]amine), a phase-transfer catalyst that helps to solvate counter ions, so facilitating the reaction.[23] This method was further enhanced by Maercker by use of less expensive bases and reduced reaction times.[24] Route B[25] is not as widely used due to the unavailability of cyclopropanones and low reactivity of its synthetic equivalent cyclopropane hemiacetal.[7]



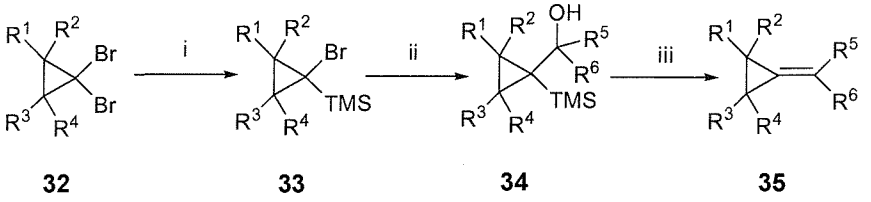
Scheme 6

Alkylidene cyclopropanes can also be synthesised via a method described by Petasis.[26] In this method, biscyclopropyl titanocene is reacted with a carbonyl compound. Biscyclopropyl titanocene **28** is prepared by reacting titanocene dichloride **26** with cyclopropyllithium **27**, which in turn is generated from cyclopropyl bromide and lithium metal. Heating biscyclopropyl titanocene in toluene with carbonyl compounds gives the corresponding cyclopropylidenes **30** (Scheme 7). During isolation some of the alkylidene cyclopropanes partially isomerise to give vinyl cyclopropanes **31**. The method can also be used with enolisable carbonyl compounds.[26]



Scheme 7

A more versatile method for the synthesis of alkylidene cyclopropanes is *via* Peterson olefination.[27] This method enables synthesis of alkylidene cyclopropanes that have substituents in the cyclopropane ring. α-Bromo-α-silylcyclopropane **33** is formed by reacting 1,1-dibromocyclopropane **32** with *n*-BuLi and quenching the resulting anion with trimethylsilyl chloride. The α-bromo-α-silylcyclopropane **33** is then reacted with *n*-BuLi followed by an aldehyde or a ketone to give a β-silyl alcohol **34**, which when treated with KH gives alkylidene cyclopropanes **35** (Scheme 8).



i) 1. *n*-BuLi, THF, -100 °C, 2. TMSCl, THF, -100 °C to -20 °C, ii) 1. *n*-BuLi, THF,-78 °C, 2. $R^5(CO)R^6$, 3. H_2O, iii) KH, THF, 20 °C

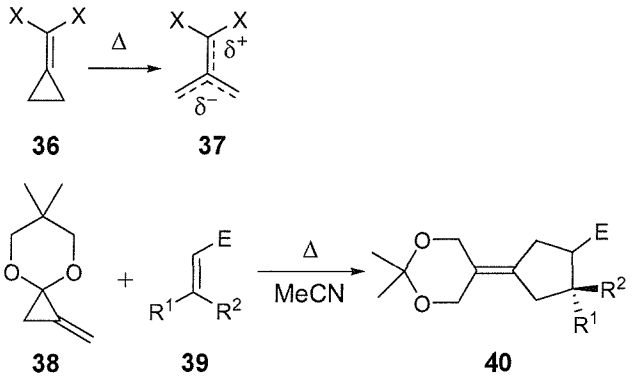
Scheme 8

1.1.3. Use of methylenecyclopropanes in chemistry

Over the last few decades use of methylenecyclopropane in organic synthesis has been widely developed. Methylenecyclopropanes are used in a variety of reactions, for example [3+2] cycloadditions, 1,3-dipolar cycloadditions, Diels-Alder reactions and Pauson-Khand reactions.[28]

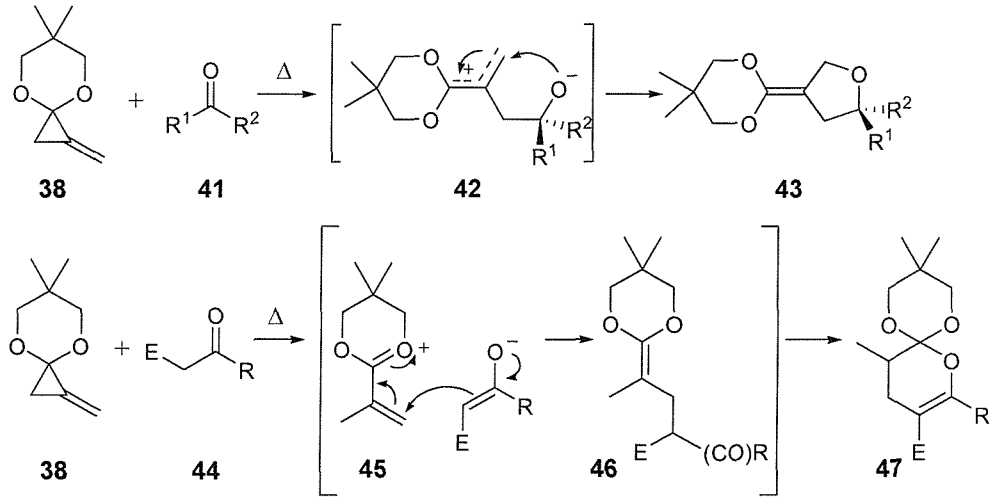
1.1.3.1. Thermal rearrangements

Trimethylene methane (TMM) species **37** can be reversibly generated from methylenecyclopropanes in many ways,[28,29] one of which is thermolysis. TMMs undergo [3+2] and [3+3] cycloadditions with C=X bonds or acetylenic receptors, giving access to various different heterocycles. They also react in 1,3-dipolar reactions with nitrones to give spirocyclic products that give both mono- and bicyclic heterocycles *via* rearrangement.[30-32]



Scheme 9

One of the [3+2] cycloaddition reactions known in TMM chemistry is a reaction of methylenecyclopropane ketals with C=X species such as electron-deficient olefins,[33,34] alkenes, alkynes,[34] acetals[35] oximes[36,37] or carbonyl compounds (Scheme 9).[34,38] When heated to moderate temperatures, methylenecyclopropane ketals form TMM species that are stabilised by the presence of the electron rich ketal in the molecule.[34] The formed TMM species can then undergo cycloaddition reactions with C=X species to give five-membered cyclic products **43** (scheme 10).

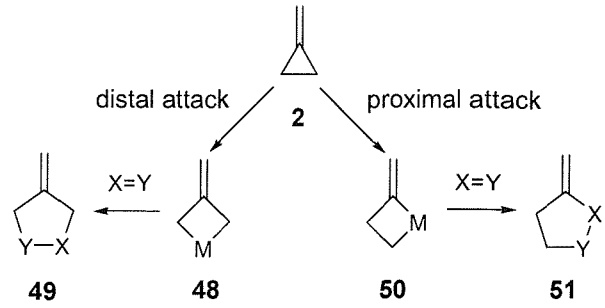


Scheme 10

When reacted with carbonyl compounds, TMM ketals give functionalised tetrahydrofurans **43**. These reactions can be performed in very mild conditions, with good regioselectivity.[39] A similar reaction with 1,3-dicarbonyl compounds gives dihydropyrans **47** as products (Scheme 10).[38]

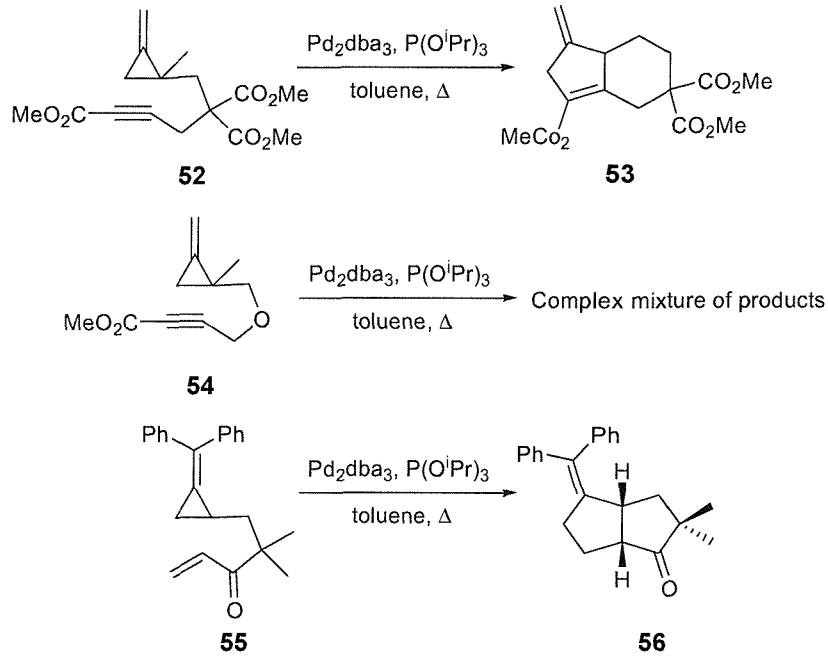
1.1.3.2 Transition metal catalysed cycloaddition reactions

Transition metal catalysed [3+2] cycloaddition reactions of methylenecyclopropanes have been extensively studied as they allow the formation of cyclopentane rings.[2,40,41] The most commonly used catalysts are palladium and nickel complexes. Depending on the catalyst used the reaction can proceed *via* two different pathways leading to two regioisomeric products. When a palladium catalyst is used, the reaction proceeds mainly through distal attack on the methylenecyclopropane. Nickel catalysts give predominantly proximal cleavage with methylenecyclopropane, but as substitution is added onto the methylenecyclopropane, distal cleavage becomes more favourable (Scheme 11).[28,41] Exclusive distal ring opening occurs if the methylenecyclopropane is substituted with a diaryl moiety at a cyclopropyl carbon or vinylic carbon.[42]



Scheme 11

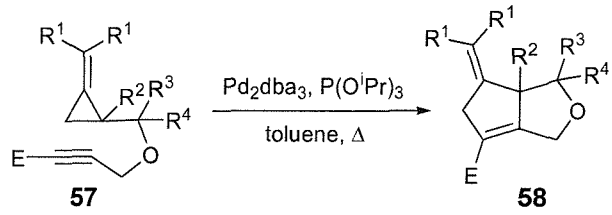
Intermolecular cycloaddition reactions of methylenecyclopropanes are largely affected by dimerisation problems and lack of stereochemical control.[43] This problem is avoided in intramolecular cyclisations in which the reaction components are tethered together. Motherwell[44,45] has studied the Pd(0) catalysed intramolecular cycloaddition of acetylenes and alkenes such as **52**, **54** and **55** to methylenecyclopropane (Scheme 12).



Scheme 12

Lautens[42,46,47] has studied the effect of substitution at different positions in the molecule (Scheme 13). Substitution at R^3 and R^4 positions had no effect on the cyclisation, nor did substitution on the methylene carbon R^1. The nature of the substituent on the

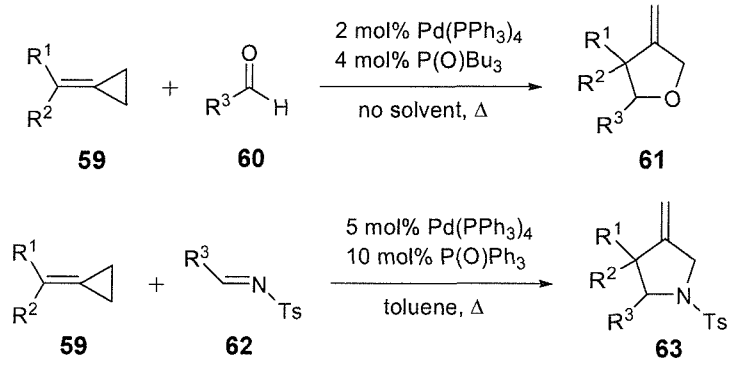
cyclopropyl carbon R^2 and on the acetylene (E) had a marked effect on the reaction. The reaction proceeded smoothly when R^2 = H or OMe, but when R^2 = Me no reaction was observed. When the catalyst was changed to $Pd(PPh_3)_4$, the reaction with R^2 = Me proceeded in moderate yields. Reactions with substrates where E is a strong electron withdrawing group such as an ester or a ketone proceeded in good yields. Even as E was changed to less electron withdrawing group yields were excellent, except when E = Me, when hardly any product was formed.



57 **58**

Scheme 13

Alkylidene cyclopropanes have also been shown to perform [3+2] cycloaddition reactions with aldehydes[48] and imines [49] to give substituted tetrahydrofurans **61** and pyrrolidines **63**, respectively (Scheme 14).

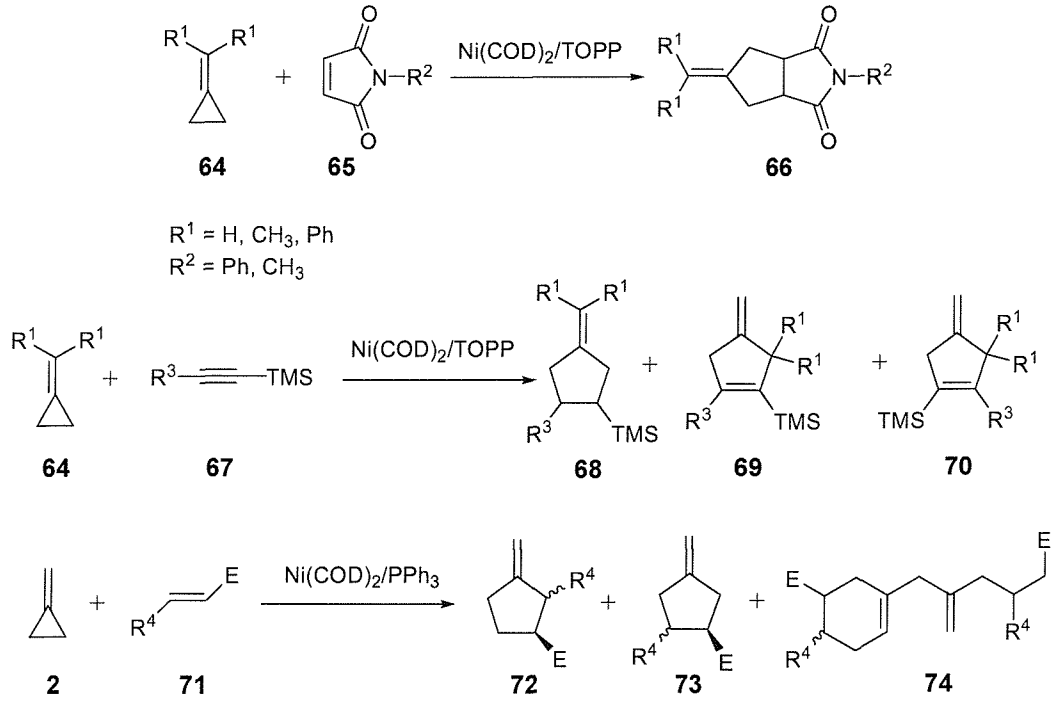


59 **60** **61**

59 **62** **63**

Scheme 14

Nickel catalysed cycloadditions are not as widely studied as the palladium catalysed ones. Binger[50-52] has studied Ni catalysed cycloadditions of methylenecyclopropanes to substituted maleimides **65**, electron-deficient alkenes **71** and alkynyl trimethylsilanes **67** (Scheme 15). Regioselectivity in these reactions is often very poor, making them less applicable to organic synthesis.

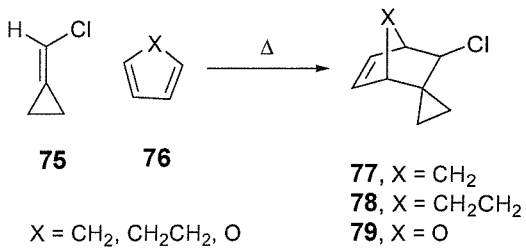


Scheme 15

Reaction of substituted MCPs with *N*-substituted maleimides **65** gave bicycles **66** in good yields, but no product was formed in the case of unsubstituted maleimides or malic anhydride. Also reaction with unsubstituted MCP failed.[51] Reactions of MCPs with alkylidene trimethylsilanes and electron deficient olefins gave a mixture of products, except in some individual cases.[50,52]

1.1.3.3 Diels-Alder reactions

The Diels-Alder reaction with methylenecyclopropanes has not been very extensively reported in literature. Intermolecular Diels-Alder reactions between furans and halomethylene cyclopropanes have been studied by Bottini.[53] Chloromethylenecyclopropane **75** reacted with cyclopentadiene, furan, and 1,3-cyclohexadiene at 190 °C to give compounds **77** – **79** in good yields (Scheme 16).



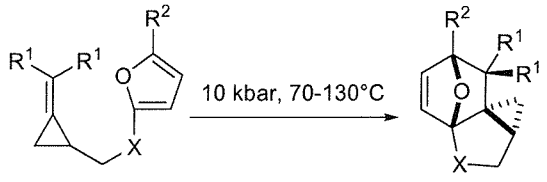
75 **76**

X = CH_2, CH_2CH_2, O

77, X = CH_2
78, X = CH_2CH_2
79, X = O

Scheme 16

Intramolecular Diels-Alder reactions of methylenecyclopropane furans **80** when exposed to high pressure give interesting complex fused ring structures in good yields, as shown by Meijere (Scheme 17).[54-56]

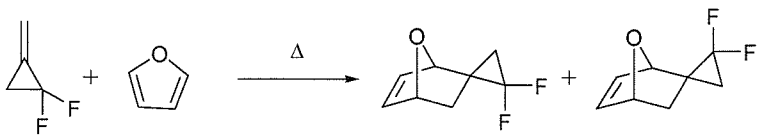


80 **81**

R^1 = CH_2, H
R^2 = CH_2, CH_2O, $SiMe_2O$

Scheme 17

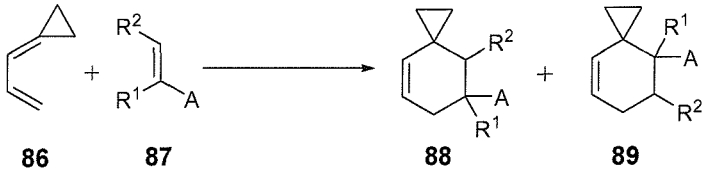
Substitution of two or more of the ring protons with fluorine markedly increases the dienophilicity of methylenecyclopropane.[57] For example, 1,1-difluoromethylenecyclopropane **82** undergoes a Diels-Alder cyclisation with furan, giving spirofused heterocyclic products, almost solely the endo-adduct **84** (Scheme 18).



82 **83** **84** **85**

Scheme 18

Alkylidene cyclopropanes such as **86** can also act as dienophiles in Diels-Alder reactions. When Krief reacted alkylidene cyclopropane **86** with different electrophilic olefins, **88** was obtained in moderate to good yields, and in some cases also **89** as a minor product (Scheme 19). [58]



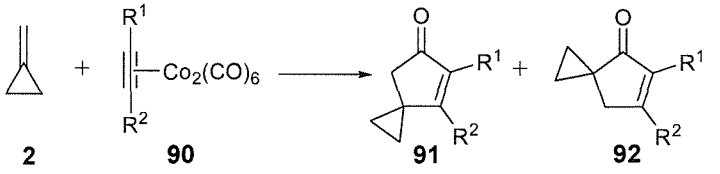
86 **87** **88** **89**

R^1 = H, CH_3
R^2 = H, CH_3
A = CO_2CH_3, CHO, NO_2

Scheme 19

1.1.3.4 Pauson-Khand reactions with methylenecyclopropane

The ring strain on methylenecyclopropane facilitates Pauson-Khand reactions between dicobalthexacarbonyl alkyne complexes and the methylenecyclopropane double bond. The intermolecular reaction of methylenecyclopropane with alkyne cobalt complex **90** has been shown to require dry reaction conditions previously developed for Pauson-Khand reactions,[59,60] where no solvent is used, and the reagents are adsorbed onto chromatography adsorbents such as SiO_2 or Al_2O_3. Smit studied the intermolecular Pauson-Khand reaction between methylenecyclopropane and various different alkynes, also changing the nature of the solid support. [60] Cyclopentanones **91** and **92** were obtained as a mixture, in moderate to good yields (Scheme 20).

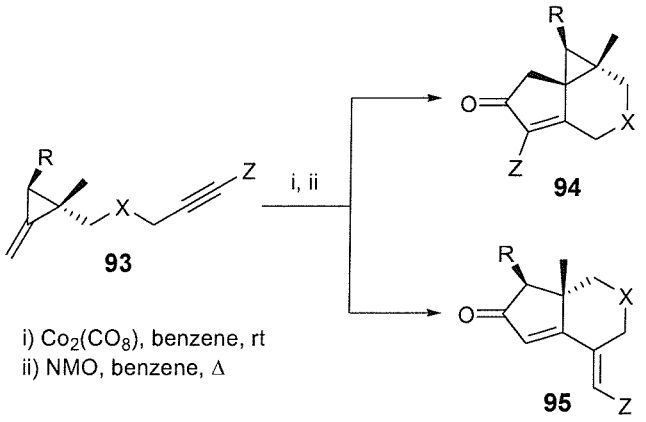


2 **90** **91** **92**

Scheme 20

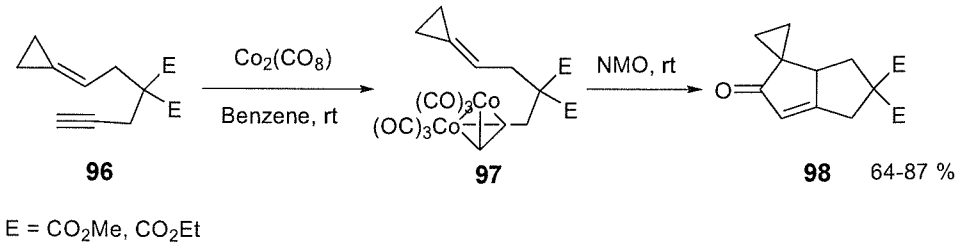
Motherwell has studied intermolecular Pauson- Khand reactions between substituted methylenecyclopropanes and alkynes, but these reactions gave mixtures of compounds

in poor to moderate yields.[61] He also studied intramolecular reactions of methylenecyclopropyl alkylidenes where the alkylidene was tethered to the cyclopropyl ring.[62] Reaction of **93** with $Co_2(CO)_8$ gave either **94** or **95** depending on the substiuents on the cyclopropyl ring and the alkyne (Scheme 21).



Scheme 21

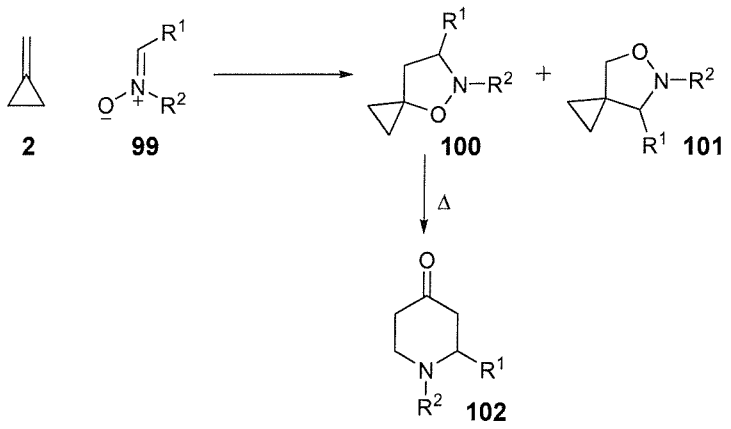
De Meijere has studied intramolecular Pauson-Khand reaction of **96**, in which the alkyl moiety is tethered to the methylene carbon.[63] Reacting cobalt complex **97** in the presence of NMO gave bicyclic **98** in moderate to excellent yields (Scheme 22).



Scheme 22

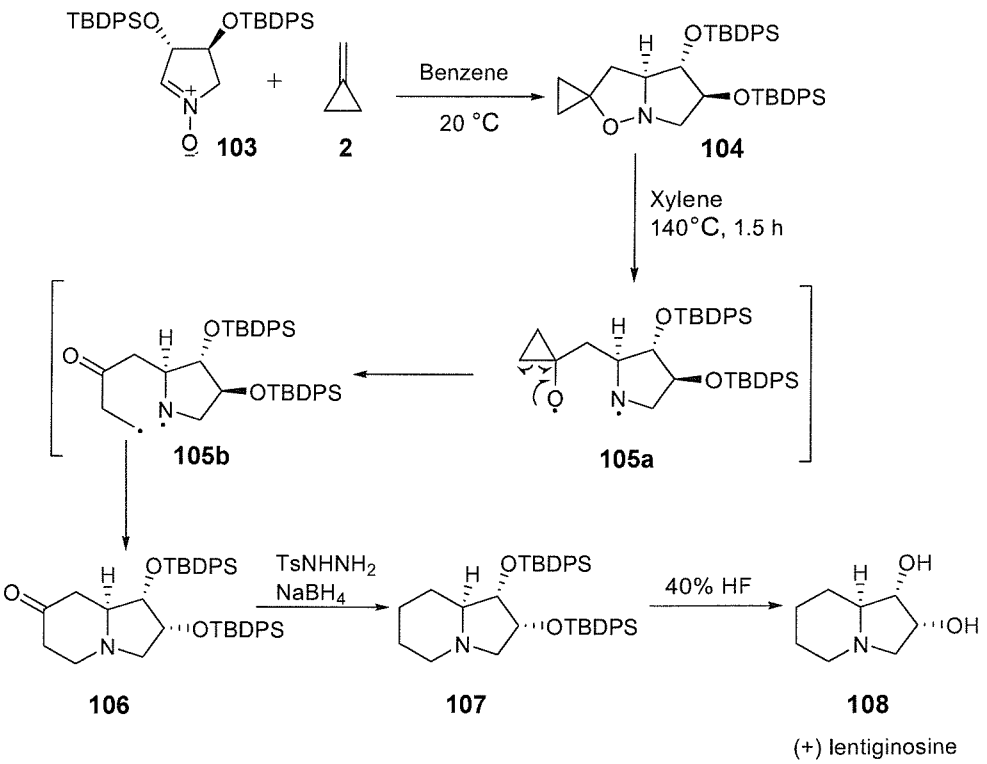
1.1.3.5 Cycloadditions of methylenecyclopropanes with nitrones

Methylenecyclopropanes add to nitrones in [3+2] fashion to form spiro-fused heterocycles, which via thermal rearrangement provide a route to indolizidines **102** (Scheme 23).[30-32,64-67]



Scheme 23

Nitrones with different substituents give varying ratios of **100** and **101**.[68] The steric hindrance of the substituents R^1 and R^2 guides the reaction towards a greater proportion of **100** compared to **101**.[32]

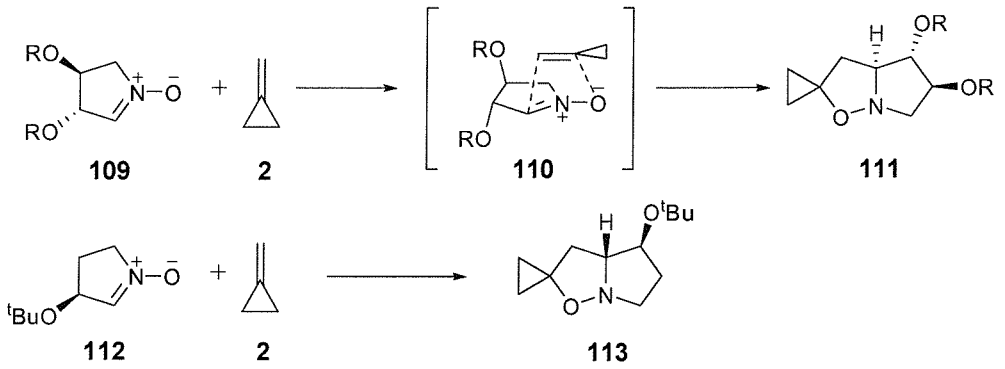


Scheme 24

When cyclic nitrones are used, bicyclic ketones with nitrogen at the bridgehead can be obtained. This provides a synthetic route to many naturally occurring alkaloids. This method had been utilised by Brandi to synthesise (-) and (+)-lentiginosine **108** (Scheme 24).[31,64,66,67]

Spirocyclopropane **104** was obtained from a reaction between methylenecyclopropane **2** and nitrone **103**. Spirocyclopropane **104** then underwent a thermal rearrangement to give indolizidine **106**. Reduction followed by deprotection gave lentiginosine **108** in good yield.

The key to successful stereoselective synthesis of lentinginosine is the use of chiral nitrones (Scheme 25). The stereoselectivity of the L-tartaric acid derived nitrones **109** depends on the size of the hydroxyl protecting groups, giving mainly *anti*-product **111**. When nitrone **112** derived from L-malic acid was used, *syn*-product **113** was formed exclusively (Scheme 25).[16,68]

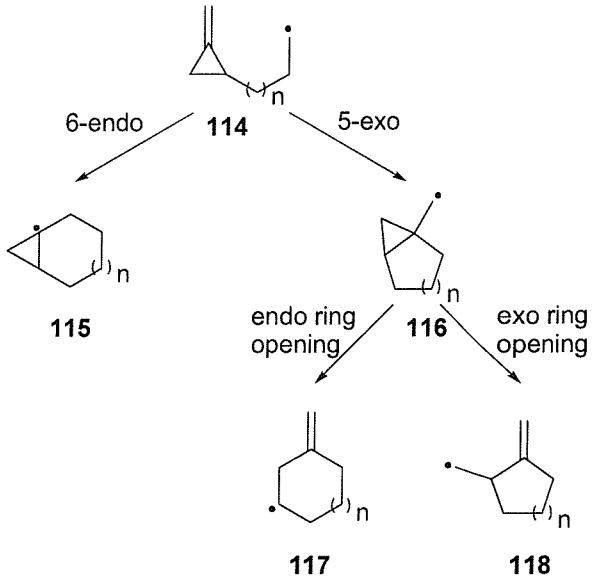


Scheme 25

1.1.3.6 Radical cyclisations of methylenecyclopropyl derivatives

Radical cyclisations of methylenecyclopropyl derivatives have been extensively investigated in the recent years. The first studies were conducted by Destabel and Kilburn, who investigated the cyclisation of methylenecyclopropyl radical **114** to establish general rules for the cyclisation of methylenecyclopropyl radicals.[69-71]

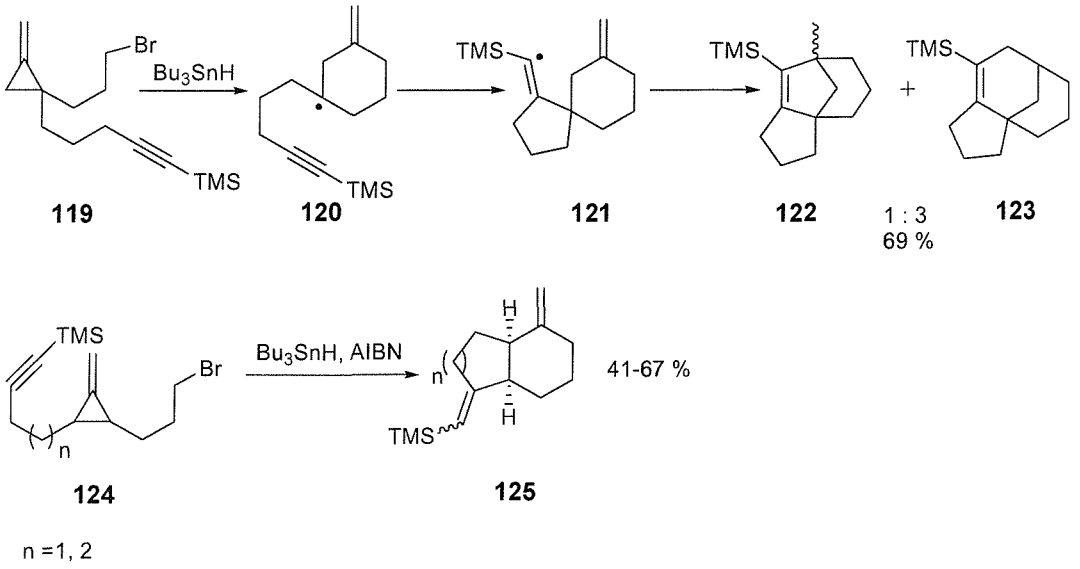
There are two possible initial cyclisation pathways, 6-*endo* and 5-*exo*. The 6-*endo* would be favoured due to less steric hindrance, leading to a relatively stable cyclopropyl radical **115**. The 5-*exo* cyclisation leads to a less stable cyclopropyl methyl radical **116**, which would be expected to open rapidly to give either the ring expanded methylenecycloalkyl radical **117** or the cycloalkylmethyl radical **118** (Scheme 26).



Scheme 26

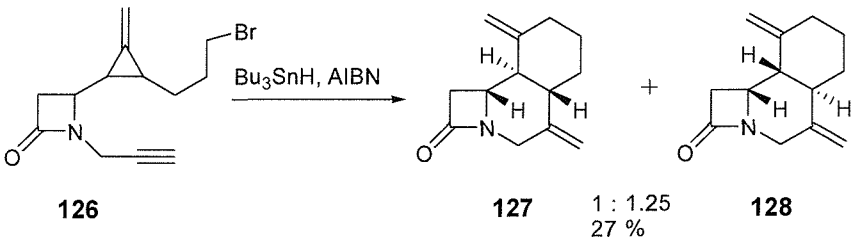
It was found that methylenecyclopropyl propyl radical (n = 1) cyclised exclusively *via* the 5-*exo* cyclisation route, followed by *endo* ring opening, whereas methylenecyclopropyl butyl radical (n = 2) gives a mixture of 5-*exo* and 6-*endo* products.

The radical cyclisations were extended to cascade cyclisations by Santagostino[72,73] to afford spirocyclic products, and by Pike[74] to give fused 6,5- and 6,6-bicyclic compounds (Scheme 27).



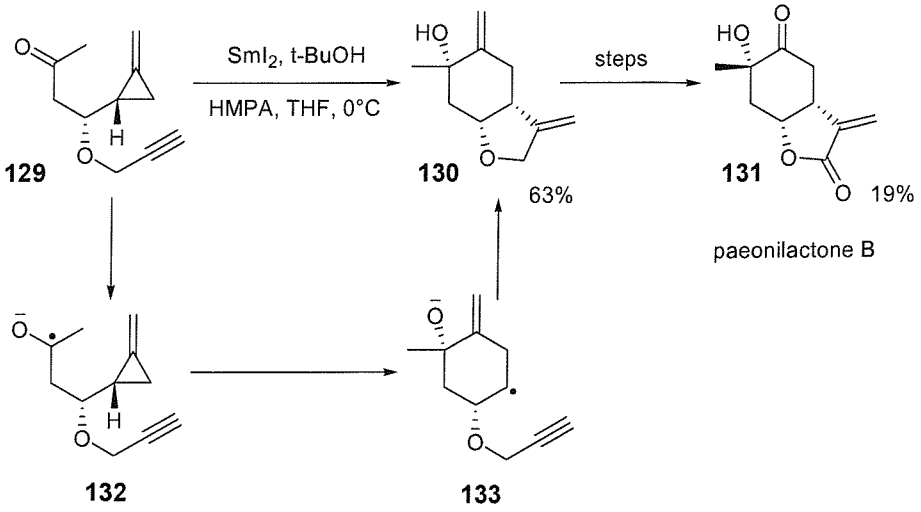
Scheme 27

Penfold[75] extended the cascade cyclisations to methylenecyclopropyl azetidinone **126** to synthesise a tricyclic β-lactam. Bu_3SnH treatment of azetidinone **126** gave an alkenyl radical, which added onto methylenecyclopropane to give tricyclic lactams **127** and **128** as a 1 : 2.25 mixture of diastereomers (Scheme 28).



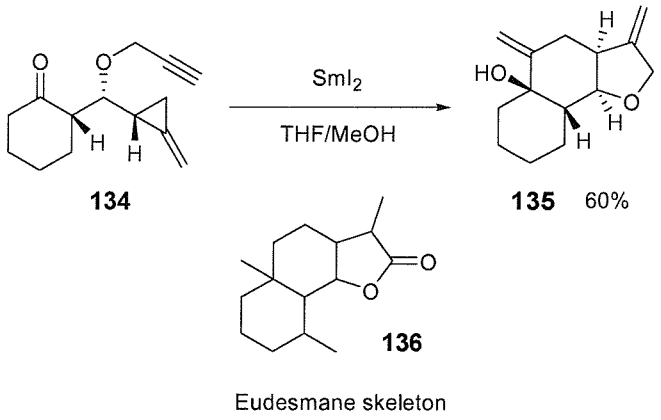
Scheme 28

Boffey[76-78] utilised SmI_2 mediated cyclisation of **129** in the synthesis of natural product paeonilactone B **131** (Scheme 29). SmI_2 treatment of ketone **129** generated a ketyl radical anion, which cyclised to give a methylenecyclohexyl radical **133**, which underwent a second cyclisation to give **130**. Functional group transformations then gave paeonilactone B **131**.



Scheme 29

Recently, Watson[79] used the same method to synthesise the tricyclic framework of eudesmane **136**. Watson treated ketone **134** with SmI_2 to give tricycle **135** in good yield (Scheme 30).



Scheme 30

1.2 Lewis Acids and Allylsilanes

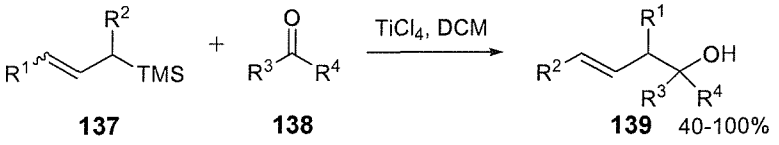
The use of Lewis acids in organic synthesis in recent years has risen almost exponentially. Although Lewis acids are now routinely used in many reactions, the process of choosing the appropriate Lewis acids for novel reactions can often be quite difficult. A review by Carlson defines thermodynamic parameters of many different

Lewis acids. Knowing the thermodynamic properties of different Lewis acids can help to choose the Lewis acid used in novel reactions.[80]

There are many examples of use of the Lewis acids in reactions of allyl silanes or allyl stannanes with carbonyl compounds or imines. These reactions are of particular interest in methylenecyclopropyl chemistry, as allyl silanes and allyl stannanes have a highly reactive double bond, like methylenecyclopropane. Indeed, silyl-substituted methylenecyclopropanes can be seen as cyclic allyl silanes, the ring strain of MCP providing the double bond with even greater reactivity.

1.2.1 Allyl silanes and carbonyl compounds

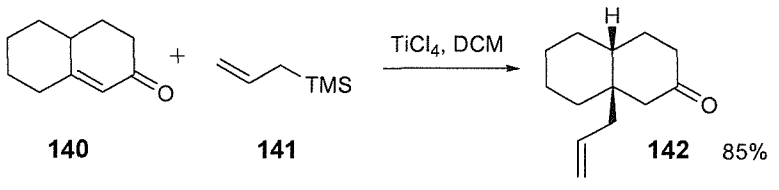
Addition of allyl silanes to aldehydes and ketones in presence of a Lewis acid to give a β-allyl alcohol is a reaction widely utilised in synthetic chemistry. One of the first examples of these reactions is the Sakurai reaction, where addition of a ketone or an aldehyde to an allyl silane is catalysed with $TiCl_4$ (Scheme 31).[81] This reaction can be performed with various different aliphatic and aromatic substituents both on the allyl silane and on the carbonyl compound.



137 **138** **139** 40-100%

Scheme 31

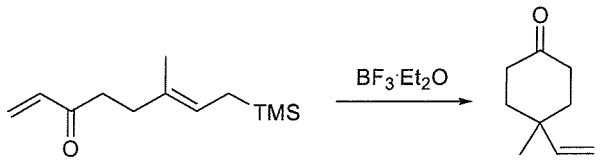
Later Sakurai extended this method to cyclic α,β-unsaturated ketones to give **142** in good yield[82] (Scheme 32).



140 **141** **142** 85%

Scheme 32

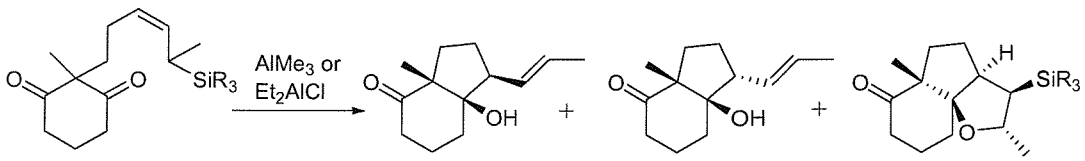
In 1982 Price published the first intramolecular example of the Hosomi-Sakurai reaction (Scheme 33).[83] Schinzer has also extensively studied the factors contributing to the stereochemical outcome of these reactions.[84,85]



143 **144** 73%

Scheme 33

A good example of how the nature of achiral starting materials and Lewis acids can affect the stereochemical outcome of reactions of carbonyls with allyl silanes is the synthesis of bicyclic and tricyclic furans by an intramolecular tandem reaction of allylsilyl-1,3-diketone **145**.[84] When Et_2AlCl was used, a mixture of **146** and **147** in 3:1 ratio was obtained, with tricycle **148** as a side product. When $AlMe_3$ was used as a catalyst, **148** was obtained as the major product and the ratio of **146** and **147** changed to 1:4. When SiR_3 was changed from $SiMe_3$ to Si^iPr_3 and $AlMe_3$ was used as a catalyst, **148** was obtained as the only product in excellent yields. (Scheme 34).

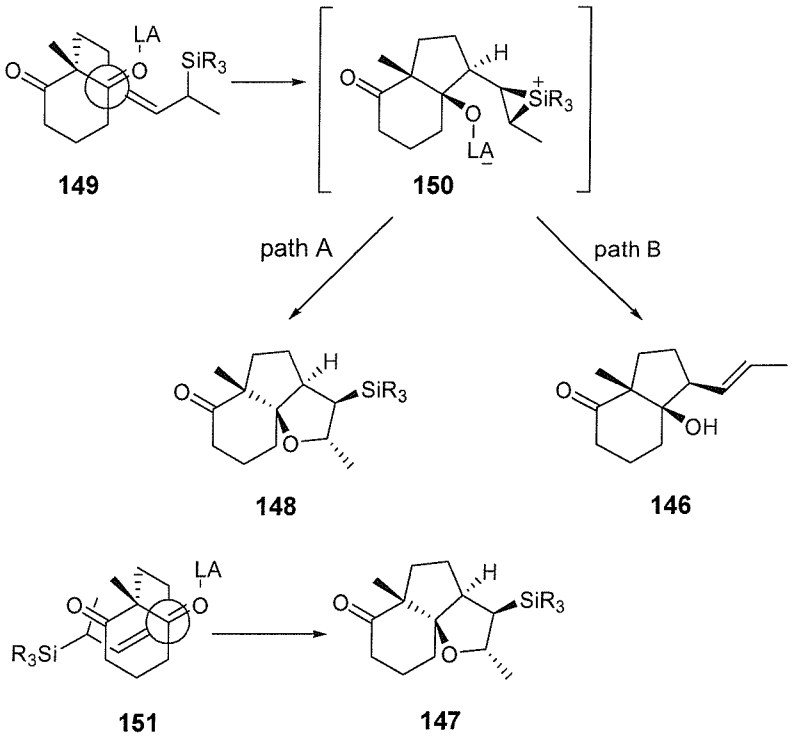


145 **146** **147** **148**

Scheme 34

Formation of compounds **146** and **148** can be explained by a *synclinical* transition state **149** (Scheme 35). The intermediate **150** can react via two different paths. Path A goes via an *exo-5-tet*-cyclisation and forms tricycle **148**. This path is favoured by bulky silyl groups and branched allyl silanes because the hindered environment prevents fast desilylation. **148** is formed from **150** by a sila-Wagner-Meerwein silyl shift, assisted by the alkoxide formed in the initial cyclisation step. With smaller silyl groups

intermediate **150** collapses by an attack on the silyl atom to form **146**. The anti-periplanar transition state **151** explains the formation of bicycle **147**.



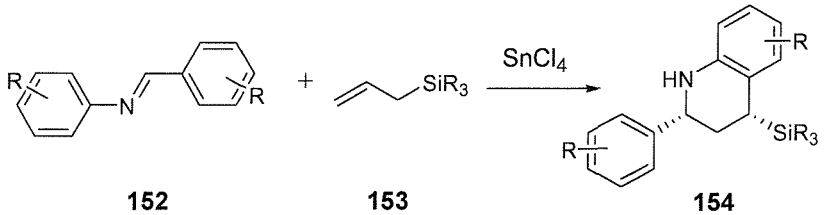
Scheme 35

Reactions of carbonyl compounds with allylsilanes have later been improved by various groups to give enantiomerically pure products by the use of chiral starting materials[86,87] or chiral Lewis acids.[88,89]

1.2.2 Allylsilanes and imines

Reactions of allyl silanes with imines are not as common as reactions with carbonyl compounds. These reactions can be problematic to perform due to the low nucleophilicity of allyl silanes and the poor electrophilicity of imines. In fact, the reactions reported are normally specific cases and cannot be easily modified for other reaction systems. Reactions of allyl stannanes with imines are more common despite the high toxicity of tin, as changing the metal from silicon to tin enhances the nucleophilicity of the allyl compound.[90-95] Reaction rates can also be enhanced by the use of iminium ions instead of imines.[96-99]

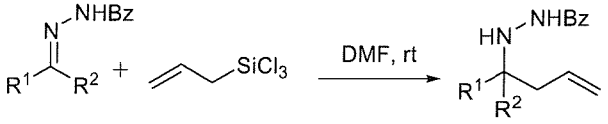
Akiyama[100] has synthesised tetrahydroquinolines *via* an acid promoted hetero Diels-Alder reaction by treating aromatic imines derived from aromatic aldehydes and anilines with allylsilane in the presence of $SnCl_4$ in excellent yields (Scheme 36).



152 **153** **154**

Scheme 36

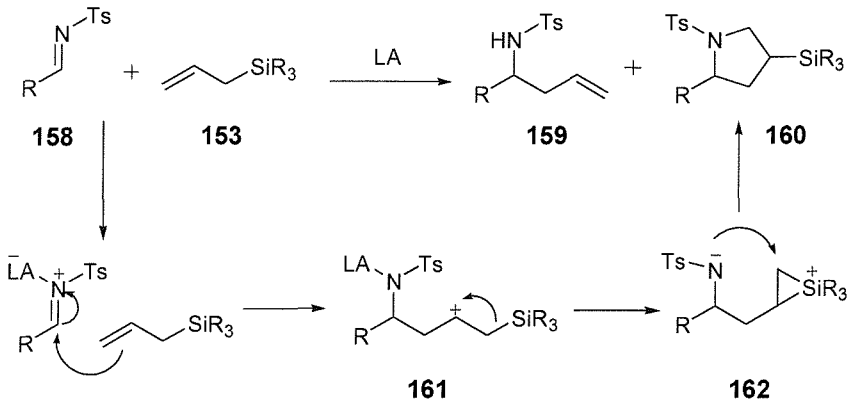
Reactions of benzyl- and tosylhydrazones with allyl silanes are more common than the corresponding reactions of imines. Kobayashi has shown that reaction of benzyl hydrazone with allyltrichlorosilane gives homoallylic amines in good yields when reacted with allyltrichlorosilanes in neutral reaction conditions (Scheme 37).[101-103]



155 **156** **157**

Scheme 37

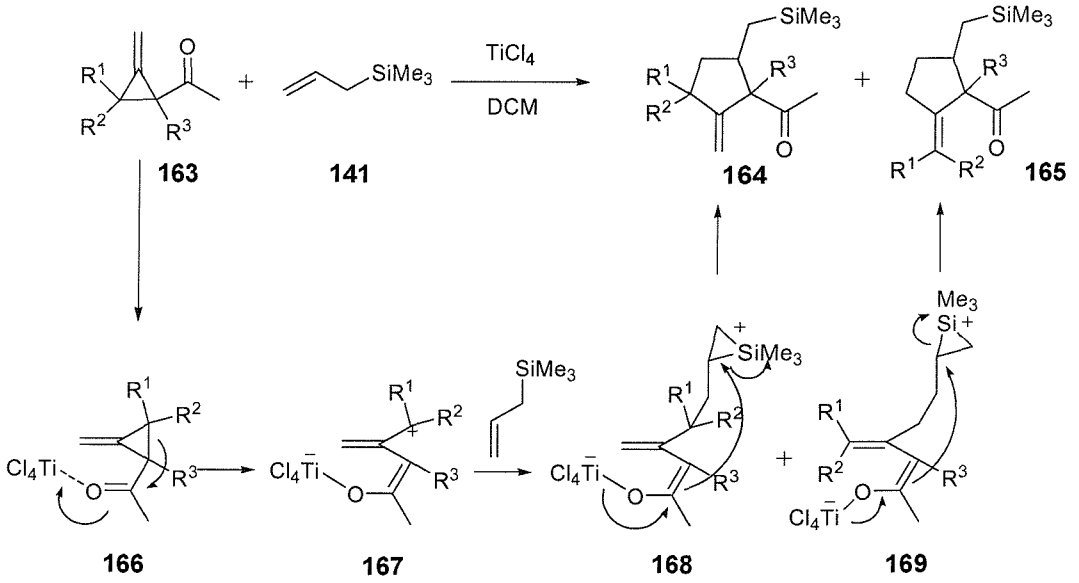
Similar reactions have also been carried out with tosylimines **158**. When treated with a Lewis acid, as well as the acyclic compound **159**, also **160** can be obtained, the outcome of the reaction depending on the starting materials and reaction conditions (Scheme 38).[96,104,105]



Scheme 38

1.3 Lewis acids and methylenecyclopropane

Lewis acid mediated reactions of methylenecyclopropanes have only been studied in the recent years. Work was initiated by Monti,[106,107] and soon followed by Hosomi.[108] Monti studied the Lewis acid mediated [3+2] cycloannulation of methylenecyclopropyl ketones **163** and allyl silane to give methylenecyclopentane **164** and **165** (Scheme 39).



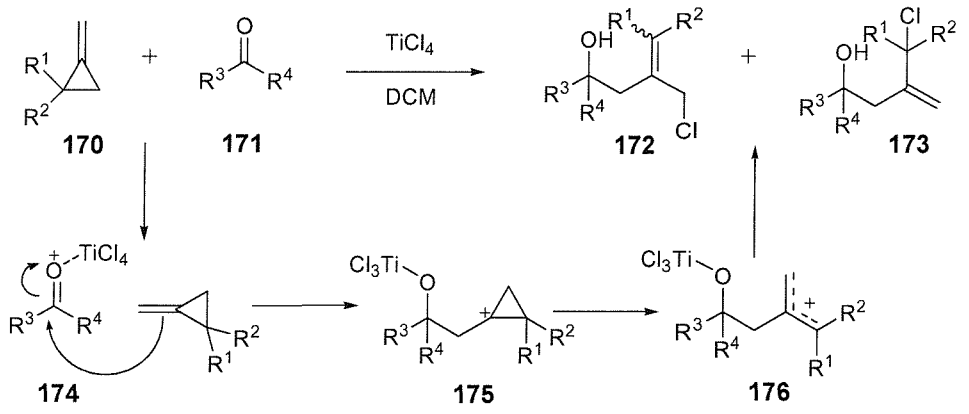
Scheme 39

The reaction is assumed to proceed via the allyl cation intermediate **167** due to the chelation between $TiCl_4$, the carbonyl and the exocyclic double bond of

methylenecyclopropane (**166**). Addition of the allyl silane to the cation gives siliranium cations **168** and **169**, which then collapse to give **164** and **165**.

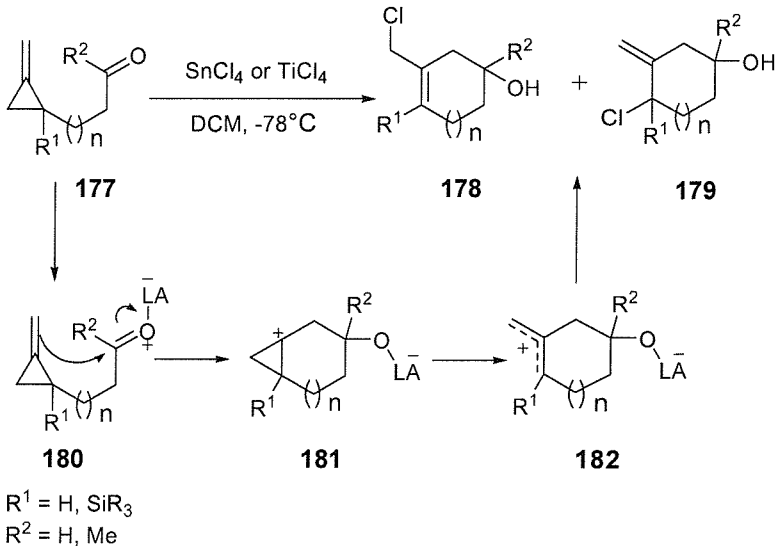
Hosomi[108] showed that methylenecyclopropanes couple to carbonyl compounds in the presence of a Lewis acid to give acyclic alcohols **172** and **173** (Scheme 40). Hosomi experimented with various different Lewis acids, and the best results were obtained with aldehydes and unsubstituted methylenecyclopropane, using $TiCl_4$ as catalyst.

Hosomi proposed a mechanism for the allylation, where the Lewis acid coordinates to the carbonyl to form complex **174**. Methylenecyclopropyl olefin then attacks the carbonyl carbon leading to π-allyl cation **176**, that is in turn quenched by chloride to give chloroalkenols **172** and **173** (Scheme 40).



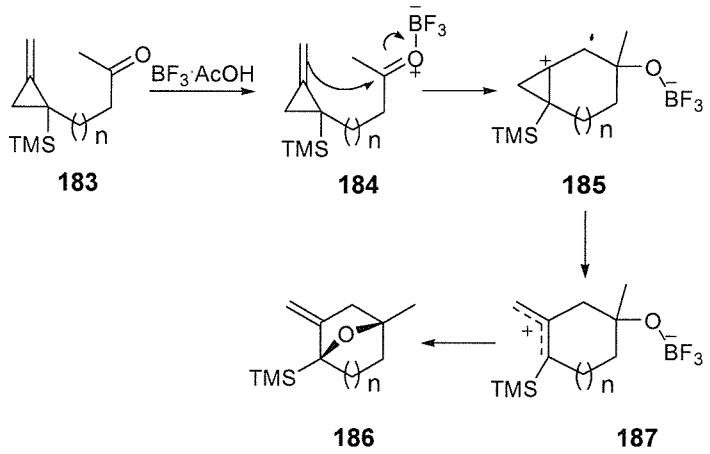
Scheme 40

Following Hosomi's work, Peron[109,110] tethered the carbonyl moiety onto methylenecyclopropane to study the intramolecular reactions of methylenecyclopropane with a carbonyl group. The reaction worked well with both ketones and aldehydes, giving cyclic compounds with six- and seven membered rings. The mechanism of the reaction was consistent with the mechanism proposed by Hosomi (Scheme 41).



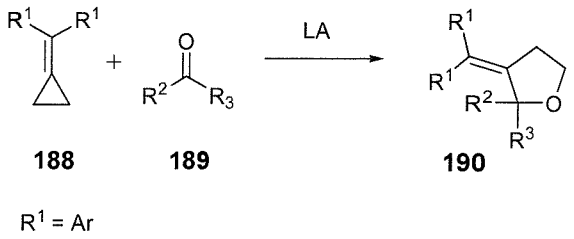
Scheme 41

Changing R^1 = H to R^1 = $SiMe_3$ was found to increase the yields of the cyclisation reactions markedly, as this enhanced the nucleophilicity of the methylenecyclopropane olefin. Silicon stabilises the β-silyl cation in intermediate **181**. Normally silicon elimination from a β-silyl cation is rapid, but in this case rearrangement of the cyclopropyl ring to the unstable allyl cation **182** is much faster, and **182** is quenched to give **178** and **179** (Scheme 41). Peron also found that changing the Lewis acid to BF_3·AcOH resulted in bridged ether **186** as a result of intramolecular trapping of cation **187** by the oxygen (Scheme 42).



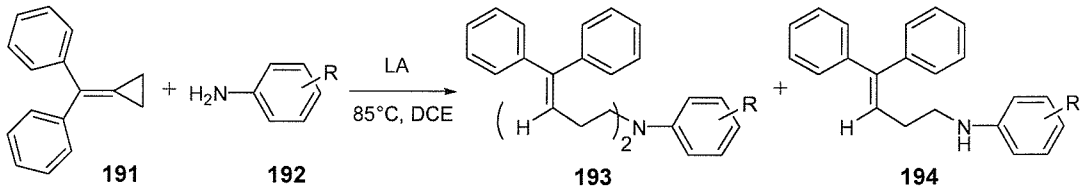
Scheme 42

Shi[111] has reacted alkylidenecyclopropanes **188** with aldehydes and ketones to synthesise functionalised tetrahydrofurans **190** (Scheme 43). The best yields were achieved with $Yb(OTf)_3$ as Lewis acid, and DCM or DCE as solvent.



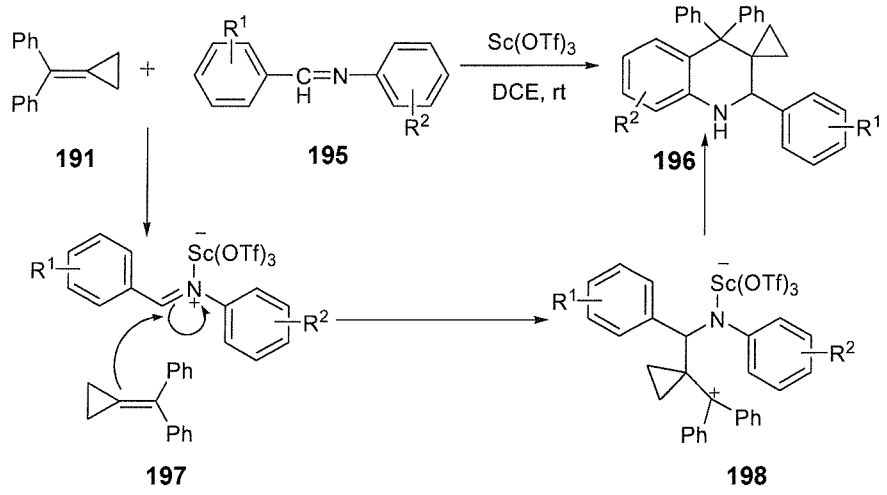
Scheme 43

Shi also used aromatic amines[112] and imines[113] to add to alkylidenecyclopropanes. The reaction between aromatic amines and **191** gives both monoalkylated and dialkylated homoallylic amines (Scheme 44). The introduction of electron withdrawing groups on the benzene ring gives high yields of dialkylated amines and none of the monoalkylated amine, whereas introduction of electron donating groups has no effect on the outcome of the reaction.



Scheme 44

Aromatic imines reacted with alkylidenecyclopropane **191** in an aza-Diels-Alder reaction to give spirocyclic product **196** in good yield. The alkylidenecyclopropane adds onto the imine through the cyclopropyl end of the double bond giving cation **198**, stabilised by the two neighbouring benzene rings. The aza-Diels-Alder product **196** is then formed through an intramolecular Friedel-Crafts reaction (Scheme 45).

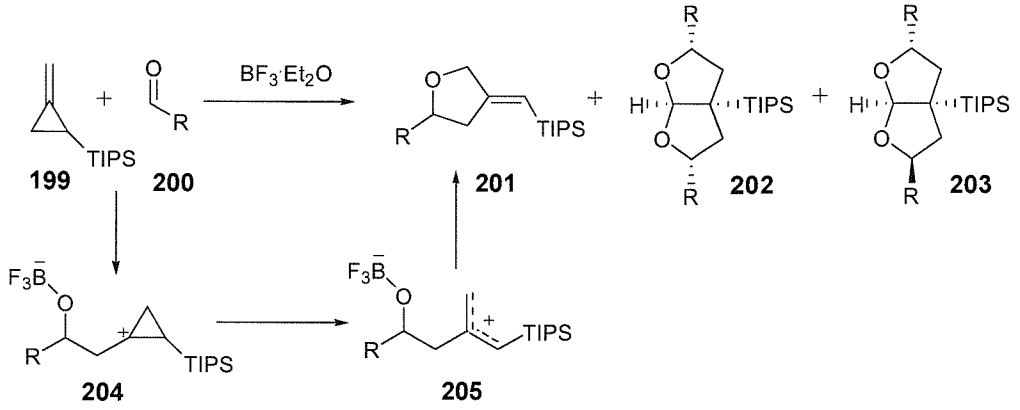


Scheme 45

Substituents on the benzene rings of the alkylidenecyclopropane significantly affected the reaction. Electron withdrawing groups (Cl) inhibited the reaction completely.

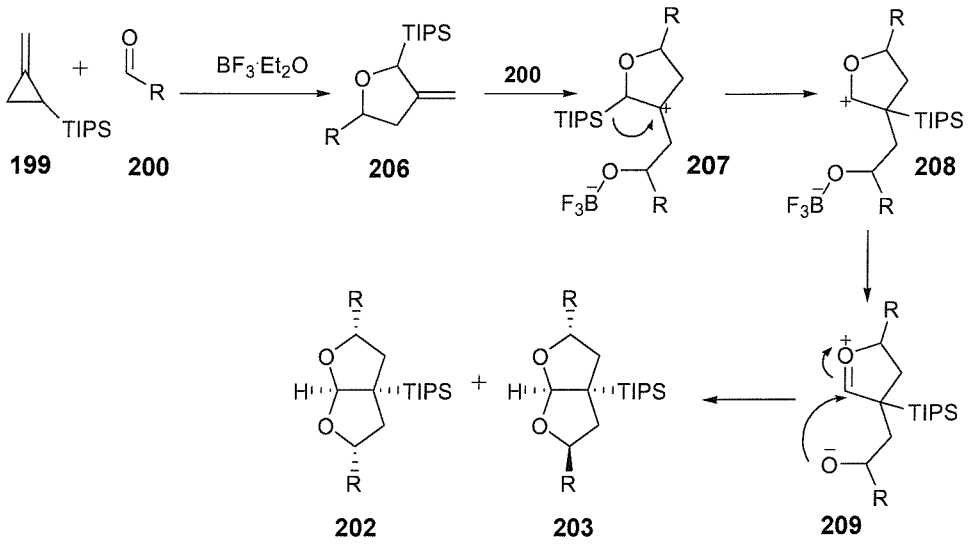
Patient[114] has made an extensive study into both intermolecular reactions of methylenecyclopropanes with aldehydes and ketones, and intramolecular cyclisations of methylenecyclopropyl imines.[114]

$BF_3{\cdot}Et_2O$ catalysed reaction of tri-isopropylsilylmethylenecyclopropane **199** with aldehyde **200** gave a mixture of 3 products, product **201** via the expected mechanism, together with furofurans **202** and **203** (Scheme 46).



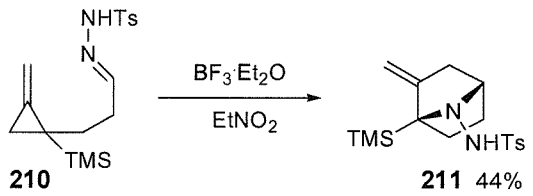
Scheme 46

The formation of furofurans **202** and **203** can be explained by a reaction of tetrahydrofuran **206**, formed following the expected mechanism, reacting with a second equivalent of the carbonyl compound to give cation **209**, which is quenched in an intramolecular fashion by the alkoxide to give **202** and **203** (Scheme 47).



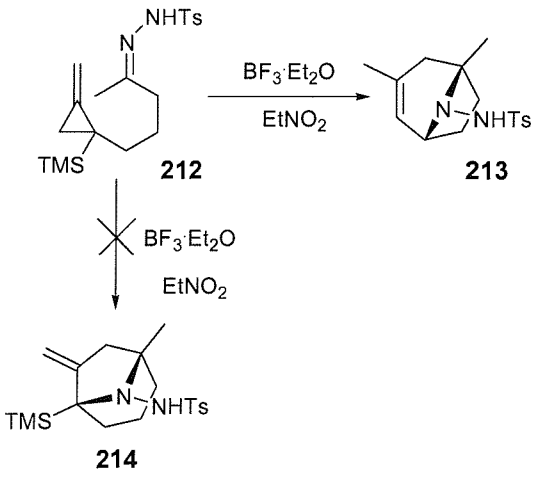
Scheme 47

Cyclisation of methylenecyclopropyl hydrazone **210** in the presence of $BF_3{\cdot}Et_2O$ gave the expected azabicycle **211** in good yield (Scheme 48). This product is formed following the mechanism previously reported (Scheme 42).[17]



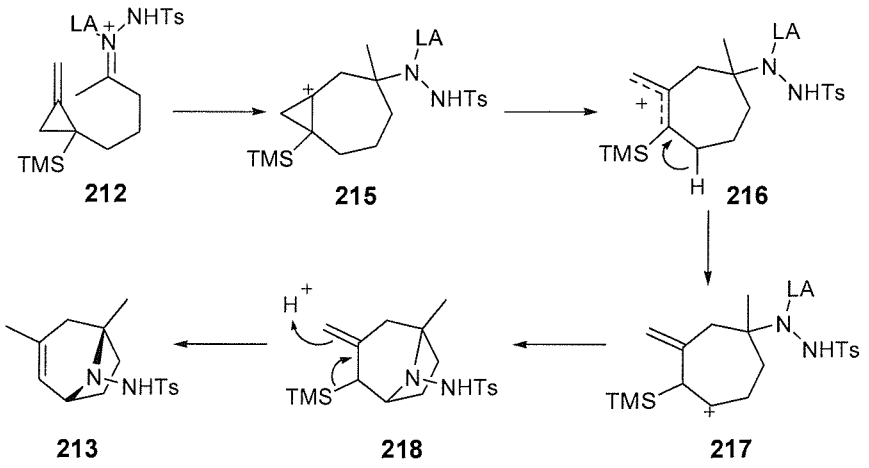
Scheme 48

Surprisingly, when **212** was cyclised under the same conditions, the reaction proceeded *via* a different mechanism giving **213** instead of the expected **214** (Scheme 49).



Scheme 49

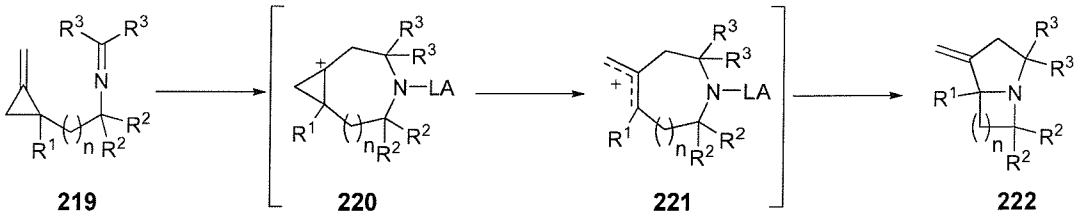
The mechanism proposed for the formation of this product initially follows the one reported by Peron,[17] until the formation of π-allyl cation **216**. Instead of the cation being quenched by nitrogen, a 1,2-hydride shift takes place, followed by quenching of cation **217** by the hydrazinyl anion and protodesilylation to give **213** (Scheme 50).



Scheme 50

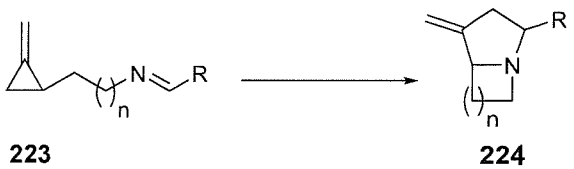
1.4 Program of work

Following from Peron's work on intramolecular cyclisations of methylenecyclopropyl aldehydes and ketones, the aim of this project was to investigate the intramolecular cyclisations of imines (Scheme 51). Lewis acid activation of the imine followed by intramolecular nucleophilic attack by the double bond should lead to **221**, and *via* trapping of the cation by the nitrogen to **222**, a common skeleton of many natural products.



Scheme 51

The first objective of this project was to study the cyclisation of simple imines **223**, changing the R group and studying the cyclisation with different Lewis acids. These imines were anticipated to give cyclic compounds **224** (Scheme 52).



Scheme 52

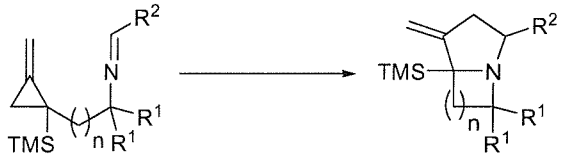
Second, the effect of different silyl substituents on the cyclopropane ring on the cyclisation was to be investigated by synthesising imines **225** and studying their cyclisation (Scheme 53).

225 **226**

n = 2-4
R^1 = TMS, TBDMS, DMPS

Scheme 53

Last, the effect of substituent on the alkyl chain on the cyclisation was to be investigated by synthesising imines with varying substitution. Increasing substitution on the alkyl chain was expected to facilitate the cyclisation by encouraging conformations suitable for cyclisation (Scheme 54).



227 **228**

n = 2, 3

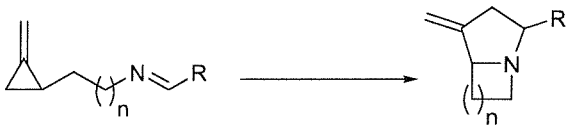
Scheme 54

Chapter 2

Cyclisation studies of simple methylenecyclopropyl imines

2.1 Aims

The aim of this research was to study the Lewis acid mediated cyclisation of methylenecyclopropyl imines, where the length of the alkyl chain linking the imine moiety onto methylenecyclopropane is varied, as this would give a facile route to pyrrolizidine and indolizidine type bicyclic structures (Scheme 52, reproduced for clarity).



223 **224**

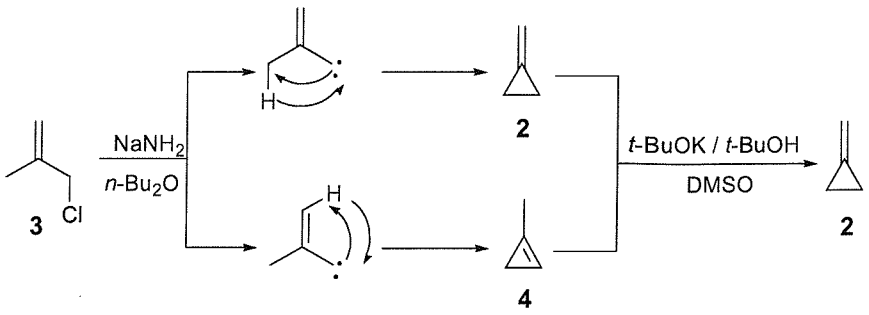
n = 2, 3

Scheme 52

2.2 Synthesis of precursors

2.2.1 Synthesis of methylenecyclopropane

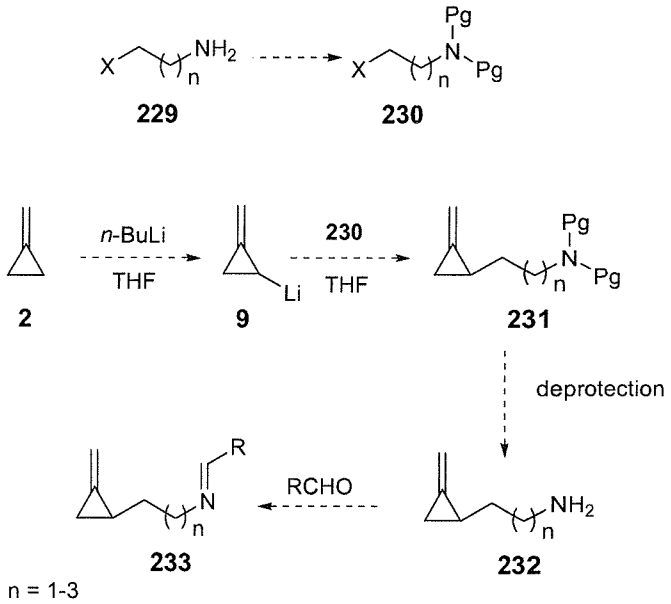
Methylenecyclopropane was synthesised following the procedure of Binger[11] from methallyl chloride. Deprotonation of methallyl choride with sodium amide produces a carbene, which then inserts to either the methyl CH to give methylenecyclopropane **2**, or into the methylene CH to give methylcyclopropene **4**. The mixture of **2** and **4** was obtained in 4.7:1 ratio, respectively. The obtained mixture of **2** and **4** is then fully isomerised to methylenecyclopropane by treatment with ^{t}BuOK and ^{t}BuOH in DMSO, giving MCP in 52 % yield (Scheme 55).



Scheme 55

2.2.2 Synthesis of protected methylenecyclopropyl amines

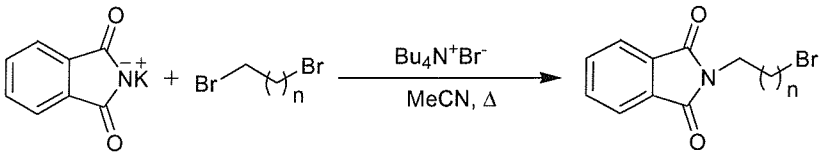
The most logical approach for the synthesis of methylenecyclopropyl amines was to synthesise protected alkylamines **230** that could be employed to alkylate methylenecyclopropane, thus giving protected methylenecyclopropyl amine **231** in only two steps. Deprotection of **231** would then directly allow the free amine **232**, ready for forming imine **233** for the cyclisation studies (Scheme 56).



Scheme 56

The first protecting group to be investigated was phthalimide, as this removes both of the basic hydrogens from the amine that could cause quenching of the

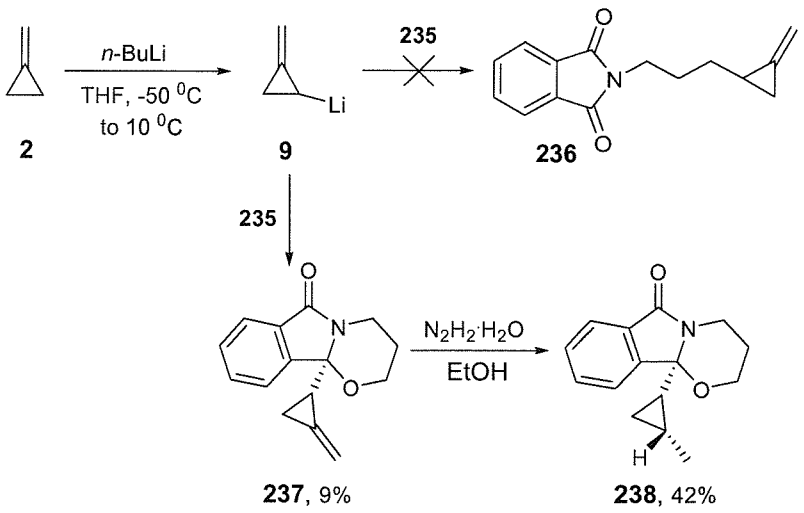
methylenecyclopropyl anion **9**. *N*-(2-Bromoethyl)-phthalimide **234** and *N*-(3-Bromopropyl)-phthalimide **235** were both synthesised using a method described by Quici,[115] by reacting 1,2-dibromoethane and 1,3-dibromopropane with potassium phthalimide in the presence of tetrabutylammonium bromide in acetonitrile. *N*-(2-Bromoethyl)-phthalimide **234** and *N*-(3-bromopropyl)-phthalimide **235** were both obtained in reasonable yields (Scheme 57).



234 n=1, 62%
235 n=2, 54%

Scheme 57

Methylenecyclopropyl anion **9** was generated by reacting MCP with *n*-butyllithium in THF at -78 °C. The formed anion can be used in alkylation reactions directly in a facile one-pot synthesis by adding the halide directly to the reaction mixture after the formation of the anion is complete. When alkylation of lithiated MCP was attempted by adding a solution of **234** in THF into **9** in THF at -78 °C, surprisingly, none of the expected product was formed. Alkylation of lithiated MCP with **235** also failed, giving **237** as the only isolable product instead of the expected **236** (Scheme 58).



2 **9** **236**

237, 9% **238**, 42%

Scheme 58

As the identity of compound **237** was not completely clear from the characterisation data, deprotection of **237** with hydrazine monohydrate in ethanol was attempted. Trace amounts of oxygen in the reaction mixture effected the reduction of the double bond of methylenecyclopropane, leading to crystalline **238** (Scheme 58). Crystal structure determination of this product confirmed its identity and that of the precursor **237** (Figure 2).

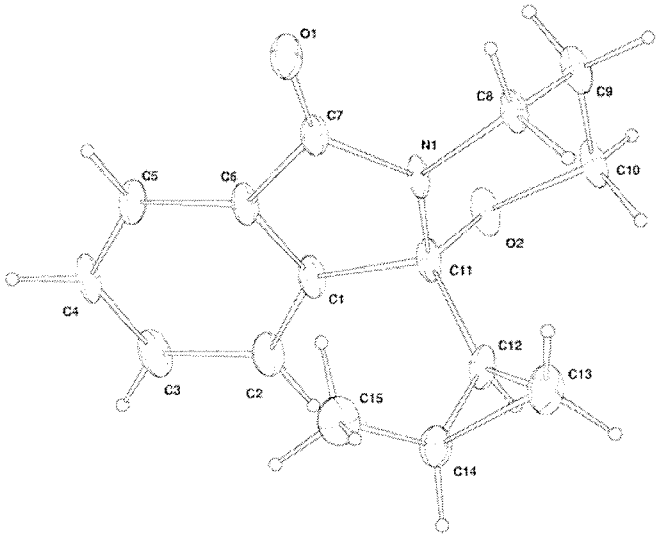
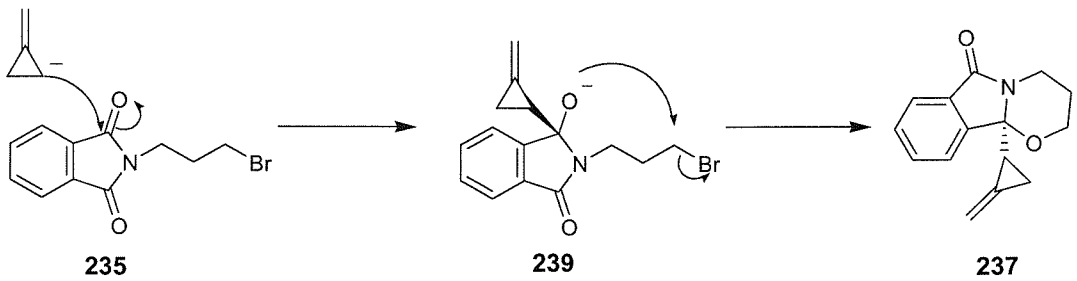


Figure 2

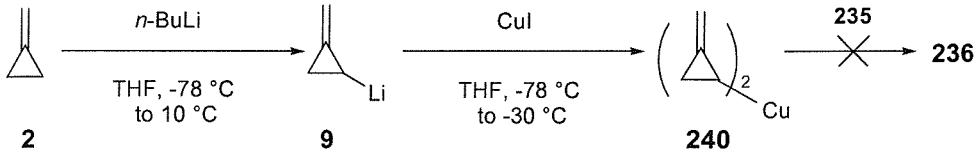
X-ray crystal structure of **238**.

Methylenecyclopropyl anion attacks one of the carbonyl carbons on phthalimide, and the formed oxygen anion **239** cyclises onto the bromide CH_2 losing bromide anion, and so giving **237** (Scheme 59).



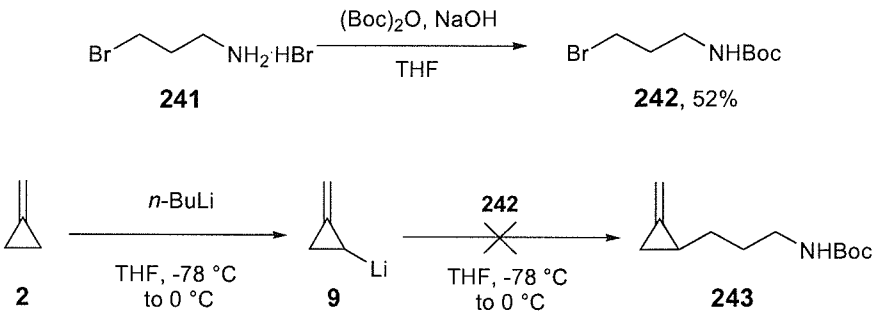
Scheme 59

Cuprates are significantly softer nucleophiles than carbanions, but still reactive enough for coupling with halides. Peron has shown that methylenecyclopropyl cuprate **240** can be synthesised from methylenecyclopropane by first deprotonating it with *n*-butyllithium, and then reacting the formed anion with CuI.[17] As using a softer nucleophile than methylenecyclopropyl anion might avoid the attack on the phthalimide carbonyl, methylenecyclopropyl copper complex **240** was used instead. **240** was synthesised by cannulating **9** into a rapidly stirred suspension of CuI in THF, and then used immediately by adding **235** in THF directly to the reaction mixture. However, this method did not lead to the formation of **236** (Scheme 60).



Scheme 60

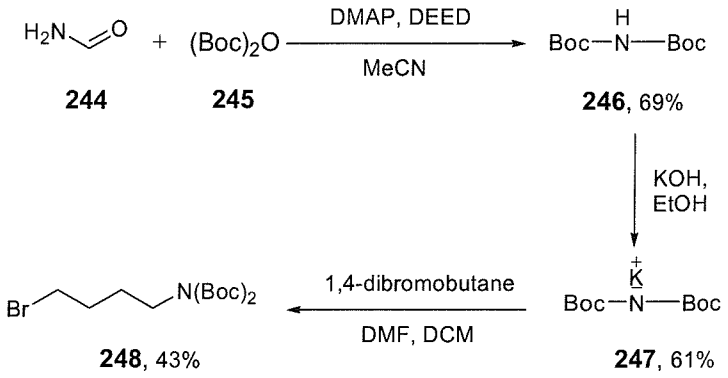
As alkylation with phthalimide protected amines was unsuccessful, mono-Boc protected amine **242** was synthesised by reacting 3-bromopropylamine hydrobromide with Boc-anhydride. It was thought that alkylation reaction might be faster than deprotonation of the basic NH present in **242** by methylenecyclopropyl anion **9**. This was not the case however, and alkylation of **9** with **242** was unsuccessful (Scheme 61).



Scheme 61

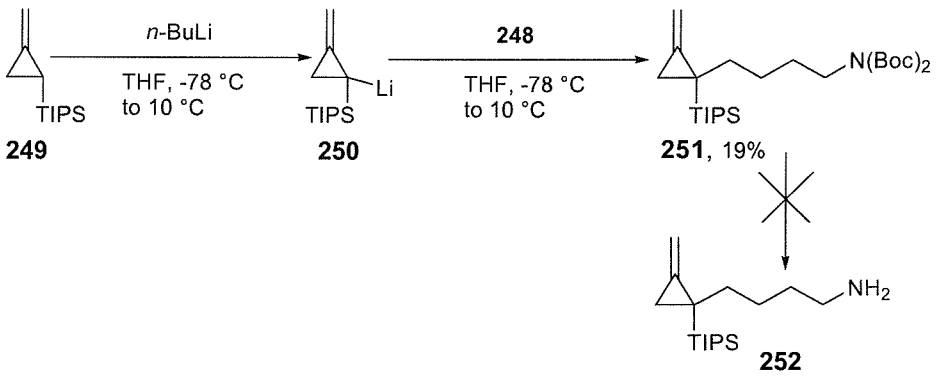
Introducing a second protecting group on the nitrogen avoids the problem caused by the basic hydrogen, and therefore di-Boc protected amine **248** was synthesised. **246** Was obtained *via* a method described by Grehn[116] from formamide and $(Boc)_2O$ in good

yield. This was first deprotonated to give potassium salt **247**, and then reacted with 1,4-dibromobutane following a procedure of Mutter[117] to afford **248** in moderate yield (Scheme 62).



Scheme 62

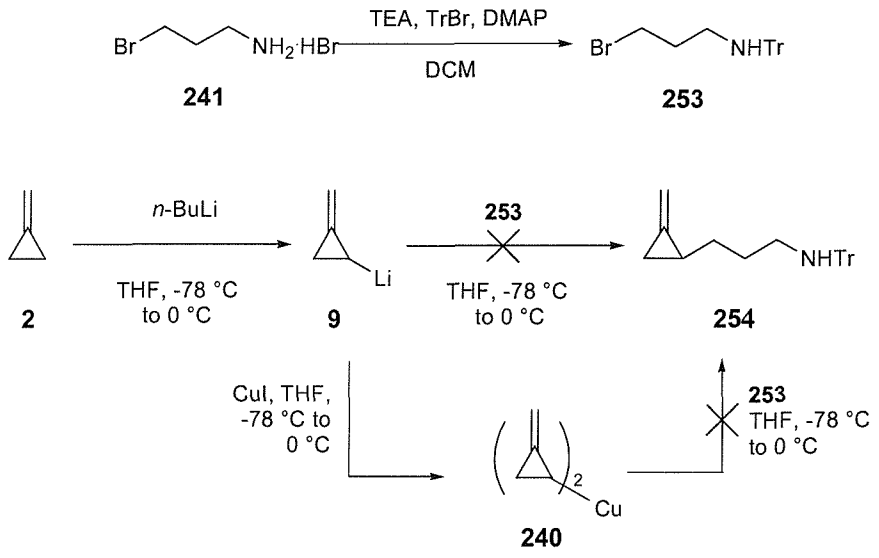
TIPS-MCP **249** was deprotonated with *n*-BuLi in THF, and the formed anion was coupled with **248** in a one-pot synthesis to give di-Boc protected amine **251**, although in poor yield (Scheme 63). Deprotection of **251** was attempted both with 5% TFA in DCM as well as with *p*-toluenesulphonic acid in refluxing DCM, leading to rapid decomposition of **251** in both cases (Scheme 63).



Scheme 63

Last, alkylation of methylenecyclopropane with 3-bromopropyl tritylamine **253** was attempted, as trityl group is easy to remove in mild conditions, and the benzyl rings were expected to provide enough steric hindrance to avoid deprotonation of the amine

NH by methylenecyclopropyl anion. Trityl NH is also not very acidic, unlike the carbonyl NH in **242** (Scheme 61).

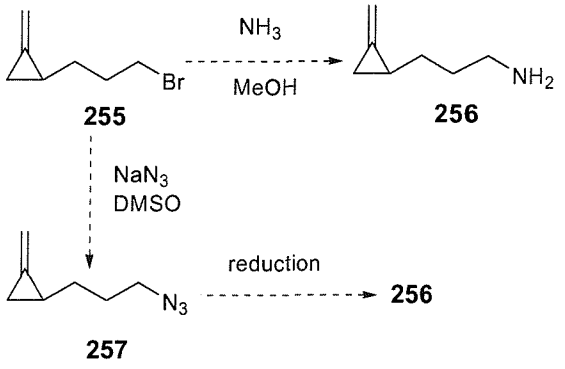


Scheme 64

Tritylated bromopropylamine **253** was synthesised by a method described by Casas[118] from 3-bromopropylamine hydrobromide and trityl hydrobromide in moderate yield, giving as a side product trityl alcohol. Unfortunately, alkylation of methylenecyclopropane with tritylbromide **253** proved to be unsuccessful both by direct alkylation of **9** and *via* methylenecyclopropyl cuprate **240** (Scheme 64).

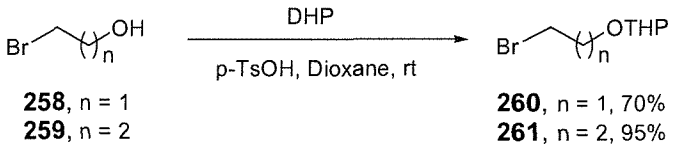
2.2.3 Synthesis of Methylenecyclopropyl Amines by Functional Group Transformation

Pike[74] has previously synthesised bromide **255** in good yield. This bromide should be easily converted to amine **256** by direct amination with ammonia, or *via* azide **257**, reducing the azide to amine **256** (Scheme 65).



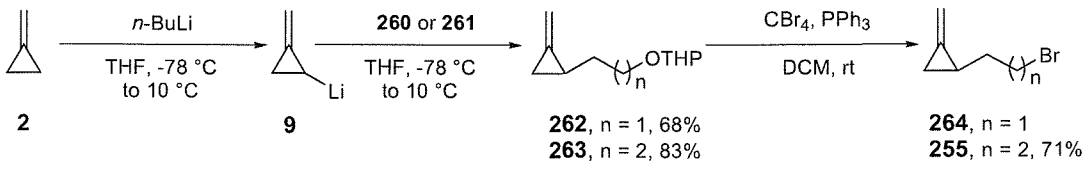
Scheme 65

THP protected bromoalcohols **260** and **261** were synthesised in good yield following a procedure by Dado,[119] reacting bromoethanol **258** and bromopropanol **259** with DHP in dioxane in the presence of catalytic amount of *p*-toluenesulphonic acid (Scheme 66).



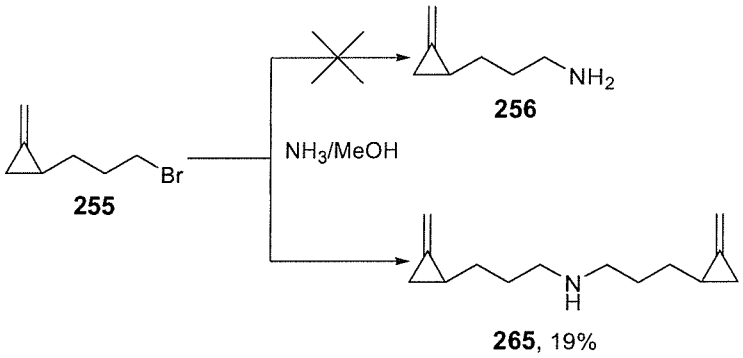
Scheme 66

The protected alcohols **260** and **261** were then used to make protected methylenecyclopropyl alcohols **262** and **263**, respectively, in good yield by a method described by Destabel[120]. The protected alcohols **262** and **263** were directly converted to the corresponding bromides **264** and **265** with CBr_4 and PPh_3 in DCM, as described by Pike.[121] Bromide **264** could not be isolated from the reaction mixture due to its high volatility. Bromide **255** was obtained in good yields by keeping the temperature low during the isolation process (Scheme 67).



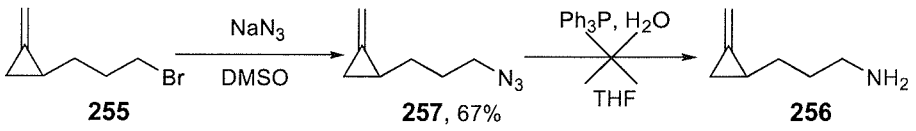
Scheme 67

Conversion of bromide **255** to amine **256** was then attempted by direct amination, stirring a solution of **255** in saturated methanolic ammonia for 3 days as decribed by Pillai.[117] Although the reaction was carried out in very dilute conditions, the formation of dimer **265** was rapid, and none of **256** was obtained (Scheme 68).



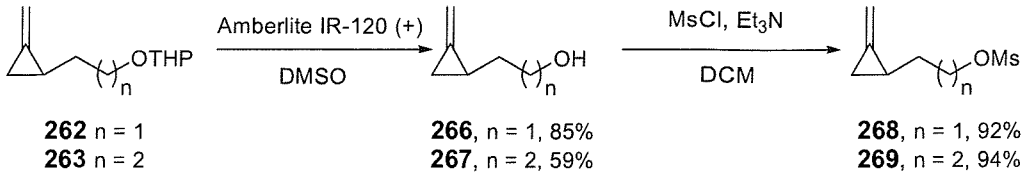
Scheme 68

As direct amination of **255** to **256** failed, it was decided to attempt synthesis of **256** *via* azide **257** (Scheme 65). Conversion of bromide **255** to azide **257** with NaN_3 in DMSO proceeded smoothly, giving **257** in excellent yield.[73] Reduction of **257** to the amine **256** proved to be difficult, and even after several attempts, reaction conditions mild enough to reduce the azide without affecting the methylenecyclopropyl moiety could not be found (Scheme 69).



Scheme 69

As the route above was unsuccessful, amine **256** was instead synthesised via nitrile **270** (Scheme 71). THP alcohol was deprotected with Amberlite IR 120 (+) ion exchange resin in methanol, following a method reported by Destabel[120] to give alcohol **266** and converted to the mesylate **268** in standard conditions (Scheme 70).



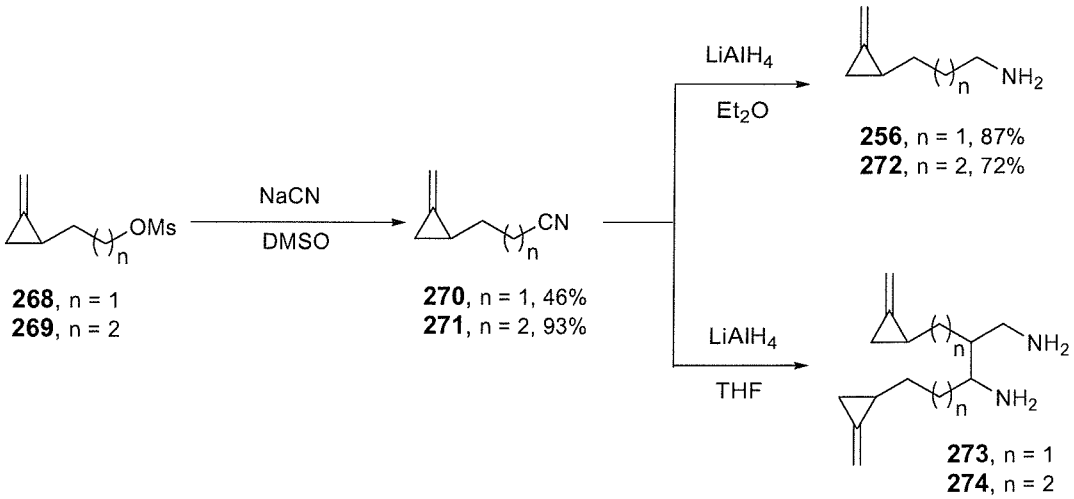
262 n = 1
263 n = 2

266, n = 1, 85%
267, n = 2, 59%

268, n = 1, 92%
269, n = 2, 94%

Scheme 70

The obtained mesylate was then converted to nitrile **270** with NaCN in DMSO using a method described by Fish,[122] and then reduced to give amine **256** (Scheme 65). The reduction of nitrile **270** with $LiAlH_4$ in THF gave dimer **273** as the major product, as can be seen from mass spectroscopy data, and the monomer **256** only in poor yield, whereas when the reduction was carried out in diethyl ether, **256** was obtained as the only product in excellent yield.[123] Amine **272** was synthesised *via* the same route in good overall yield (Scheme 71).



268, n = 1
269, n = 2

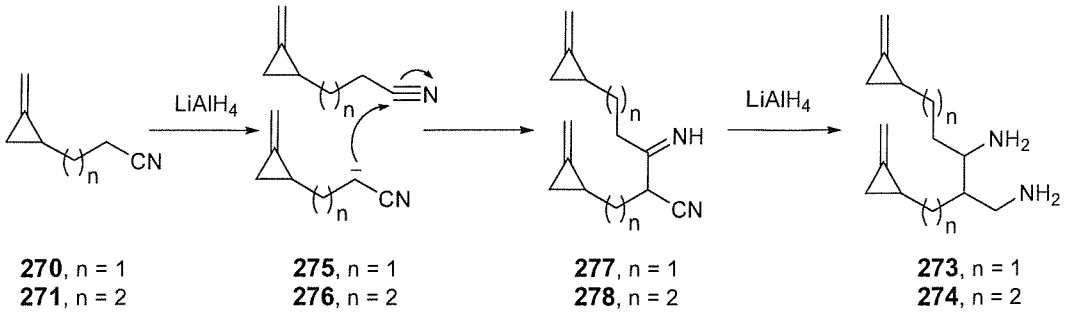
270, n = 1, 46%
271, n = 2, 93%

256, n = 1, 87%
272, n = 2, 72%

273, n = 1
274, n = 2

Scheme 71

Formation of dimers **273** and **274** is thought to arise from deprotonation of the mildly acidic CH_2 adjacent to the nitrile moiety. The formed carbanions **275** and **276** add onto another molecule of **270** and **271**, respectively, and adducts **277** and **278** are finally reduced by $LiAlH_4$ to give dimeric amines **273** and **274** (Scheme 72).[123]



270, n = 1
271, n = 2

275, n = 1
276, n = 2

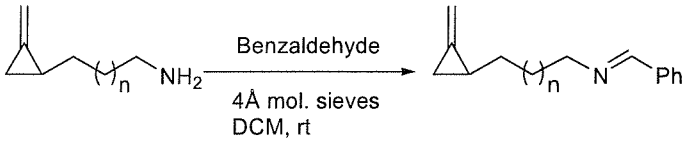
277, n = 1
278, n = 2

273, n = 1
274, n = 2

Scheme 72

2.2.4 Synthesis of methylenecyclopropyl imines and HCl salts of methylenecyclopropyl amines

Imines **279** and **280** were synthesised in excellent yields by reacting amines **256** and **272**, respectively, with benzaldehyde in DCM with 4Å molecular sieves (Scheme 73).

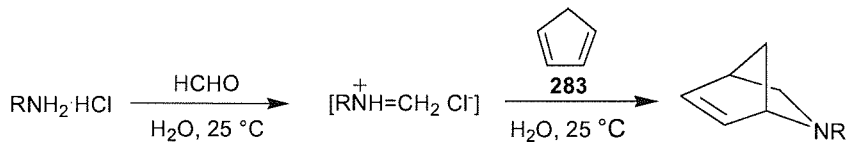


256, n = 1
272, n = 2

279, n = 1, 86%
280, n = 2, 79%

Scheme 73

Grieco has studied the formation of piperidines via a Diels-Alder reaction of hydrochloride salts of amines with formaldehyde in water with good results (Scheme 74).[99,124,125]

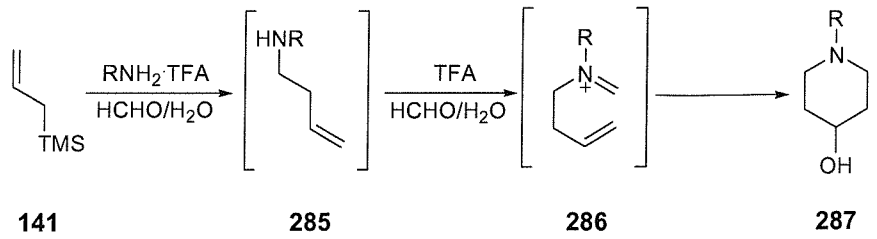


281 **282** **284**

Scheme 74

Grieco also studied reactions of homoallyl amines derived from allyl silanes. These homoallyl amines were generated in situ, and reacted with formaldehyde to give

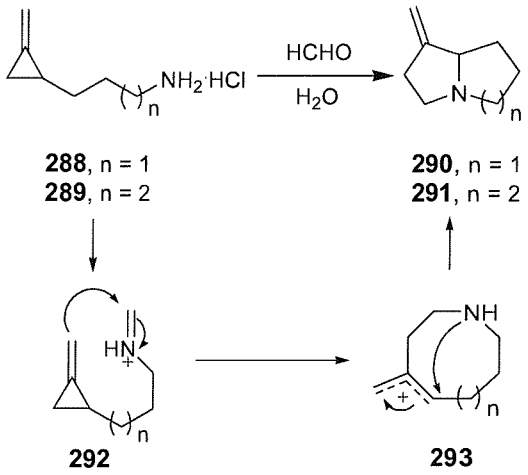
iminium ions, which *via* an intramolecular olefin-iminium ion cyclisation gave *N*-alkylpiperidines (Scheme 75).



141 **285** **286** **287**

Scheme 75

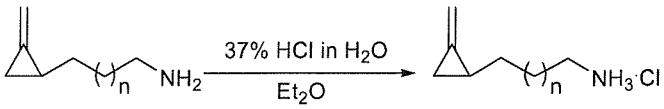
Encouraged by the results obtained by Grieco, it was decided to attempt cyclisation of imines formed in situ from amines **288** and **289** with formaldehyde. Cyclisation was expected to give bicycles **290** and **291** (Scheme 76).



292 **293**

Scheme 76

For the cyclisation studies, hydrochloride salts of amines **256** and **272** were synthesised by treating a solution of amine in diethyl ether with 37% aqueous hydrochloric acid. HCl salts **288** and **289** were both obtained in good yields (Scheme 77).



256, n = 1
272, n = 2

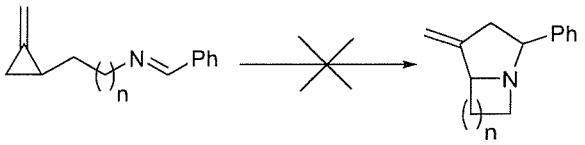
288, n = 1, 66%
289, n = 2, 79%

Scheme 77

2.3 Cyclisation studies

2.3.1 Cyclisation studies of imines 279 and 280

Cyclisation of imines **279** and **280** was attempted with two different Lewis acids, $TiCl_4$ and $BF_3{\cdot}Et_2O$. The reactions were carried out in DCM, adding the Lewis acid into the solution of imine at -78 °C, and then monitoring the reaction while letting the reaction mixture slowly warm to room temperature. In the case of $TiCl_4$, only decomposition of the starting material was observed as the reaction temperature was raised, whereas with $BF_3{\cdot}Et_2O$ no reaction was observed even after keeping the reaction mixtures at room temperature overnight, and amines **256** and **272** were recovered almost quantitatively (Scheme 78).



279, n = 2
280, n = 3

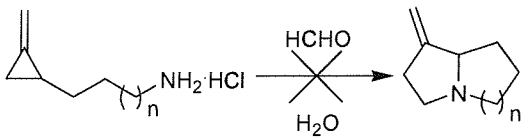
294, n = 2
295, n = 3

Scheme 78

2.3.2 Cyclisation studies of 288 and 289

Cyclisation studies of **288** and **289** were carried out in formalin. Even after heating the reaction mixtures to 50-90 °C from 2 hours to overnight, and conducting the reactions at room temperature for several days, no reaction occurred, and again amines **256** and **272** were recovered almost quantitatively. When the cyclisation reaction mixtures were

heated to elevated temperatures for longer times, decomposition of the starting materials occurred (Scheme 79).



288, n = 1
289, n = 2

290, n = 1
291, n = 2

Scheme 79

2.4 Conclusions

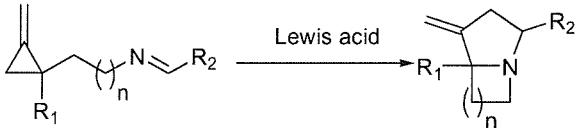
A straightforward route for preparing methylenecyclopropyl amines, and consequently methylenecyclopropyl imines from methylenecyclopropyl alcohols in good yield was developed. Disappointingly, the cyclisation of the prepared imines **279** and **280** did not give any of the desired cyclic compounds, probably due to the poor reactivity of imines and the non-activated olefin of methylenecyclopropane. Cyclisation of **288** and **289** also failed, again probably due to the poor reactivity of the starting material. However, the developed synthetic method for preparing methylenecyclopropyl imines can easily be adapted to synthesis of silyl-substituted methylenecyclopropyl imines, thus giving a route to more reactive species.

Chapter 3

Cyclisation studies of silylated methylenecyclopropyl imines

3.1 Aims

In chapter 2 various methylenecyclopropyl imines were synthesised, but unfortunately the cyclisation of these imines failed. Research conducted by Peron showed that cyclisation of methylenecyclopropyl carbonyl compounds can be facilitated by introducing a trialkylsilyl group onto the methylenecyclopropyl ring.[17] It was therefore decided to synthesise silyl substituted methylenecyclopropyl imines with different chain lengths. Cyclisation of these imines was assumed to be facilitated by activation of the methylenecyclopropyl double bond by trialkylsilyl substitution, as this converts the olefin double bond into an allyl silane. The silyl substituent was also varied to evaluate the importance of the substitution on the silicon for the cyclisation reaction (Scheme 53, reproduced for clarity).



225 **226**

n = 2-4
R_1 = TMS, TBDMS, DMPS

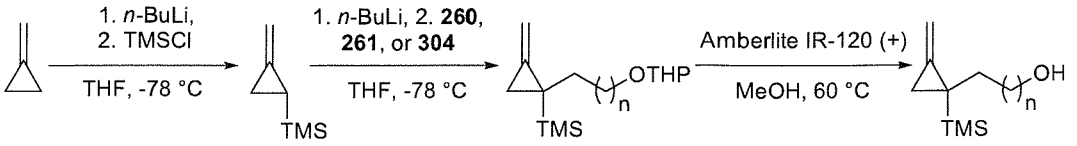
Scheme 53

3.2 Synthesis of precursors

3.2.1 Synthesis of methylenecyclopropyl amines with a trimethylsilyl group

Methylenecyclopropyl alcohols **300-302** were prepared in a two-step one-pot synthesis described by Destabel.[120] Methylenecyclopropane was deprotonated using *n*-BuLi and the subsequent anion was quenched with one equivalent of TMSCl to give **296**. A

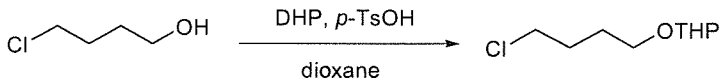
second equivalent of *n*-BuLi was added and the resulting anion was coupled with bromide **260**, **261**, or chloride **304**. Protected alcohols **297**, **298**, and **299**, respectively, were all obtained in good yields. Deprotection of THP ethers **297-299** with Amberlite IR-120 (+) ion exchange resin in methanol at 60 °C gave alcohols **300-302** in good yields (Scheme 80).



2 **296** **297**, n = 1, 68% **298**, n = 2, 79% **299**, n = 3, 67% **300**, n = 1, 45% **301**, n = 2, 66% **302**, n = 3, 59%

Scheme 80

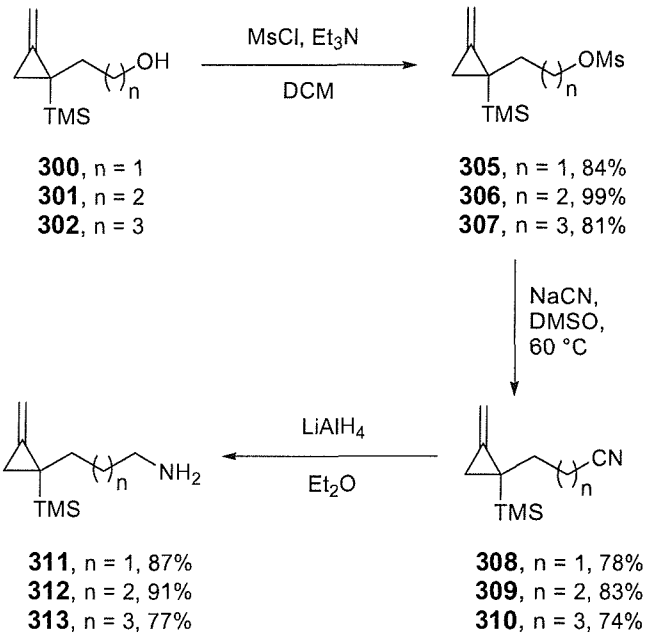
Chloride **304** used in the synthesis of **302** was synthesised by reacting 4-chloro-1-butanol with DHP in dioxane in the presence of substoichiometric amount of *p*-toluenesulphonic acid (Scheme 81).[119]



303 **304**, 82%

Scheme 81

Alcohols **300-302** were converted to mesylates **305-307** using standard conditions. Mesylates **305-307** were obtained in excellent yields, and displacement of the mesylate with cyanide in DMSO gave nitriles **308-310** in good yields.[122] Reduction of the nitriles **309-311** with $LiAlH_4$ in diethyl ether gave the desired amines **311**, **312** and **313** in good yields (Scheme 82).[123]



300, n = 1
301, n = 2
302, n = 3

305, n = 1, 84%
306, n = 2, 99%
307, n = 3, 81%

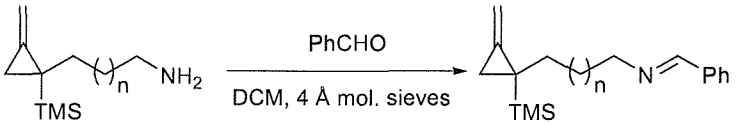
311, n = 1, 87%
312, n = 2, 91%
313, n = 3, 77%

308, n = 1, 78%
309, n = 2, 83%
310, n = 3, 74%

Scheme 82

3.2.2 Synthesis of methylenecyclopropyl imines with a trimethylsilyl group

For initial cyclisation studies, benzyl imines **314-316** were synthesised from amines **311**, **312** and **313**, respectively, by reacting them with benzaldehyde in DCM in the presence of 4 Å molecular sieves. Imines **314-316** were all obtained in excellent yields by removal of the solvent, and in greater than 95% purity as judged by ^{1}H NMR (Scheme 83).



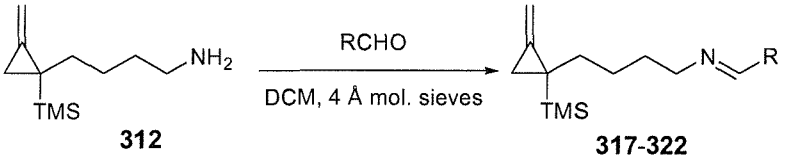
311, n = 1
312, n = 2
313, n = 3

314, n = 1, 92%
315, n = 2, 84%
316, n = 3, 87%

Scheme 83

Imines **317-322** (Table 1) were synthesized from amine **312** using the methods explained previously, reacting amine **312** with a range of different aldehydes and ketones in DCM in the presence of 4 Å molecular sieves (Scheme 84). The imines

317–322 were obtained by removal of the solvent in excellent yields, and in all cases greater than 90% purity. Aldehydes and ketones used in the synthesis of the imines, as well as the yields of the condensation reactions are summarised in table 1.



312 **317-322**

Scheme 84

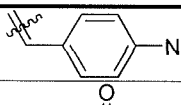
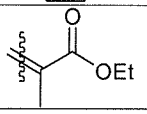
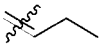
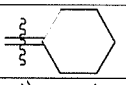
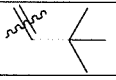
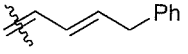
Entry	R	Aldehyde / Ketone	Yield
317		*p*-nitrobenzaldehyde	83%
318		ethyl pyruvate	82%
319		propionaldehyde	84%
320		cyclohexanone	71%
321		pivalaldehyde	80%
322		cinnamaldehyde	95%

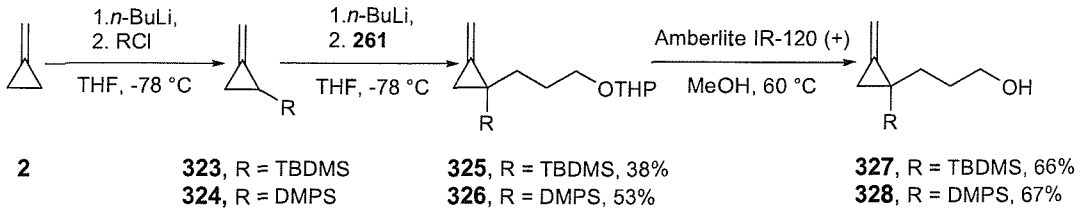
Table 1

Aldehydes and ketones used in the synthesis of imines **317-322**

3.2.3 Synthesis of benzyl imines with other silyl groups

Benzyl imines with *t*-butyldimethylsilyl (**335**) or dimethylphenylsilyl substitution (**336**) on the cyclopropyl ring were synthesised *via* the same route as imines **317-322**. Methylenecyclopropane was deprotonated using *n*-BuLi and the subsequent anion was quenched with one equivalent of TBDMSCl or DMPSCl. A second equivalent of *n*-BuLi was added and the resulting anions were coupled with bromide **261**. Protected alcohols **325** and **326** were achieved in good yields. Deprotection of THP ethers **325**

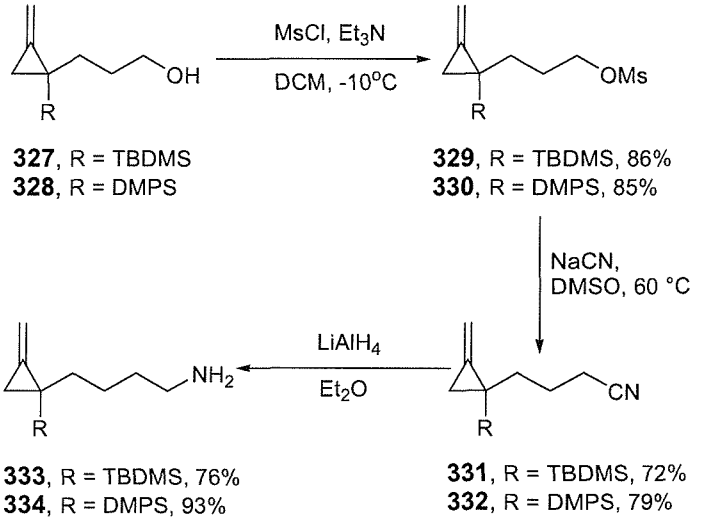
and **326** with amberlite IR-120 (+) ion exchange resin in methanol gave alcohols **327** and **328**, respectively, in good yields (Scheme 85).



2 **323**, R = TBDMS; **324**, R = DMPS; **325**, R = TBDMS, 38%; **326**, R = DMPS, 53%; **327**, R = TBDMS, 66%; **328**, R = DMPS, 67%

Scheme 85

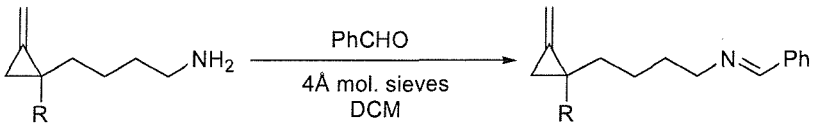
The alcohols were converted to the mesylates **329** and **330** in excellent yields using standard conditions, and displacement of the mesylate with cyanide gave nitriles **331** and **332**. Reduction of the nitriles **331** and **332** with $LiAlH_4$ in diethyl ether gave the desired amines **333** and **334** in excellent yields (Scheme 86).[123]



327, R = TBDMS; **328**, R = DMPS; **329**, R = TBDMS, 86%; **330**, R = DMPS, 85%; **331**, R = TBDMS, 72%; **332**, R = DMPS, 79%; **333**, R = TBDMS, 76%; **334**, R = DMPS, 93%

Scheme 86

Imines **335** and **336** were obtained by reacting amines **333** and **334** with benzaldehyde in DCM in the presence of 4 Å molecular sieves (Scheme 87).



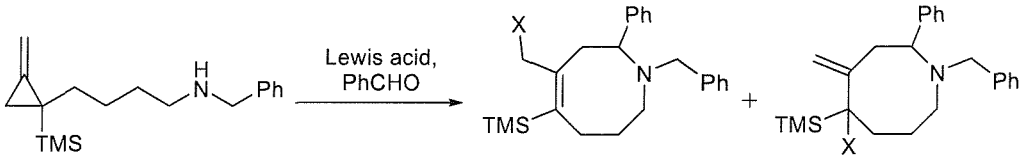
333, R = TBDMS
334, R = DMPS

335, R = TBDMS, 92%
336, R = DMPS, 94%

Scheme 87

3.2.4 Synthesis of secondary amine 337

As cyclisation of imines can be facilitated by use of iminium ions instead of imines,[96,97] cyclisation of a methylenecyclopropyl iminium ion was also to be studied. Secondary amine **337** was synthesised for cyclisation studies of an iminium ion formed in situ from amine **337** and benzaldehyde (Scheme 88).

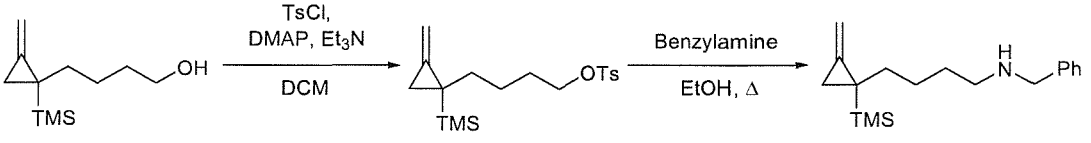


337 **338** **339**

X = OH, Cl, F

Scheme 88

Amine **337** was synthesised from alcohol **302** in two steps. Alcohol **302** was converted to tosylate **340** using *p*-toluenesulphonyl chloride in DCM in the presence of DMAP and triethylamine.[126] Tosylate **340** was obtained in moderate yield. Displacement of the tosyl ester with benzylamine in refluxing ethanol proceeded with excellent yield to give amine **337** (Scheme 89).[127]

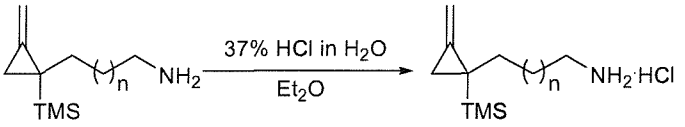


302 **340**, 58% **337**, 90%

Scheme 89

3.2.5 Synthesis of amine salts with trimethylsilyl group

As previously the cyclisation of amines **287** and **288** with formaldehyde had failed (Scheme 79), it was of interest to see whether also in this case the cyclisation could be facilitated by introduction of a silyl group into the methylenecyclopropyl ring. For the cyclisation studies, hydrochloride salts of amines **310** and **311** were synthesised by treating a solution of amine in diethyl ether with 37% aqueous hydrochloric acid. HCl salts **341** and **342** were both obtained in good yields (Scheme 90).



311, n = 1
312, n = 2

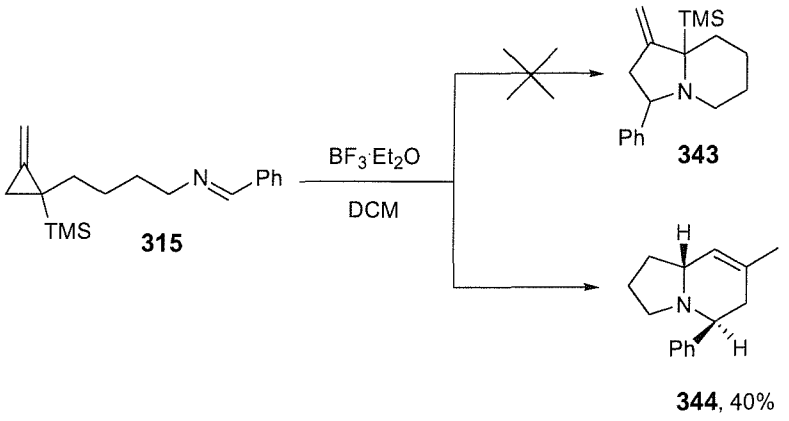
341, n = 1, 99%
342, n = 2, 96%

Scheme 90

3.3 Cyclisation studies

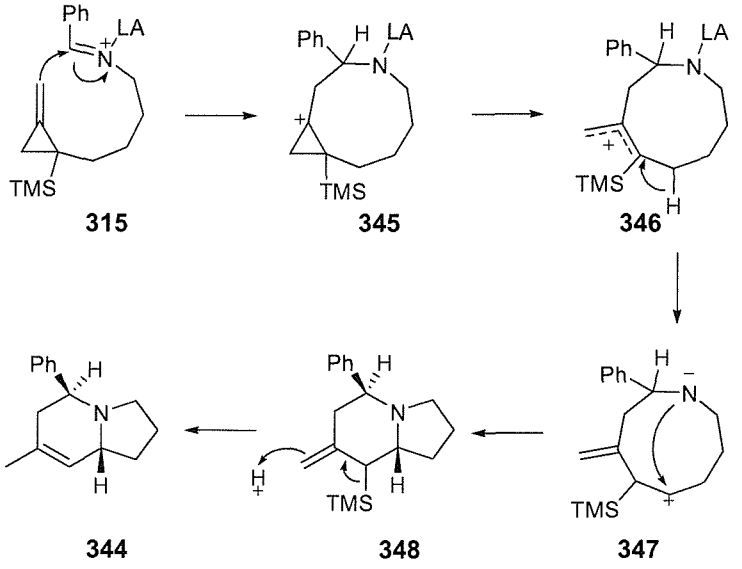
3.3.1 Cyclisation studies of imines with trimethylsilyl group

The initial cyclisation studies with imines **314**, **315** and **316** were performed using either $TiCl_4$ or $BF_3{\cdot}Et_2O$ as catalyst, and DCM as solvent. The Lewis acid was added into the reaction mixture at -78 °C, and the reaction mixtures were allowed to warm up slowly while the reaction was monitored by TLC. Reactions with $TiCl_4$ did not react at low temperatures, and when allowed to warm up only decomposition of starting materials was observed in each case. When the cyclisation reactions were performed with $BF_3{\cdot}Et_2O$, imines **314** and **316** gave only some recovered starting materials accompanied by decomposition. Imine **315**, however, did give a new product in moderate yield, although it was not the anticipated **343**. Instead, ^1H NMR studies indicated that it was bicycle **344** as a single diastereomer (Scheme 91).



Scheme 91

A possible mechanism for the formation of bicycle **344** involves initial cyclisation to give cyclopropyl cation **346**, that rearranges to π-allyl cation **346** by ring opening of the cyclopropyl ring. A 1,2-hydride shift then takes place to give β-silyl cation **347**. Quenching of cation **347** by nitrogen followed by protodesilylation finally gives bicycle **344** (Scheme 92).

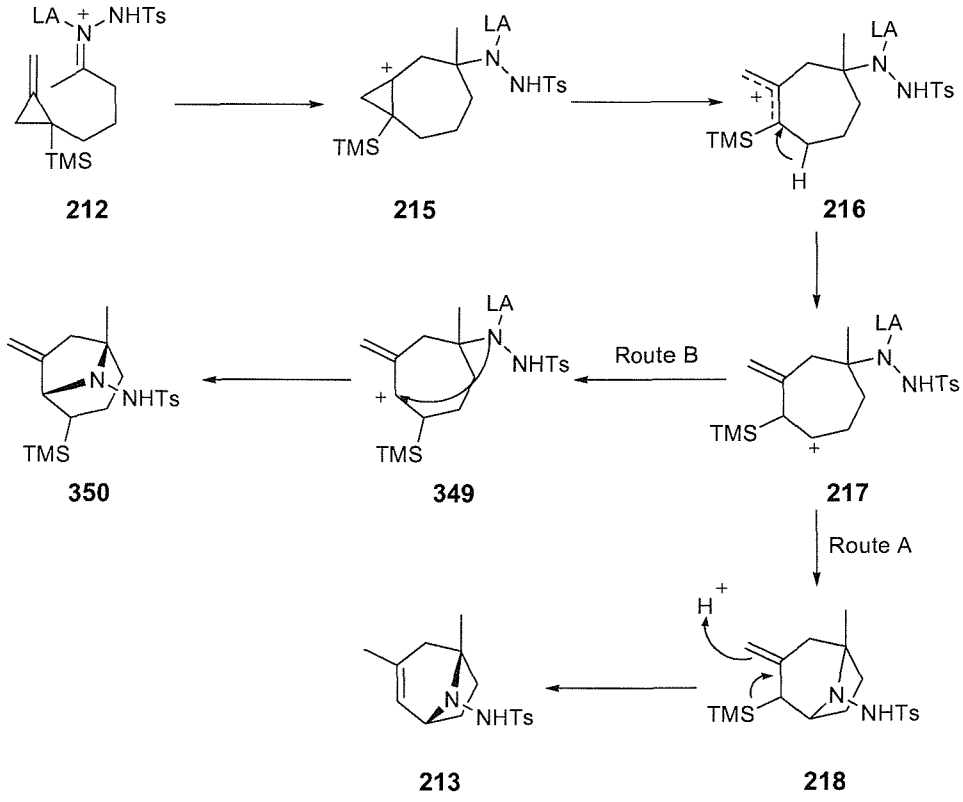


Scheme 92

Cation **346** is sterically much more hindered that cation **347**, and therefore 1,2-hydride shift is assumed to proceed faster than attack of nitrogen on cation **346**. Cation **347** formed from the hydride shift may also be more stable than cation **346**. The

environment of cation **347** is less congested than that of cation **346**, and therefore the quenching of the cation by nitrogen can occur more easily than before the 1,2-hydride shift. This consideration of the steric aspects of the cyclisation explains why bicycle **344** was the only product obtained, and none of the expected bicycle **343** was formed. The relative stereochemistry of **343** is propably due to the orientation of the phenyl group in the transition state, which inhibits the formation of the other possible diastereomer.

Although the formation of **344** was unexpected, the suggested mechanism is precedented by work by Patient (Scheme 93).[128] This mechanism follows that reported by Peron[110] (Scheme 42) until the formation of π-allyl cation **216**. Instead of the cation being quenched by the nitrogen, a 1,2-hydride shift takes place giving stabilised β-silyl cation **217**. Cation **217** can then be quenched by nitrogen followed by either a protodesilylation step to give **213** (Route A), or a 1,2-silyl shift to give β-silyl π-allyl cation **349** (Route B). Cation **349** can then be quenched by nitrogen to give **350** as the product.



Scheme 93

To elucidate the stereochemistry of **344** GOESY studies were conducted. Irradiation of H_A caused no enhancement in H_B. This suggests that H_A and H_B are on the opposite sides of bicycle **344**. Irradiation of H_A caused 0.59% enhancement in H_C, which in turn suggests that H_A and H_C are in close proximity (Figure 3).

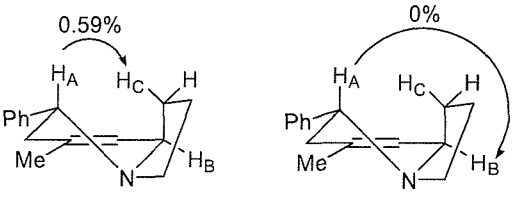
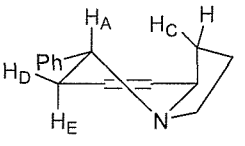


Figure 3

GOESY studies of **344**

Further information on the conformation of the molecule was gained from the ^1H NMR studies. The coupling pattern of proton H_A with a small axial-equatorial coupling to H_D and a bigger axial-axial coupling to H_E suggest that H_A is in pseudoaxial position and the phenyl group is in an pseudoequatorial position (Figure 4), and as the GOESY studies indicate that H_A and H_D are at close proximity to each other, all the information of both studies indicates that also the cyclopentyl ring is in an pseudoaxial position. Therefore, the conformation of bicycle **344** can safely be assumed to be that shown in figures 3 and 4.



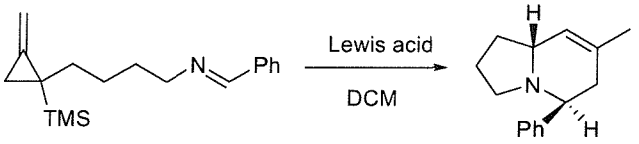
H_A, dd *J* 3, 8 Hz
H_D, dd, *J* 3, 14 Hz
H_E, dd, *J* 8, 14 Hz

Figure 4

Coupling patterns of **344**

For optimisation of the synthesis of **344,** cyclisation of imine **315** was also attempted in different solvents and employing different Lewis acids. The reaction conditions are summarised in table 2. Lanthanide Lewis acids were among those chosen for these reactions, as recently they have became more common in reactions of allyl silanes and carbonyl compounds or imines alongside with the more conventional $TiCl_4$ and

$BF_3{\cdot}Et_2O$.[129-131] Cyclisation could successfully be carried out using either $EtNO_2$ or DCM as solvent, and 1 equivalent of $BF_3{\cdot}Et_2O$ or $In(OTf)_3$ as catalyst with no significant change in yields or purity of the reaction, and in each case approximately 20% of the unreacted amine and almost all of the benzaldehyde could be recovered (Table 2). This indicates that the low yields of the cyclisation reaction are possibly due to the hydrolysis of imine **315** and decomposition of the methylenecyclopropyl moiety, than decomposition of the imine moiety. When other Lewis acids were used as catalyst either in DCM or $EtNO_2$, no reaction occurred and amine **312** was recovered nearly quantitatively. When MeCN was used as solvent, only decomposition of the starting material was observed. Cyclisation reactions of imine **315** were also carried out in DCM with only catalytic amounts of $BF_3{\cdot}Et_2O$ or $In(OTf)_3$, from 10 mol% to 30 mol%, but no reaction was observed.



315 **344**

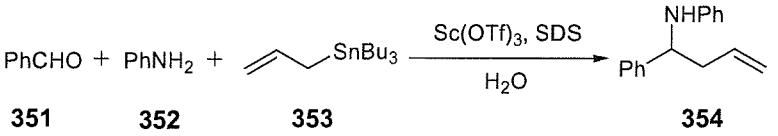
Scheme 94

Imine	Lewis acid	Solvent	Yield
315	$BF_3{\cdot}Et_2O$	MeCN	—
315	$In(OTf)_3$	MeCN	—
315	$Cu(OTf)_3$	DCM	—
315	$InCl_3$	DCM	—
315	$Sc(OTf)_3$	DCM	—
315	$Yb(OTf)_3$	MeCN	—
315	$Yb(OTf)_3$	$EtNO_2$	—
315	$BF_3{\cdot}Et_2O$	$EtNO_2$	37%
315	$In(OTf)_3$	$EtNO_2$	35%
315	$BF_3{\cdot}Et_2O$	DCM	40%
317	$BF_3{\cdot}Et_2O$	DCM	33%
317	$In(OTf)_3$	DCM	36%

Table 2

Optimisation of cyclisation reactions of imines **315** and **317**

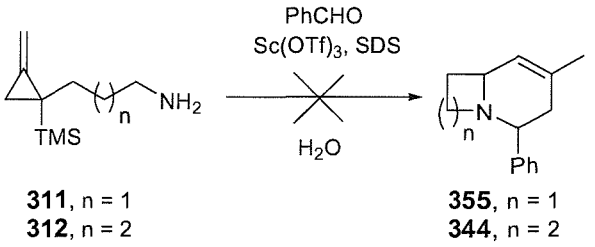
Kobayashi[95] has succesfully performed a synthesis of homoallylamines by reacting allyl stannanes with iminium ions derived *in situ* from amine and aldehyde. The reaction was catalysed by scandium triflate and carried out in water in micellar systems created by sodium dodecyl sulfate (SDS) (Scheme 95).



Scheme 95

As the reactions carried out by Kobayashi had very good outcomes and they could be performed in aqueous media, it was interesting to attempt cyclisation of imines formed *in situ* from amines **311** and **312** with benzaldehyde in reaction conditions similar to those used by Kobayashi.

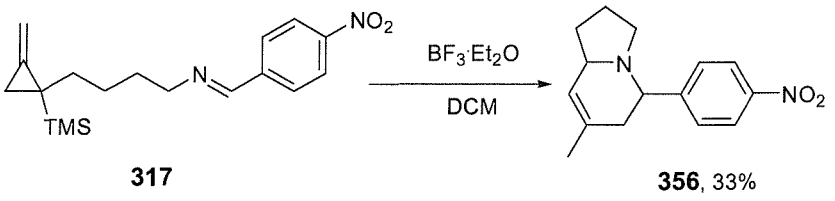
Cyclisation studies of **311** and **312** were conducted using conditions described by Kobayashi:[95] A solution of amine, 1 equivalent of benzaldehyde, 0.2 equivalents of scandium triflate and 0.2 equivalents of SDS in water was stirred at room temperature for 24 hours. No reaction occurred with either **311** or **312**, and starting materials were recovered quantitatively in both cases (Scheme 96).



Scheme 96

In order to obtain a crystal structure of the cyclised product, cyclisation of imine **317** was carried out in DCM with 1 equivalent of $BF_3{\cdot}Et_2O$ as catalyst (Scheme 97). Bicycle

356 was obtained in good yield as a brown solid, but unfortunately the quality of the crystals was not high enough to allow the crystal structure determination.

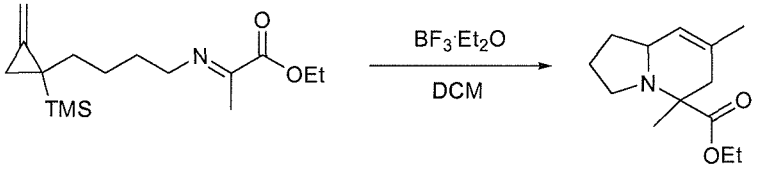


317 **356**, 33%

Scheme 97

Cyclisation studies of imines **318** - **322** were carried out in DCM with $BF_3 \cdot Et_2O$ as the catalyst, as these conditions had been found to give the best yields of cyclised product with imine **315**. Only imine **319** gave isolable amounts of cyclised product.

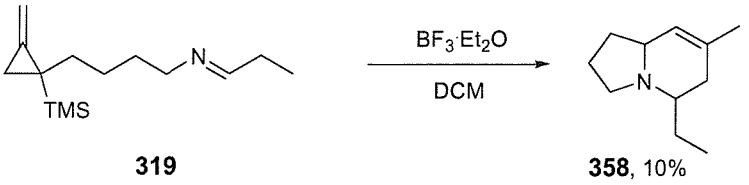
Imine **318** gave mostly decomposed material together with a trace amount of bicycle **357** according to ^1H NMR, but it was not possible to isolate bicycle **357** pure enough for complete characterisation. The decomposition of the starting material may be due to the unreactivity of the doubly substituted imine (Scheme 98).



318 **357**, trace

Scheme 98

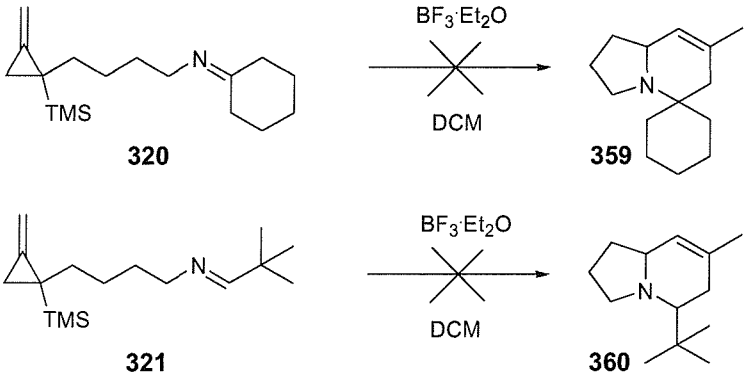
Imine **319** gave more of the cyclised product **358** than imine **318**, and also some of the non-reacted amine **312** and all of the benzaldehyde could be recovered (Scheme 99). The yield of this reaction is lower than the cyclisation of imine **315** probably due to the presence of a hydrogen in α position in respective to the imine double bond, which makes possible an equilibrium between imine **319** and the enamine form of this compound.



319 **358**, 10%

Scheme 99

Imines **320** and **321** gave no cyclised product, and most of amine **312** could be recovered in both cases. This is probably due to the steric hindrance caused by the cyclohexyl and *t*-butyl groups on the imine double bond which impedes the reaction between the imine double bond and methylenecyclopropyl olefin (Scheme 100).

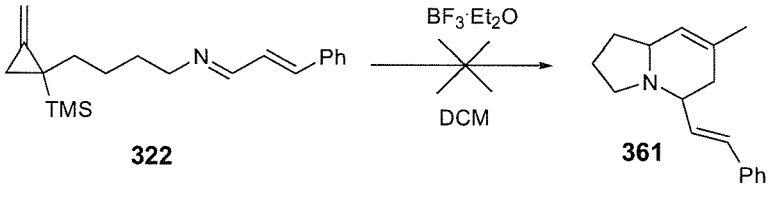


320 **359**

321 **360**

Scheme 100

Cyclisation of imine **322** led to complete decomposition of the starting material. Addition of another double bond onto the imine could have caused polymerisation of the starting material together with side reactions (Scheme 101).



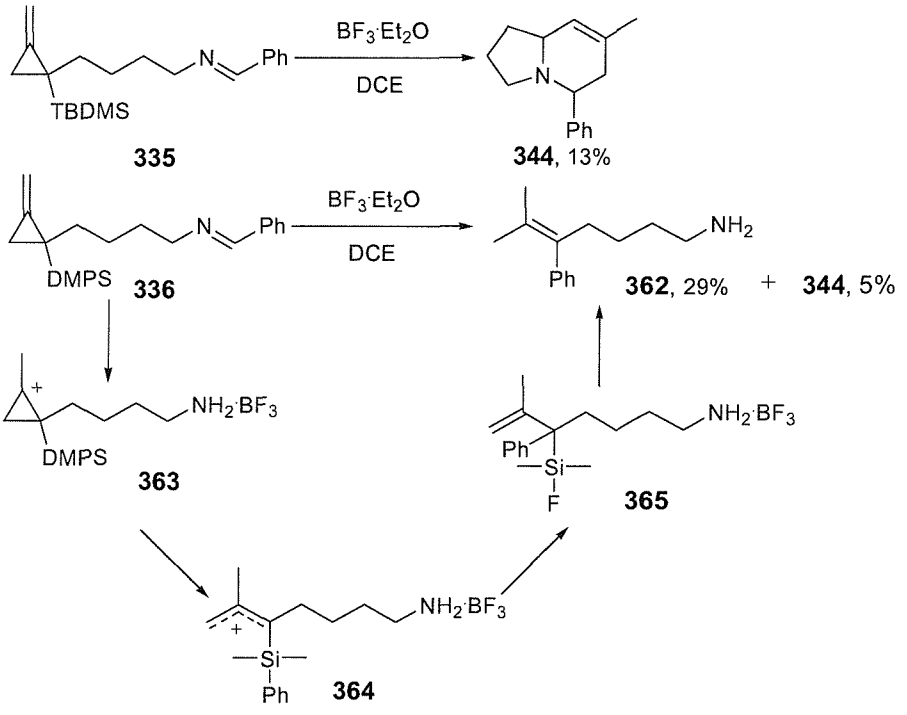
322 **361**

Scheme 101

When the cyclisation reactions of imines **318** - **322** were carried out in DCM with $TiCl_4$ as the catalyst, only slow decomposition of the starting materials was observed in all cases.

3.3.2 Cyclisation studies of benzylidene imines with other silyl groups

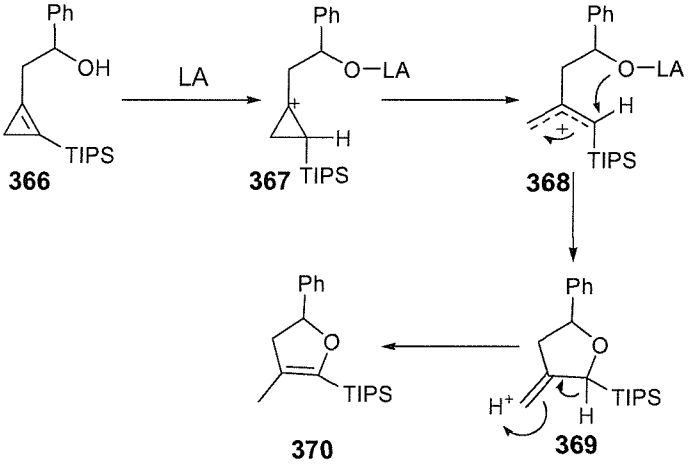
When cyclisation of imines **335** and **336** was attempted using the same conditions as for the cyclisation of imine **315**, with 1 equivalent of $BF_3{\cdot}Et_2O$ in DCM at room temperature, no reaction occurred even after 48 hours, and amines **333** and **334** were recovered quantitatively. When the cyclisation reaction of **335** was carried out in dichloroethane again with 1 equivalent of $BF_3{\cdot}Et_2O$, but this time heating the reaction mixture at 80 °C, cyclised product **344** was obtained in poor yield, with 23% of amine **333** recovered. When cyclisation of **336** was attempted in dichloroethane at 80 °C with 1 equivalent of $BF_3{\cdot}Et_2O$, after 24 hours only trace amounts of the cyclised product were obtained, the major product being **362**.



Scheme 102

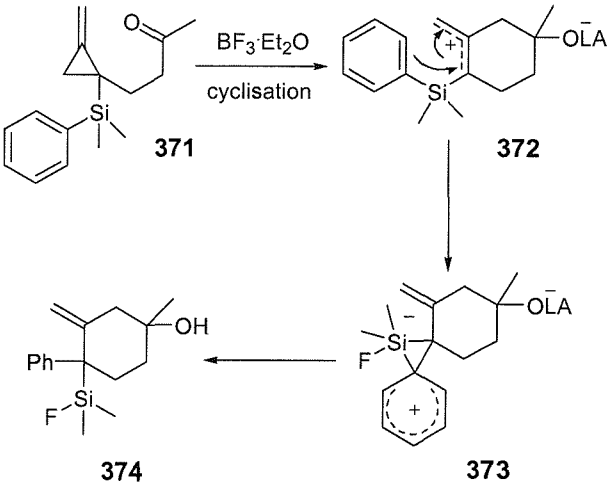
Formation of **362** can be rationalised by assuming that imine **336** was hydrolysed back to amine **334** (Scheme 86), after which methylenecyclopropyl moiety was protonated on the double bond, followed by ring opening to give cation **364**. Cation **364** is quenched by phenyl shift from the silicon, and the silyl cation is quenched by the fluoride anion derived from $BF_3{\cdot}Et_2O$. Hydrodesilylation then gives **362** (Scheme 102).

Supporting evidence for this mechanism can be found in the reaction of cyclopropene alcohol **366** with a Lewis acid.[132] The proton derived from the attack of the Lewis acid on the hydroxyl group attacks the cyclopropene double bond causing the formation of cation **367**, which via ring opening rearranges to allyl cation **368**. Allyl cation **368** is then quenched by the alcohol, and finally**370** is formed (Scheme 103).



Scheme 103

The phenyl shift such as described in scheme 102 has also been previously observed by Peron in the cyclisation of methylenecyclopropyl ketone **371** with $BF_3{\cdot}2AcOH$ as Lewis acid.[110] Cation **372** forms via the previously discussed pathway (Scheme 41), but instead of being quenched by the oxygen, a phenyl shift takes place, followed by quenching by fluoride to give **374** (Scheme 104)

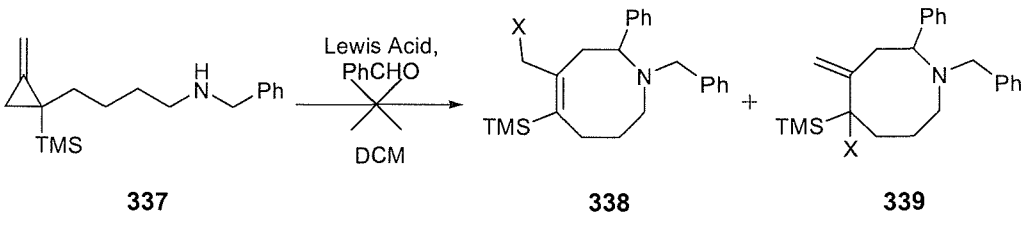


Scheme 104

As can be seen from these results, increasing the size of the substituents on the silyl group markedly decreases the yields of the cyclised product.

3.3.3 Cyclisation studies of amine 337 with benzaldehyde

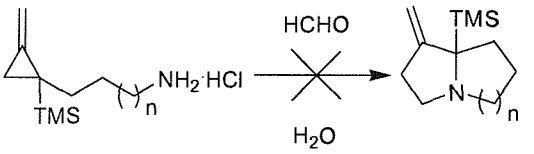
Cyclisation studies of amine **337** were carried out in DCM with 1.2 equivalents of benzaldehyde and $BF_3{\cdot}Et_2O$. Benzaldehyde and $BF_3{\cdot}Et_2O$ were added to the reaction mixture sequentially at – 78 °C, and the reaction was monitored by TLC while it was allowed to warm up. No reaction was observed until the reaction mixture reached room temperature, and after that only decomposition of the amine **337** was observed (Scheme 105).



Scheme 105

3.3.4 Cyclisation Studies of amines 341 and 342

Cyclisation studies of **341** and **342** were carried out in formalin. Even after conducting the reactions at room temperature for several days, no reaction occurred, and amines **311** and **312** were recovered almost quantitatively (Scheme 106).



341, n = 1
342, n = 2

375, n = 1
376, n = 2

Scheme 106

3.4 Conclusions

In conclusion, cyclisation of imines with 3- and 5-carbon alkyl chain (**314** and **315**) did not give desired cyclic products. Imines **315** and **317**, surprisingly, gave a different product than expected, namely, bicycles **344** and **356** *via* an interesting novel mechanism similar to the one observed previously by Patient in cyclisation reactions of methylenecyclopropyl hydrazones.[114] Cyclisation of imines with other than benzyl substitution did not give cyclised products, apart from imine **319** that gave bicycle **353** in poor yield. Investigation of the effect of the substituents on the silyl group proved that as the size of these substituens is increased, the yield of cyclised product dramatically decreases. Cyclisation of imines formed *in situ* from amines **311** and **312** with benzaldehyde in water in the presence of $Sc(OTf)_3$ did not give any product, and neither did cyclisation of hydrochloride salts **341** and **342** with formaldehyde in water. In both cases, the starting materials were recovered quantitatively.

It was proved that it is possible to cyclise methylenecyclopropyl imines with a 4-carbon alkyl chain. Other substrates with the same chain length might also give cyclised products.

Chapter 4

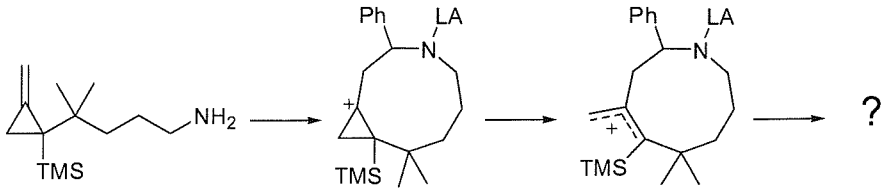
Cyclisation studies of substituted methylenecyclopropyl-silyl derivatives

4.1. Aims

Studies described in chapter 3 revealed that imine **315** did react to give cyclic product, although not the anticipated one, and in only moderate yield. It was therefore decided to study the effect of substitution on the alkyl chain on the cyclisation, e.g. using the gem dimethyl effect or incorporating a ring into the chain. Increased substitution was expected to facilitate the cyclisation reaction by orienting the imine moiety to closer proximity of the methylenecyclopropyl double bond.

Synthesis of various different substrates was thought of, and after considering the difficulties encountered previously in the synthesis of methylenecyclopropyl imines, it was decided to attempt the synthesis of imines listed below. The synthesis of these imines seemed feasible considering the limitations of synthetic procedures suitable for methylenecyclopropyl chemistry, and the effect of the substitution can also be effectively studied with these imines, as the level of substitution is increased from one imine to the other.

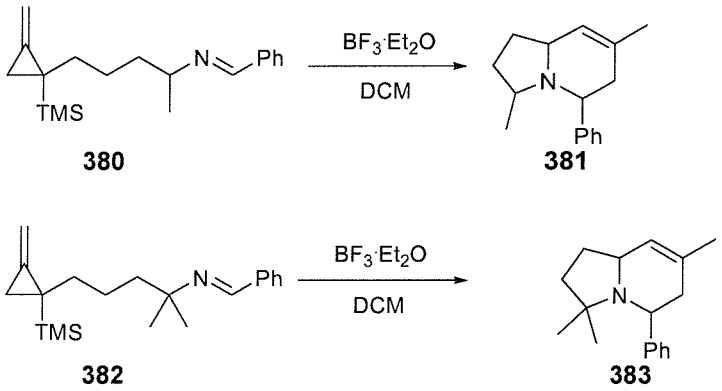
An amine with dimethyl substitution on the first carbon of the alkyl chain was to be synthesised to disable the 1,2-hydride shift observed in previous cyclisations, allowing investigation of the possible alternative reaction pathways. The gem-dimethyl effect was also expected to orient the imine moiety to closer proximity of the methylenecyclopropyl olefin, so facilitating the initial cyclisation reaction (Scheme 107).



377 **378** **379**

Scheme 107

Imines with both mono-and dimethyl substitution on the last carbon of the alkyl chain were to be synthesised to evaluate the effect of the substitution in the proximity of the imine moiety on the cyclisation. Also in the case of imines **380** and **382** the increased substitution is assumed to facilitate the cyclisation, and imine **382** was expected to give even greater yields that the monomethyl substituted imine **380** due to the gem dimethyl effect (Scheme 108).

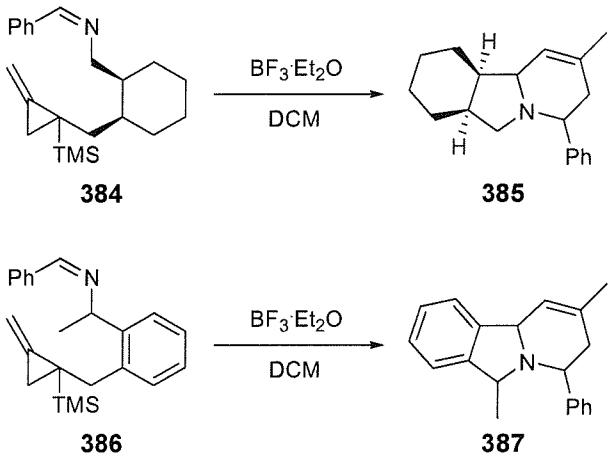


380 **381**

382 **383**

Scheme 108

Imines with cyclic substitution on the alkyl chain were also to be synthesised to evaluate whether this would further increase the yield of the cyclisation reaction, as inserting a ring into the alkyl chain would further constrain the molecule. This would again bring the imine moiety to closer proximity of the methylenecyclopropane double bond. Imines with both cyclohexyl and aromatic substitution on the alkyl chain were to be synthesised, as the conformation of the ring also effects the position of the imine moiety in the molecule (Scheme 109).

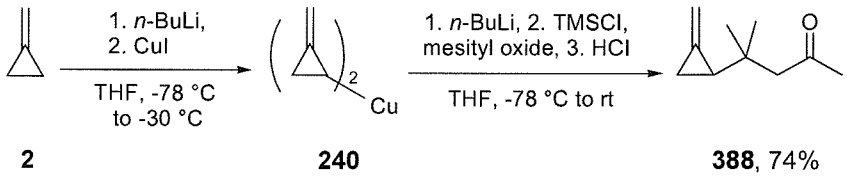


Scheme 109

4.2 Synthesis of precursors

4.2.1 Synthesis of a precursor with gem-dimethyl substitution on the first carbon of the alkyl chain

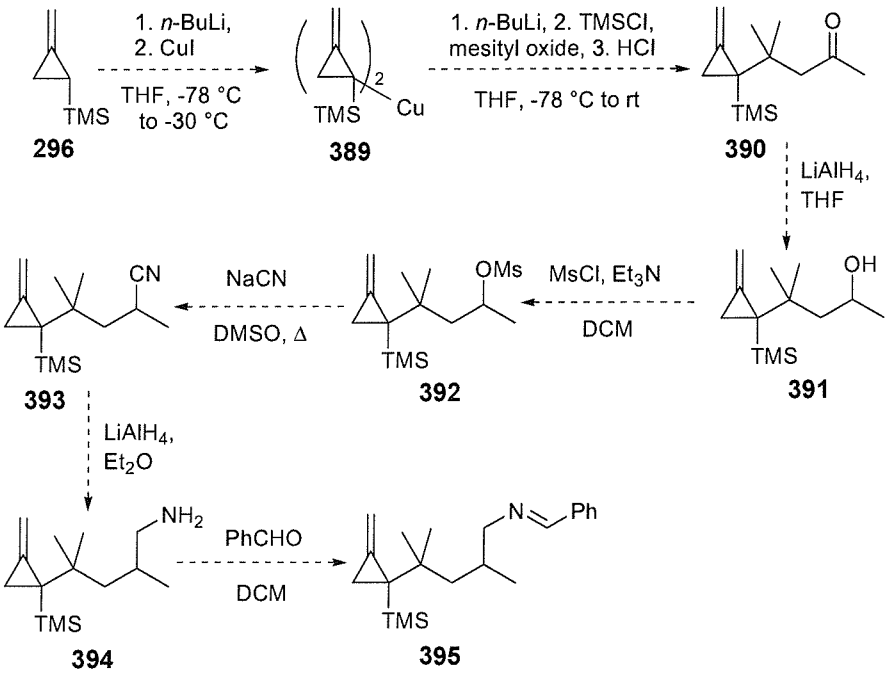
Peron has shown that Michael additions of methylenecyclopropyl cuprate **240** onto a allyl ketone or an aldehyde can be used to synthesise methylenecyclopropyl carbonyl compounds in good yields.[17] One of the substrates Peron used was mesityl oxide, which gave ketone **388** in good yield (Scheme 110).



Scheme 110

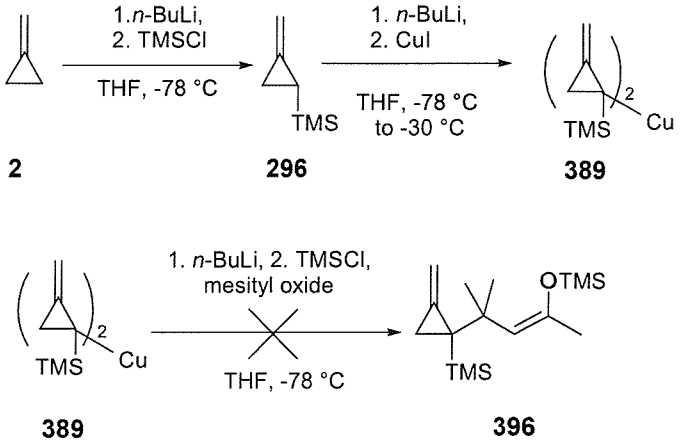
Addition of mesityl oxide to silylated methylenecyclopropyl cuprate **389** would provide access to compounds with dimethyl substitution directly adjacent to the methylenecyclopropyl moiety. Reduction of ketone **390**, conversion of the formed alcohol **391** to a mesylate followed by displacement of the mesylate with cyanide and finally reduction of the formed nitrile **393** would give amine **394**, and finally *via* a

reaction with benzaldehyde imine **395** (Scheme 111). All these reactions have been previously used successfully with methylenecyclopropyl substrates.



Scheme 111

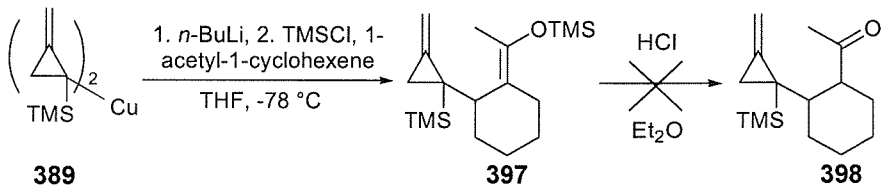
It was therefore decided to attempt the synthesis of ketone **390**. The reaction was performed *via* a method similar to the one previously described by Peron.[17] Methylenecyclopropane was deprotonated using *n*-BuLi and the subsequent anion was quenched with one equivalent of TMSCl. After a second equivalent of *n*-BuLi was added, the resulting anion was cannulated into a rapidly stirred suspension of CuI in THF. After the formation of cuprate **389** was complete, mesityl oxide and TMSCl were added to the cuprate to give silyl enol ether **396** (Scheme 110). Deprotection of the silyl enol ether **396** with HCl was then expected to give the Michael adduct **390** (Scheme 111). Although the cuprate complex seemed to form well, reaction of mesityl oxide with the cuprate complex did not yield the desired product **396**. The dimethyl substitution on the double bond may make it too hindered for successful Michael addition with an already stericly congested cuprate **389** (Scheme 112).



Scheme 112

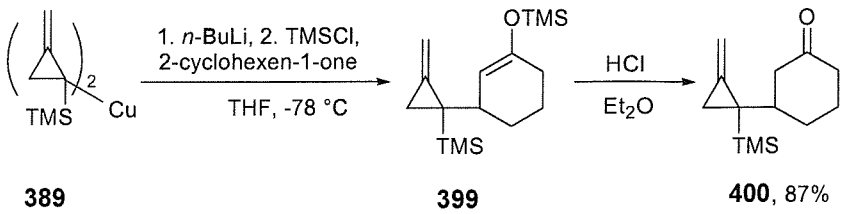
As it was interesting to see whether this reaction could be performed with other substrates, two other ketones that had previously given good yields in Michael additions with methylenecyclopropyl cuprate **240** were chosen. [17]

The first substrate chosen was 1-acetyl-1-cyclohexene, as Peron had obtained very high yields in Michael additions with this ketone.[17] Addition of cuprate **389** onto 1-acetyl-1-cyclohexene seemed to proceed cleanly to give silyl enol ether **397**, but desilylation of **397** gave an unidentified product instead of the expected ketone **398** (Scheme 113). Ketone **398** was assumed to be so reactive that it it was not possible to isolate it from the reaction mixture after the desilylation had taken place.



Scheme 113

Next, Michael addition onto 2-cyclohexen-1-one was attempted, as this substrate had also given very good yields in studies conducted by Peron, and indeed, in this case ketone **400** was obtained cleanly and in excellent yield as a single diastereomer (Scheme 114).

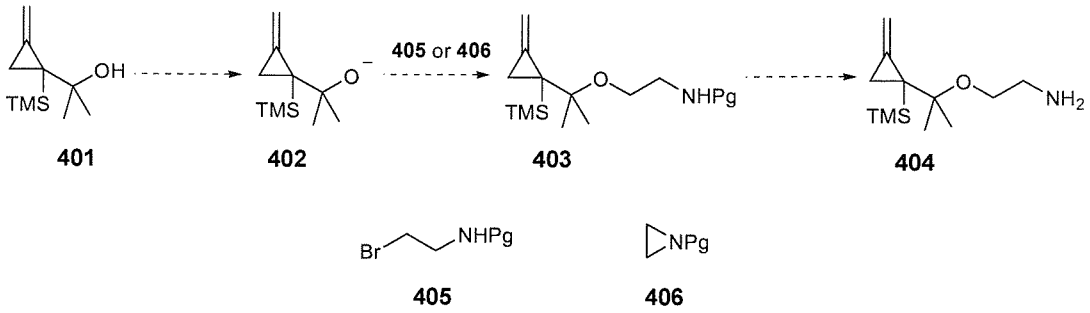


Scheme 114

The success of this reaction shows that cuprate **389** can be formed from **9**, and although here it has been shown to add onto Michael acceptors only in a few cases, it has been shown that with less hindered substrates this reaction can be expected to work well.

Although synthesis of ketone **390** failed and so disabled the use of this route to amine **377**, it might be possible to synthesise an amine with a gem-dimethyl substitution on the first carbon of the alkyl chain from methylenecyclopropyl alcohol **401** reported by Binger.[14] This would also introduce an ether functionality onto the alkyl chain.

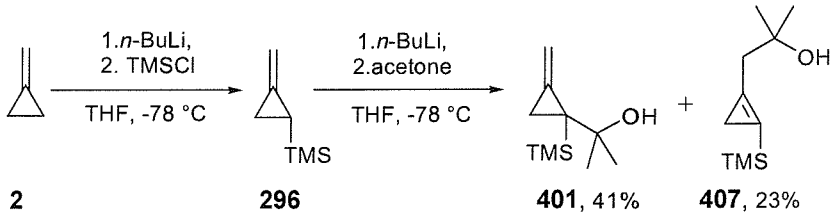
Binger[14] has reported the synthesis of alcohol **401** starting from methylenecyclopropane and acetone. Deprotonation of the alcohol followed by alkylation with a protected 2-bromo-ethylamine **405** or protected azide **406** would afford protected amine **403**, which would give amine **404** by a simple deprotection step (Scheme 115).



Scheme 115

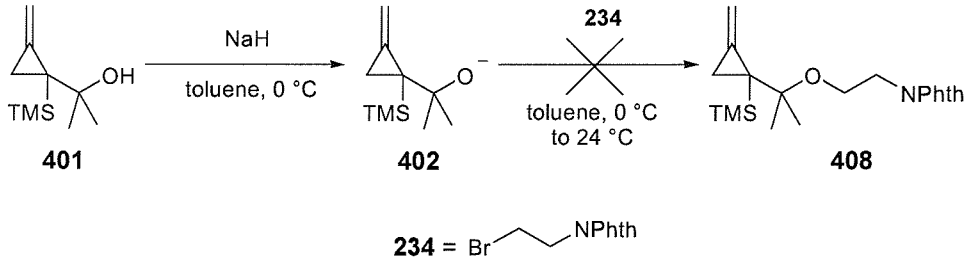
Alcohol **401** was synthesised following the literature method.[14] Methylenecyclopropane was deprotonated using *n*-BuLi and the subsequent anion was

quenched with one equivalent of TMSCl. A second equivalent of *n*-BuLi was added and the resulting anion was coupled with acetone to give alcohols **401** and **407** in 64:36 ratio, in reasonable overall yield (Scheme 116).



Scheme 116

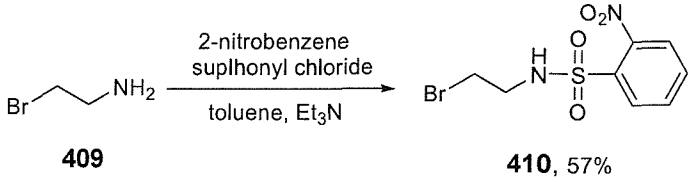
Alkylation of alcohol **401** was first attempted with phthalimide protected bromoethylamine **234**. The reaction was preformed in toluene by first deprotonating alcohol **401** at 0 °C and then adding the bromide into the rection mixture. Even after several hours at room temperature no reaction was observed, and the bromide was recovered quantitatively (Scheme 117).



Scheme 117

As the alkylation of alcohol **401** with **234** did not work, it was decided to use a different protecting group. 2-Nitrobenzenesulphonyl group was chosen for two reasons: there are several examples in the literature of alkylation of alkoxides with tosyl protected bromoamines, but removal of tosyl group requires dissolving metal reduction, which would also reduce the methylenecyclopropyl double bond. Instead, 2-nitrobenzenesulphonyl group can be removed in mild conditions with thiols or thioacetic acid, both of which were assumed not to affect the methylenecyclopropane.

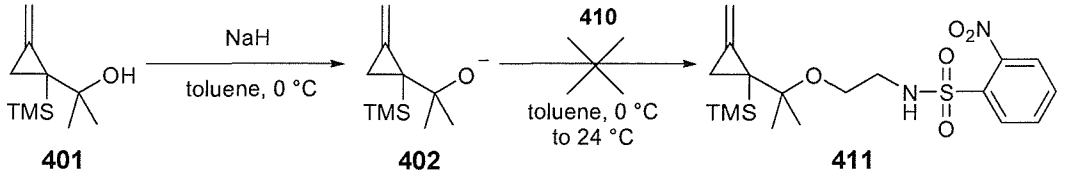
Protected bromoethylamine **410** was synthesised following a method described by Nagle.[133] 2-Bromoethylamine hydrobromide was reacted with 2-nitrobenzene sulphonyl chloride in toluene in the presence of triethylamine to afford protected bromoamine **410** in moderate yield (Scheme 118).



409 **410**, 57%

Scheme 118

Alkylation of alcohol **401** with bromoamine **410** was carried out following a method adapted from procedures described by Cahiez[134] and Grot.[135] Alcohol **401** was deprotonated with NaH in toluene at 0 °C, allowed to warm to room temperature, and bromoamine **410** was added. No reaction was observed, and both of the starting materials were recovered in quantitative yields (Scheme 119).

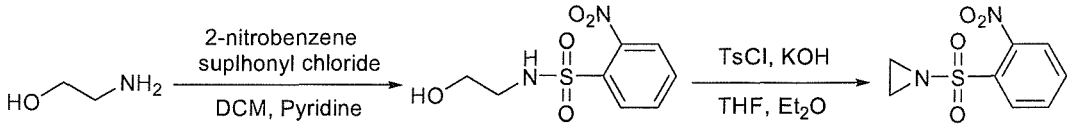


401 **402** **411**

Scheme 119

The problem with this alkylation reaction probably arises from the presence of the acidic hydrogen on **411**. This problem can be avoided by performing the alkylation with protected aziridine **414**.

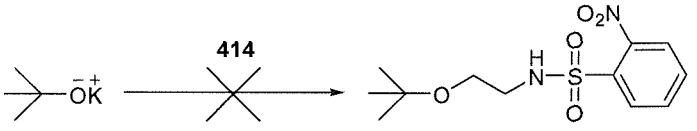
Aziridine **414** was synthesised starting from ethanolamine. Ethanolamine was reacted with 2-nitrobenzene sulphonyl chloride in DCM in the presence of pyridine, to afford protected ethanolamine **413** in moderate yield. This was then converted to aziridine **414** following a method described by Berry.[136] Protected ethanolamine **413** was reacted with tosyl chloride and potassium hydroxide in refluxing THF and diethyl ether mixture to give aziridine **414** in moderate yield (Scheme 120).



412 **413**, 58% **414**, 39%

Scheme 120

Preliminary alkylation studies were conducted with potassium *tert*-butoxide in toluene, DMF and DMSO. A solution of aziridine **415** in the reaction solvent was added to a stirred solution of potassium *tert*-butoxide at 0 °C, and the reaction was monitored by TLC while the temperature was allowed to rise. In all cases the starting materials decomposed completely (Scheme 121).

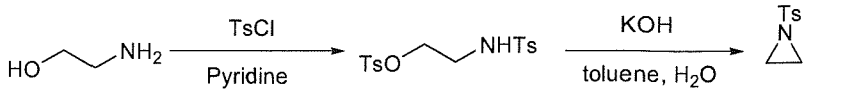


415 **416**

Scheme 121

The problem in these reactions could be the lability of the protecting group under basic conditions. Therefore, the nitrophenyl sulphoxide protecting group was abandoned. Instead, tosylaziridine **418** was synthesised in order to be used in the alkylation reaction.

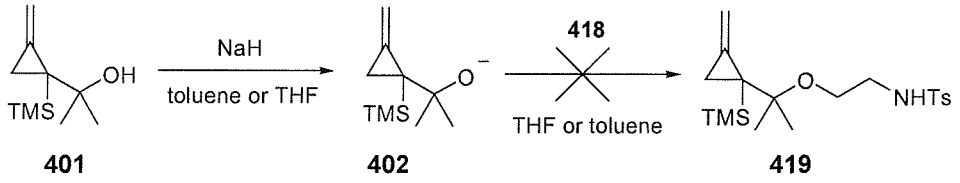
Tosylaziridine **418** was synthesised by a modified method of Hope and Horncastle.[137] Ethanolamine was reacted with tosyl chloride in pyridine to give ditosylated ethanolamine **417** in excellent yield.[138] This was then converted to tosylaziridine in good yield by reacting it with KOH (Scheme 122).[139]



412 **417**, 95% **418**, 65%

Scheme 122

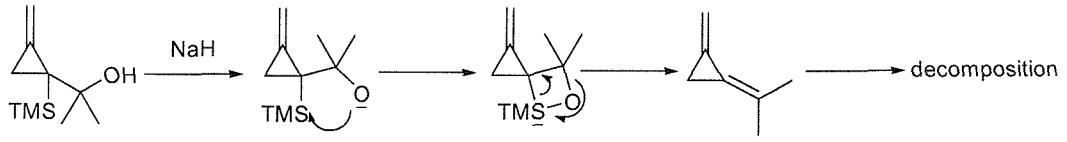
Alkylation of alcohol **401** with tosylaziridine **418** was attempted following a procedure described by Guo.[140] Alcohol **401** in THF was deprotonated with NaH at room temperature and then treated with tosylaziridine **418** in THF. Only tosylaziridine was recovered, as alcohol **401** had completely decomposed. The reaction was repeated in toluene with the same results (Scheme 123).



401 **402** **419**

Scheme 123

Alcohol **401** may have given **421** via a Peterson olefination[141] process, which would be highly reactive due to the ring strain (Scheme 124).



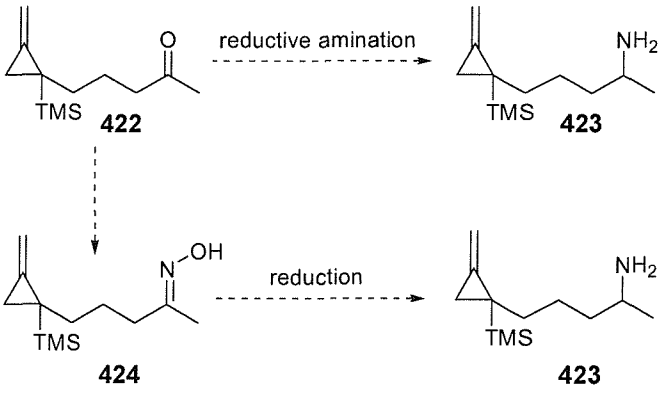
401 **402** **420** **421**

Scheme 122

As all the attempts to synthesise amine **378** failed, the synthesis of amine with gem-dimethyl substitution on the first carbon of the alkyl chain was abandoned.

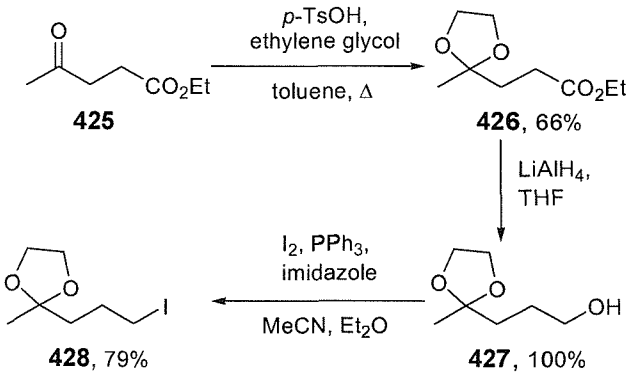
4.2.2 Synthesis of methylenecyclopropyl imine with methyl substitution on the last carbon on the alkyl chain

Peron[17] has described the synthesis of ketone **422**. This might be easily converted to amine **423** either by reductive amination, or by first forming oxime **424** and then reducing the oxime to give amine **423** (Scheme 125).



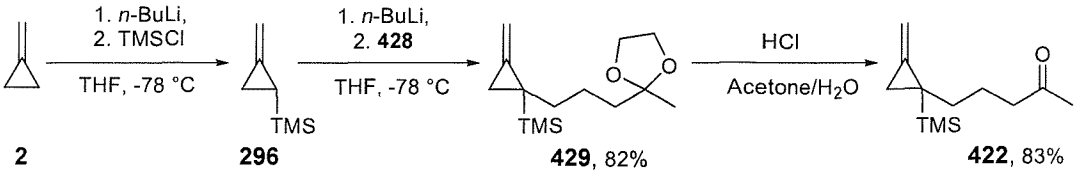
Scheme 125

Ketone **422** was synthesised as described by Peron.[17] Ethyl levulinate **425** was protected with ethylene glycol in toluene in the presence of catalytic *p*–toluenesulphonic acid to give the protected keto ester **426** in good yield. The ester moiety of **426** was then reduced with $LiAlH_4$ in THF to give alcohol **427** in quantitative yield, and the alcohol **427** was converted to iodide **428** with iodine, triphenyl phosphine and imidazole in good yield (Scheme 126).



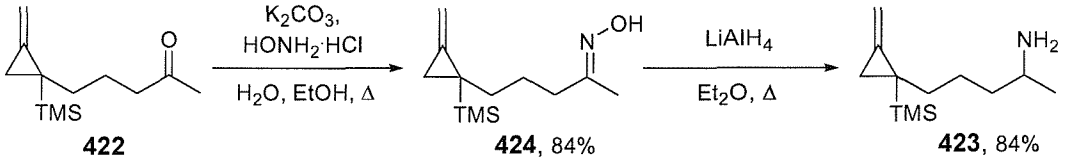
Scheme 126

Methylenecyclopropane was deprotonated using *n*-BuLi and the subsequent anion was quenched with one equivalent of TMSCl. A second equivalent of *n*-BuLi was added and the resulting anion was coupled with **428** to give protected methylenecyclopropyl ketone **429** in excellent yield. Deprotection of **429** with HCl in wet acetone then afforded ketone **422** in good yield (Scheme 127).



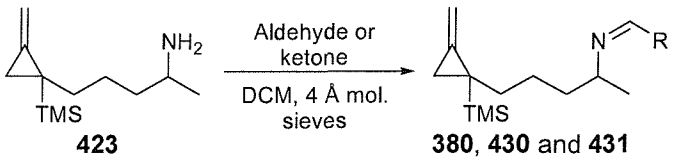
Scheme 127

Reductive amination with sodium cyanoborohydride and ammonium acetate proceeded with poor yield,[142] and therefore ketone **422** was first converted to hydroxyl oxime **424** by reaction with hydroxylamine hydrochloride.[143] The oxime **424** was then reduced with $LiAlH_4$ in Et_2O to give amine **423**. Both reactions were carried out in good yields (Scheme 128).[144]



Scheme 128

Imines **430-432** (Table 3) were synthesized from amine **423** using the methods explained previously, reacting amine **423** with different aldehydes and ketones in DCM in the presence of 4 Å molecular sieves (Scheme 129). The aldehydes and ketones used in the synthesis of the imines, as well as the yields of the condensation reactions are summarised in table 3.



423 **380**, **430** and **431**

Scheme 129

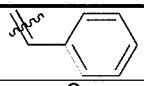
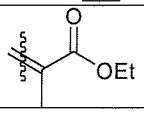
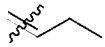
Entry	R	Aldehyde / Ketone	Yield
380		benzaldehyde	89%
430		ethyl pyruvate	86%
431		propionaldehyde	73%

Table 3

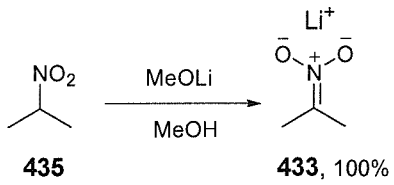
4.2.3 Synthesis of imines with gem-dimethyl substitution on the last carbon of the alkyl chain

It was felt that gem-dimethyl substituted methylenecyclopropane imines might be easily obtained by reacting bromide **432** with a lithium salt of 2-nitropropane, as described by Hamilton (Scheme 130).[145]

432 **433** **434**

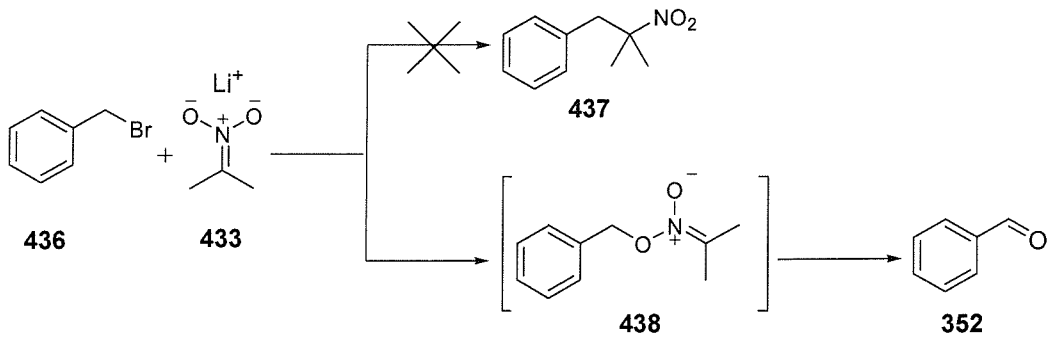
Scheme 130

2-Nitropropane **435** was reacted with freshly prepared lithium methoxide in methanol to give lithium salt of 2-nitropropane **433** in quantitative yield (Scheme 131).



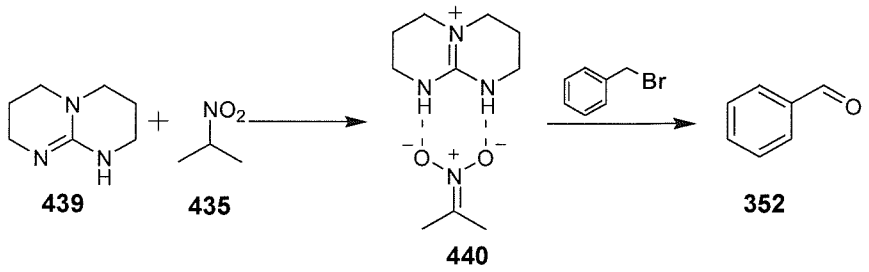
Scheme 131

Preliminary alkylation studies of benzyl bromide with **433** did not give any C-alkylated product, and benzaldehyde, resulting from O-alkylated intermediate **438**, was the only product obtained (Scheme 132).



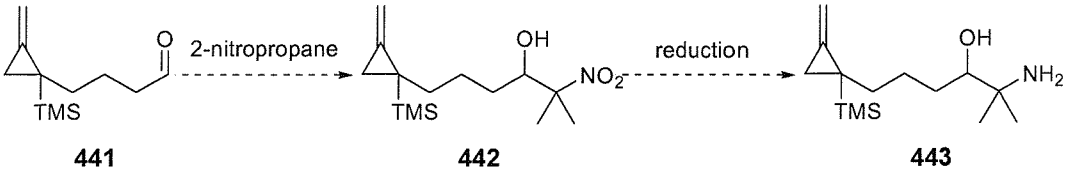
Scheme 132

Next the alkylation of benzyl bromide was attempted with a preformed complex of 2–nitropropane and guanidinium (**440**) as reported by Hamilton.[145] Again, no C–alkylation was observed, and benzaldehyde was the only product obtained (Scheme 133).



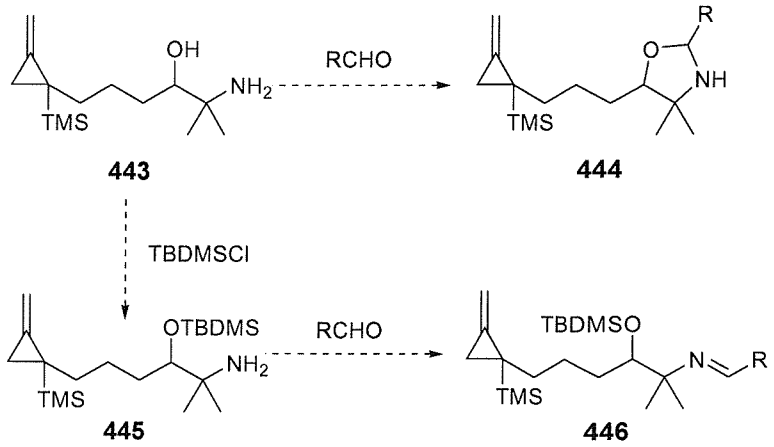
Scheme 133

As the C-alkylation of benzyl bromine failed, instead of **434** it was decided to synthesise nitroalcohol **442**. Nitroalcohol **442** can be synthesised from aldehyde **441** [114] *via* a Henry reaction with 2-nitropropane. Reduction of the nitro group then gives aminoalcohol **443** (Scheme 134).



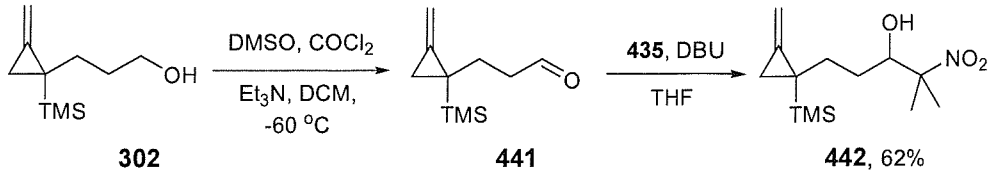
Scheme 134

Aminoalcohol **443** can be converted to oxazolidine **444** by reacting it with an aldehyde, as an oxazolidine can be considered as a masked imine. The hydroxyl group can also be protected prior to reacting the amine with an aldehyde, giving imine **446** (Scheme 135).



Scheme 135

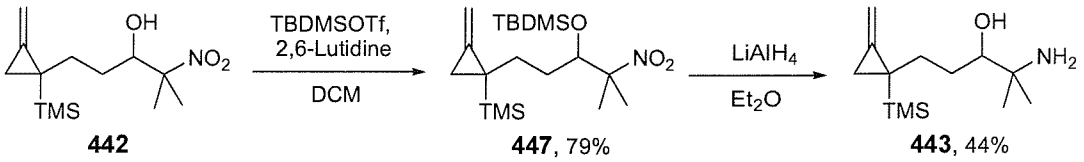
Swern oxidation[146] of alcohol **302** gave aldehyde **441** in good yield. Various reaction conditions of the Henry reaction between aldehyde **441** and 2-nitropropane were studied, and the best results were obtained by using DBU as the base (Scheme 136).[145]



Scheme 136

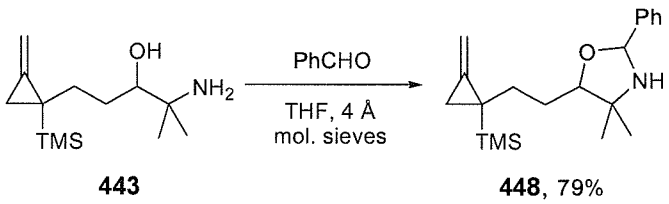
Direct reduction of nitroalcohol **442** with $LiAlH_4$ did not give the desired product. This is probably due to bond fission between the hydroxyl carbon and carbon with nitro substitution (due to formation of an alkoxide from the hydroxyl group), as has been previously observed by Robinson.[147] Therefore, nitroalcohol **442** was first protected as a silyl ether.

Protection of **442** as TBDMS ether with TBDMSOTf gave the protected alcohol **447** in good yield,[148] and reduction of **447** with $LiAlH_4$ proceeded smoothly to give directly amino alcohol **443** without need for deprotection (Scheme 137).[149]



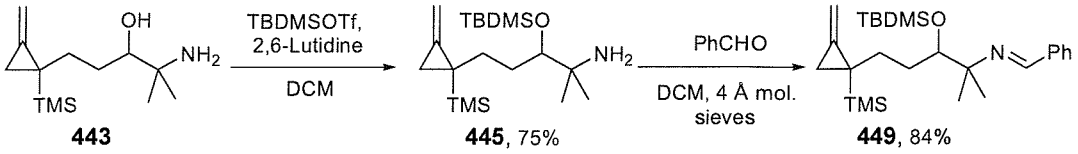
Scheme 137

Oxazolidine **448** was obtained in good yield by reacting aminoalcohol **443** with benzaldehyde in THF over 4 Å molecular sieves (Scheme 138).[150]



Scheme 138

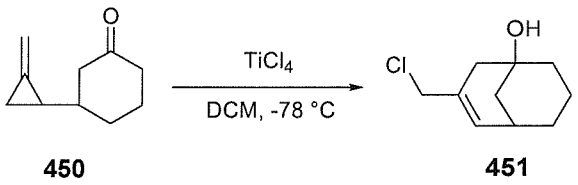
Protection of aminoalcohol **443** with TBDMSOTf gave **445** in good yield,[151] and imine **449** was obtained in good yield by reacting amine **445** with benzaldehyde in DCM over 4 Å molecular sieves (Scheme 139).



Scheme 139

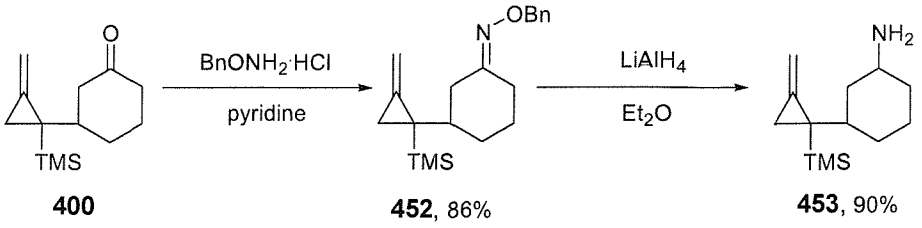
4.2.4 Synthesis of imines with a cyclohexyl substitution on the alkyl chain

Peron[17] has successfully cyclised methylenecyclopropyl ketone **450** to give bridged bicyclic alcohol **451** (Scheme 140). Successful cyclisation of **450** shows that the conformation of **450** is such that the carbonyl moiety and the olefin double bond are in close proximity, and so cyclisations of imines derived from **400** (Scheme 114) may also be successful.



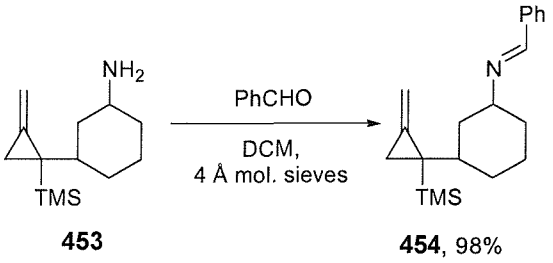
Scheme 140

Ketone **400** was easily converted to amine **455**. Benzyl oxime **452** was first synthesised in excellent yield by reacting ketone **400** with *O*-benzylhydroxylamine in pyridine.[152] Reduction of **452** with $LiAlH_4$ then afforded amine **453** in excellent yield (Scheme 141).



Scheme 141

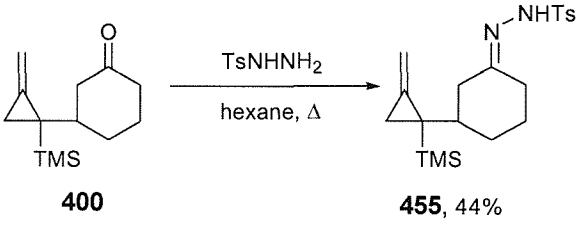
Imine **454** was synthesised in excellent yield by reacting amine **453** with benzaldehyde in DCM over 4 Å molecular sieves (Scheme 142).



Scheme 142

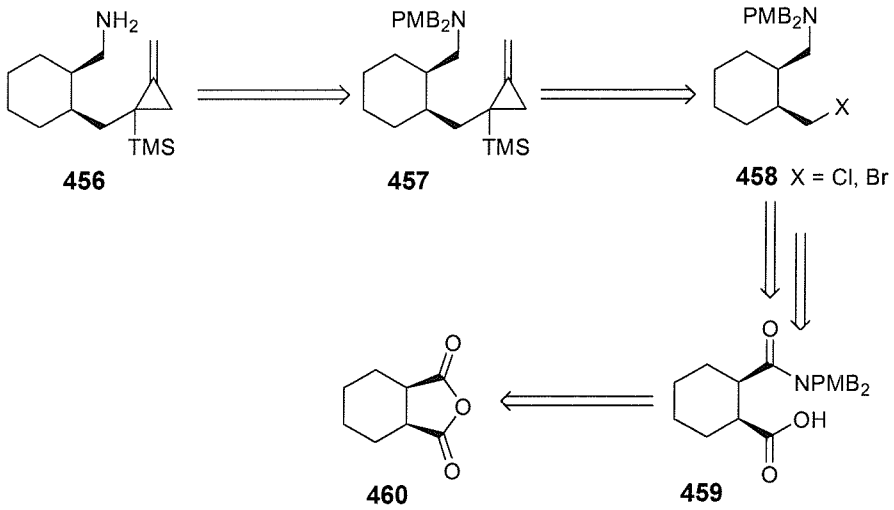
Patient[114] has reported that methylenecyclopropyl hydrazones can be cyclised in the presence of $BF_3{\cdot}Et_2O$ to give bridged cyclic compounds (Scheme 48, chapter 1). Tosyl hydrazone **455** was synthesised to evaluate whether this methodology could be extended to hydrazones with higher substitution.

Tosyl hydrazone **455** was synthesised in moderate yield using a method described by Patient.[114] Ketone **400** and tosyl hydrazide were condensed in refluxing hexane to give tosyl hydrazone **455** in moderate yield (Scheme 143).



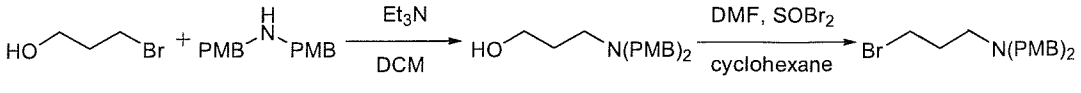
Scheme 143

It was thought that amine **456** might be easily accessible starting from anhydride **460**. Opening of the anhydride with *N,N*-di-methoxybenzyl amine would give amide **459**, and reduction of the amide followed by conversion of the carboxylic acid moiety to a leaving group would give **459**. Subsequent alkylation of methylenecyclopropane with TMSCl and **458** would give the protected methylenecyclopropyl amine **457**, and deprotection would then afford amine **456** (Scheme 144).



Scheme 144

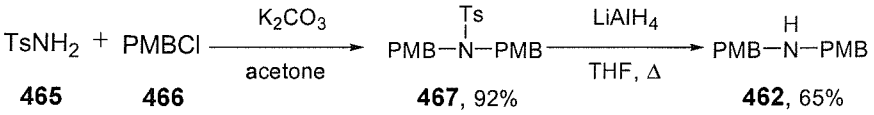
In the synthesis of previous imines used in the cyclisation studies, use of protecting groups had proven to be unsuccessful. These problems had arisen from the presence of an acidic hydrogen on the nitrogen (Scheme 61), an exposed electrophilic carbon (Scheme 58) and inability to deprotect the synthesised methylenecyclopropyl amine (Scheme 63). However, all these problems may be avoided by the use of *p*-methoxybenzyl protecting group. It has been shown in literature to be easily removable with CAN from both mono- and di-protected amines under mild conditions,[153,154] and yet it is stable to the reaction conditions used during synthesis of amine **456**. For preliminary deprotection studies **468** (Scheme 147) was synthesised starting from 3-bromopropanol. Displacement of the bromine by *N,N*-dimethoxybenzyl amine under standard conditions gave protected aminoalcohol **463**, which in turn was converted to bromide **464** *via* a reaction with thionyl bromide (Scheme 145).[133]



461 **462** **463**, 26% **464**, 64%

Scheme 145

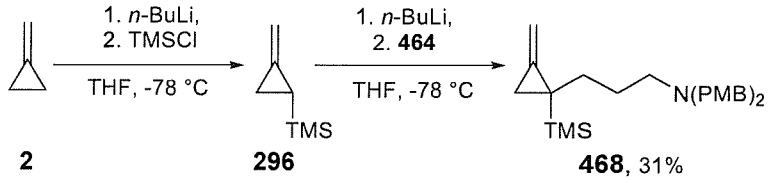
N,N-Dimethoxybenzyl amine **462** was synthesised by first protecting tosyl amide **465** with PMBCl to give protected tosyl amide **467** in excellent yield,[155] followed by reduction of **467** with $LiAlH_4$ in refluxing THF to give PMB amine **462**. The reaction proceeded in good yield (Scheme 146).[156]



465 **466** **467**, 92% **462**, 65%

Scheme 146

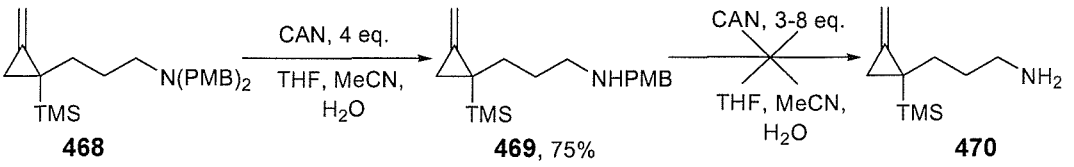
Standard alkylation procedure of methylenecyclopropane with TMSCl followed by **464** gave PMB-protected methylenecyclopropyl amine **468** cleanly, with most of the unreacted bromide **464** recovered (Scheme 147).



2 **296** **468**, 31%

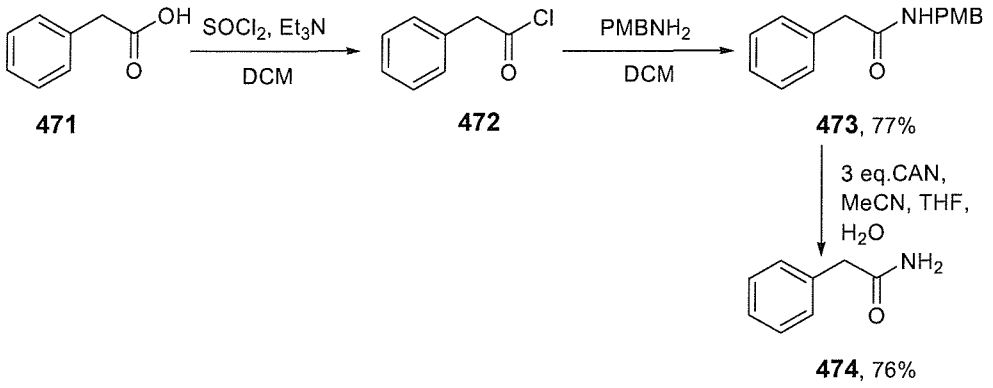
Scheme 147

Removal of one of the PMB groups from amine **468** proceeded smoothly with 3 equivalents of CAN following the method described by Davies, to give the monoprotected amine **469**.[154] Removal of the second protecting group, however, was not achieved in these mild conditions, and using greater excess of CAN caused the amine **469** to decompose (Scheme 148).



Scheme 148

It was thought that removal of a PMB group from an amide should be easier than removal from an amine. To test this hypothesis PMB protected amide **473** was synthesised by reacting acid chloride **472** derived from phenylacetic acid with *p*–methoxybenzylamine. Deprotection of **473** with 3 equivalents of CAN gave a clean 1:1 mixture of *p*-methoxybenzaldehyde and 2-phenylacetamide **474** in good yield (Scheme 149).

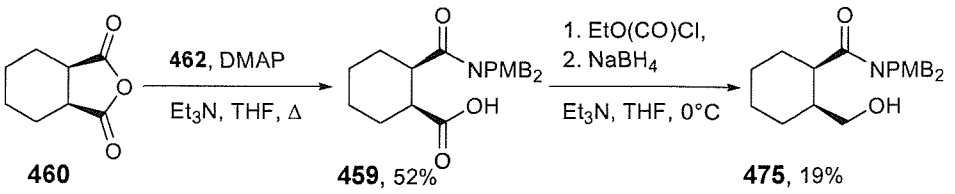


Scheme 149

As deprotection of amine **469** was unsuccessful, but phenylacetamide **474** could be deprotected cleanly, it was decided to reduce the amide moiety of **460** as the last step *en route* to amine **456** instead of reducing it at the same time with the carboxylic acid moiety.

Carboxylic acid **459** was obtained following a method described by Frechét.[157] Anhydride **460** and amine **462** were reacted in a mixture of triethylamine and THF with catalytic DMAP to give amide **459** in good yield. Selective reduction of the carboxylic acid moiety to an alcohol was achieved by forming a mixed anhydride with ethyl

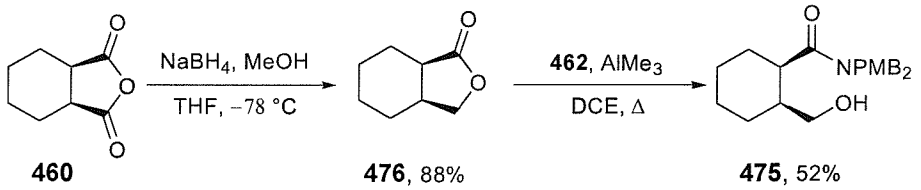
chloroformate, followed by reduction of the anhydride with $NaBH_4$ to give alcohol **475** in modest yield (Scheme 150).[158]



460 **459**, 52% **475**, 19%

Scheme 150

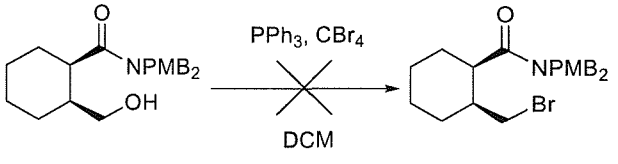
Better yields of alcohol **475** were obtained when anhydride **460** was first reduced to lactone **476** with $NaBH_4$,[159] and the lactone **476** was then opened with amine **462** (Scheme 151).[160] Both reactions proceeded cleanly and in good yields.



460 **476**, 88% **475**, 52%

Scheme 151

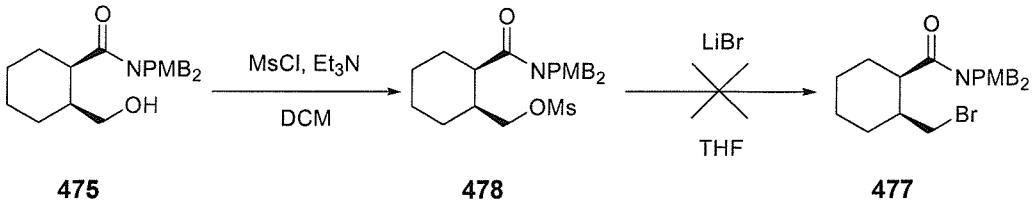
Conversion of the hydroxyl group to a halide proved to be problematic. Bromination with carbon tetrabromide and triphenylphosphine led to decomposition of the starting material with a trace amount of bromide **477**. Although some product was formed, the yield was very low, and it was not possible to isolate **477** from the side products (Scheme 152).



475 **477**

Scheme 152

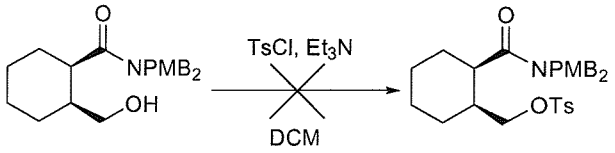
The next attempt was to first form a mesylate from **475**, and convert this to bromide **477** with lithium bromide. This approach did not give the predicted outcome, and decomposition of alcohol **475** was observed (Scheme 153).



475 **478** **477**

Scheme 153

Last, tosylation of alcohol **475** was attempted in the hope that the tosyl group could be directly displaced with methylenecyclopropyl anion. However, no product was formed, probably because of the steric hindrance caused by the two PMB groups (Scheme 154).



475 **479**

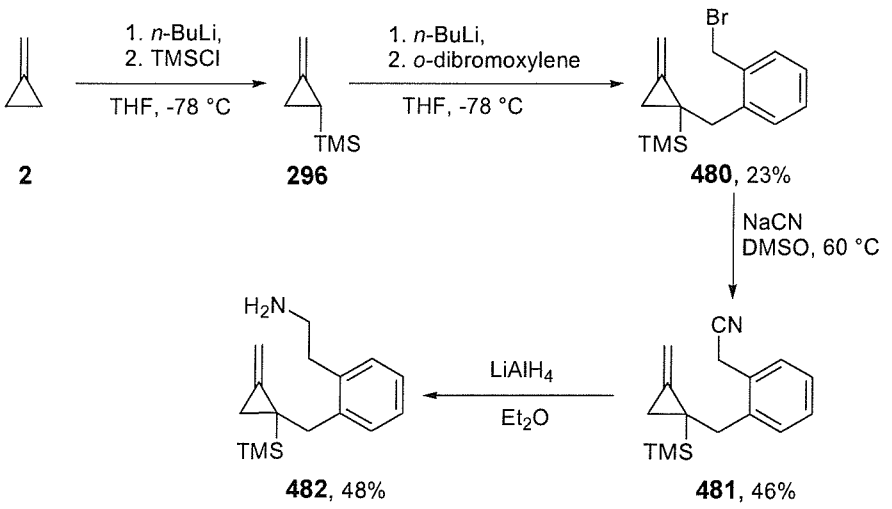
Scheme 154

As conversion of alcohol **475** to **479** with a suitable leaving group failed, synthesis of **456** was abandoned.

4.2.5 Synthesis of imines with an aromatic ring on the alkyl chain

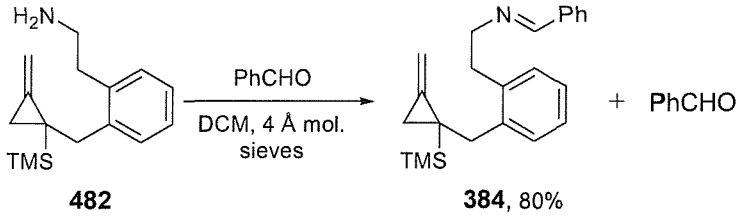
Amine **482** was synthesised starting from *o*-dibromoxylene in three steps. First, methylenecyclopropane was deprotonated using *n*-BuLi and the subsequent anion was quenched with one equivalent of TMSCl. A second equivalent of *n*-BuLi was added and the resulting anion was cannulated to a stirred solution of *o*-dibromoxylene to give bromide **480** in modest yield. Bromide **480** was used directly in the next step without further purification. Bromide **480** was converted to nitrile **481** with NaCN in DMSO in

modest yield,[122] and reduction of nitrile **481** with $LiAlH_4$ gave amine **482** in moderate yield (Scheme 155).[123]



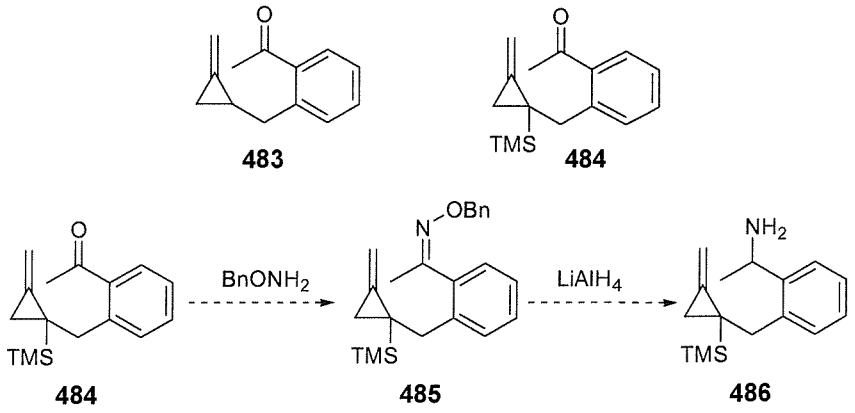
Scheme 155

Imine **384** was obtained in good yield as a mixture of imine **384** and benzaldehyde by reacting amine **482** with benzaldehyde in DCM over 4 Å molecular sieves (Scheme 156).



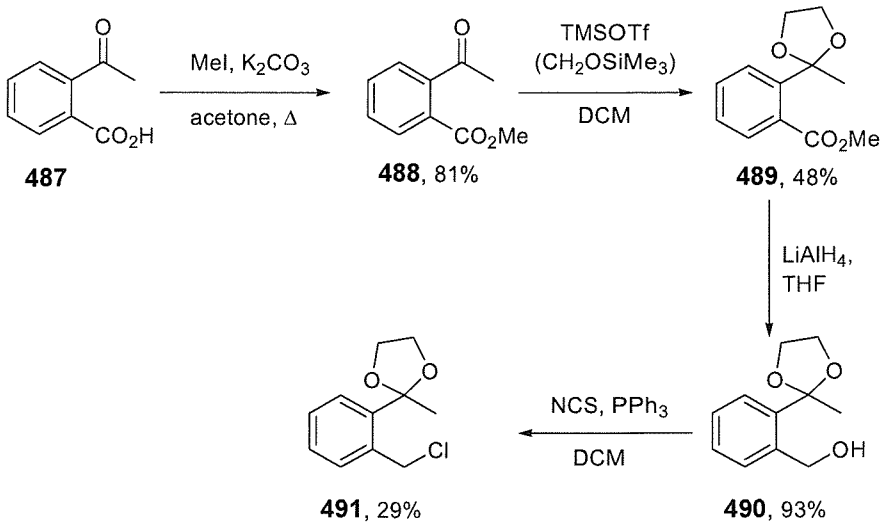
Scheme 156

Underwood[161] has developed a synthetic route for ketone **483**. By a simple modification of this route, ketone **484** can be synthesised, and formation of oxime **485** followed by reduction should give amine **486** (Scheme 157).



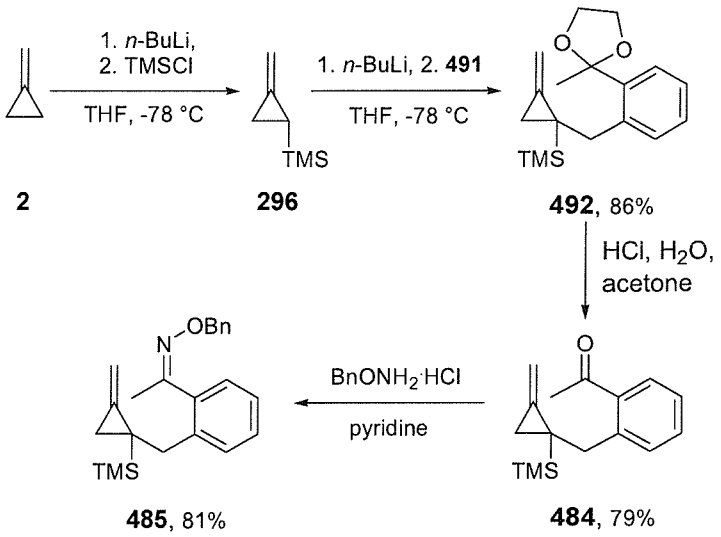
Scheme 157

2-Acetylbenzoic acid was converted to methyl ester **488** in good yield by treating caboxylate **487** with methyl iodide.[162] The carbonyl on **488** was then protected as a ethyl ketal using a procedure described by Noyori.[163] Protection of the ketone with 1,2-bis-(trimethylsilyloxy)ethane and trimethylsilyl triflate gave ketal **489** in moderate yield. Reduction of ester **489** to alcohol **490** with $LiAlH_4$ was quantitative,[164] and the alcohol **490** could be used in the next reaction step without purification. Finally, the chlorination of **490** with NCS to give chloride **491** proceeded in modest yield (Scheme 158).[165]



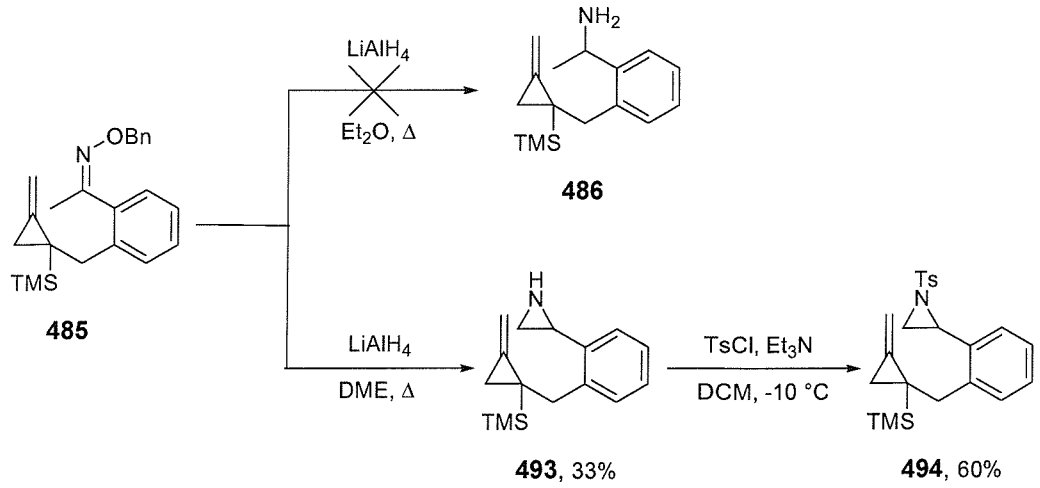
Scheme 158

Methylenecyclopropane was deprotonated using *n*-BuLi and the subsequent anion was quenched with one equivalent of TMSCl to give **296**. A second equivalent of *n*-BuLi was added and the resulting anion was coupled with chloride **491** to give **492** in excellent yield. Deprotection of **492** with HCl in 10% water in acetone gave methylenecyclopropyl ketone **484** in good yield, and ketone **484** was then converted to the corresponding benzyl oxime **485** in good yield[152] (Scheme 159).



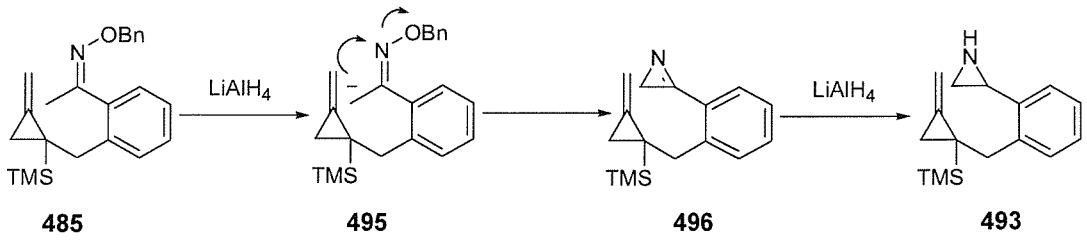
Scheme 159

Reduction of the oxime with $LiAlH_4$ in refluxing Et_2O failed,[166] giving back the starting oxime **485** quantitatively. Reduction with $LiAlH_4$ in refluxing diglyme also failed, this time giving aziridine **493** as the only isolable product. Aziridine **493** was converted to tosylaziridine **494** under standard conditions for characterisation purposes (Scheme 160).



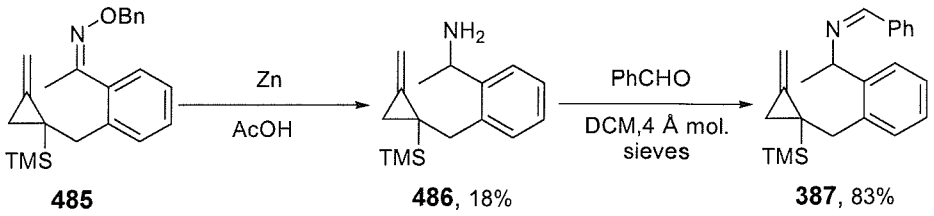
Scheme 160

The mechanism of the formation of the aziridine follows the Neber rearrangement.[167] Oxime **485** might be too hindered for reduction with $LiAlH_4$, and instead $LiAlH_4$ may act as a base creating anion **495** by removing a hydrogen from the methyl carbon. Attack of the anion on the nitrogen would then give aziridine **496**, which is finally reduced to **493** by $LiAlH_4$ (Scheme 161).



Scheme 161

Finally, reduction of oxime **485** was successful using a method described by Canary.[168] Reduction of **485** with zinc powder in acetic acid gave amine **486** in moderate yield, and imine **387** was obtained in good yield by reaction of amine **486** with benzaldehyde in DCM over 4 Å molecular sieves (Scheme 162).

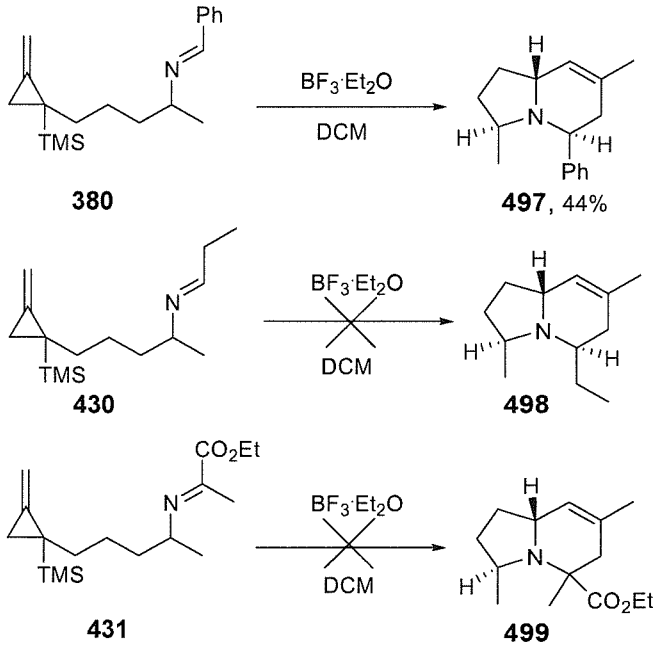


Scheme 162

4.3 Cyclisation studies

4.3.1. Cyclisation studies of imines 380, 430, and 431

Cyclisation studies of imines **380**, **430**, and **431** were carried out in DCM at room temperature, using 1 equivalent of $BF_3{\cdot}Et_2O$ as catalyst, as these conditions had been previously found to give the best results. Imines **430** and **431** did not give the desired products **498** and **499**, respectively, whereas imine **380** cyclised to give the expected bicycle **497** in slightly better yield than what had been achieved in cyclisations of imine **315** (Scheme 163).



Scheme 163

To elucidate the stereochemistry of **497** GOESY studies were conducted. Irradiation of H_A caused 3.12% enhancement of H_C and no enhancement of H_B. Irradiation of H_B caused 1.13% enhancement in the methyl goup geminal to H_C, and no enhancement in either H_C or H_A. Irradiation of H_C caused 2.10% enhancement in H_A, and no enhancement of H_B. These results indicate that H_A and H_C are on the opposite side of the molecule from H_B. Also, irradiation of H_A caused 2.49% enhancement of H_D, which indicates that H_A and H_D are in close proximity (Figure 5).

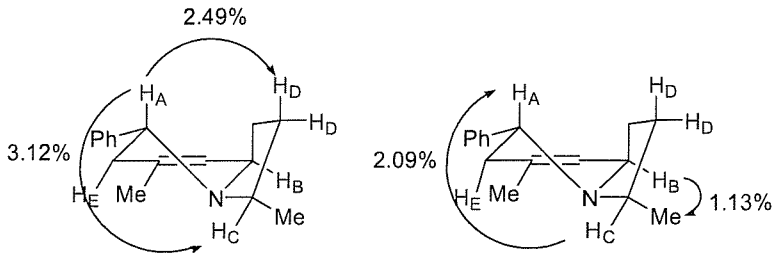
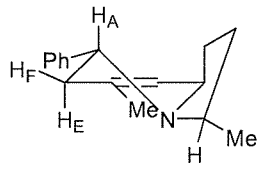


Figure 5

GOESY studies of **497**

Further evidence of the conformation of **497** was again gained from the ^1H NMR studies. The coupling pattern of proton H_A with a small axial-equatorial coupling to H_F, and an axial-axial coupling to H_E again suggest that H_A is in axial position and the phenyl group is in equatorial position (Figure 6), and as the GOESY studies indicate that H_A and H_D are at close proximity to each other as well as H_A and H_C, all the information of both studies indicates that also the cyclopentyl ring is in axial position. These results agree with the conformation assumed for bicycle **497** (Figure 5 and figure 6).



H_A, dd *J* 4, 11 Hz
H_E, dd, *J* 11, 18 Hz

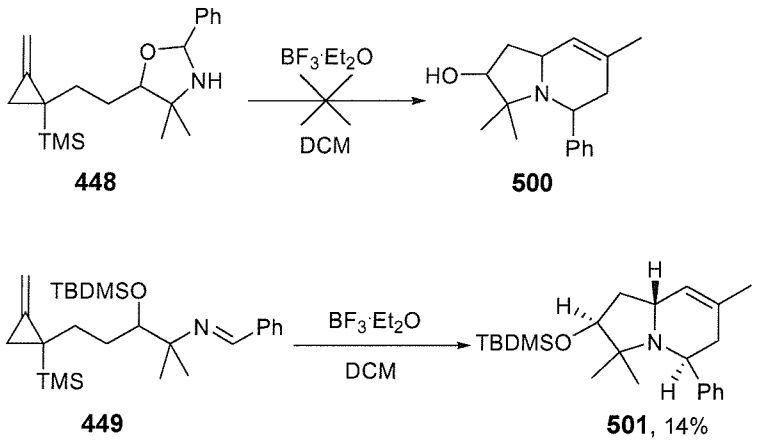
Figure 6

Coupling patterns of **497**

4.3.2 Cyclisation studies of oxazolidine 448 and imine 449

Cyclisation studies of oxazolidine **448** were carried out in DCM at -78 °C, using 1 equivalent of $BF_3{\cdot}Et_2O$ as catalyst. As the reaction mixture was allowed to warm up, only decomposition of oxazolidine **448** was observed (Scheme 164).

Cyclisation studies of imine **449**, were also carried out in DCM at -78 °C, using 1 equivalent of $BF_3{\cdot}Et_2O$. After the reaction mixture was warmed to room temperature, reaction was observed, and bicycle **501** could be isolated in 14% yield (Scheme 164). The unexpectedly low yield can be explained by the presence of the TBDMS ether on the imine **449**. The ether oxygen can also react with the Lewis acid, leading to side reactions and decomposition.



Scheme 164

To elucidate the stereochemistry of **501** GOESY studies were conducted. Irradiation of H_A caused 4.22% enhancement in Me_2 and no enhancement in H_B, H_C or Me_1. Irradiation of H_B caused 0.93% enhancement in Me_1, and no enhancement in either H_C or H_A. Irradiation of H_C caused 1.99% enhancement in Me_2, and no enhancement in H_A or H_B. These results indicate that H_A and H_C are on the opposite side of the molecule **501** from H_B (Figure 7). This relative stereochemistry was also observed in previous cyclised products (Figures 3 and 5). Irradiation of H_C caused a 2.75% enhancement on H_D, indicating that these two protons are in close proximity.

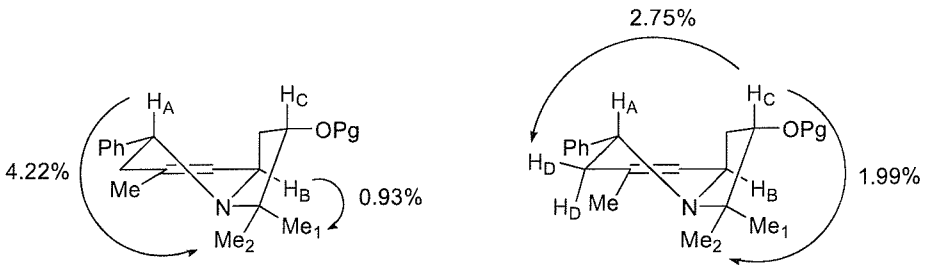


Figure 7

GOESY studies of **501**

Also the coupling pattern of H_A (Figure 8) supports the previously observed conformation of bicycles **344** and **497** by showing only the axial-axial coupling, the axial-equatorial coupling being too small to observe. This together with the results of the GOESY studies again indicates that H_A and the cyclopentyl ring are axial, and the phenyl group is equatorial.

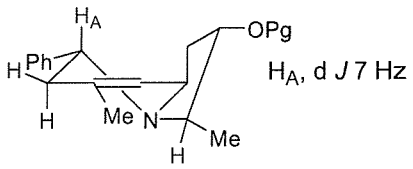


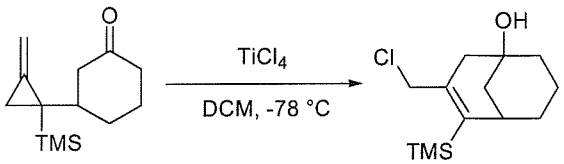
Figure 8

Coupling patterns of **501**

4.3.3 Cyclisation studies of ketone 400, imine 454 and hydrazone 455

Cyclisation studies of ketone **400** were carried out, as it was interesting to see whether the silyl substituted ketone would give better yields of cyclised product than the non-silylated precursor **450** used by Peron (Scheme 140).[17]

The cyclisation studies were carried out using the same reaction conditions as Peron, with 1 equivalent of $TiCl_4$ as the catalyst and DCM as solvent. The reaction went to completion in 5 minutes at -78 °C, and after workup bicycle **502** could be obtained quantitatively. Its purity was high enough for characterisation. Even after additional purification bicycle **502** was obtained in high yield (Scheme 165). The structure of **502** was proved by X-ray crystallography (Figure 9).



400 **502**, 67%

Scheme 165

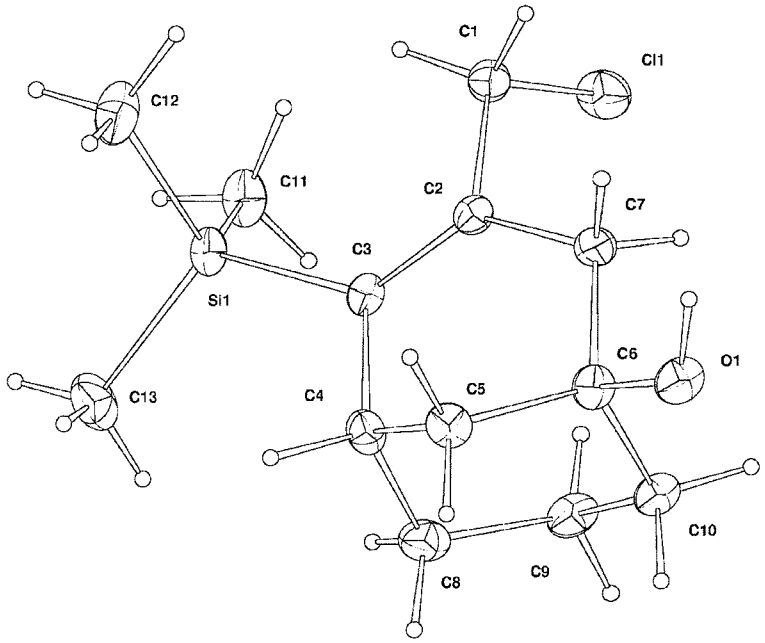
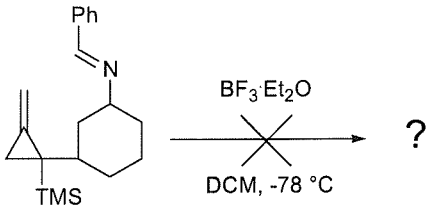


Figure 9

X-ray crystal structure of **502**

When cyclisation of **400** was attempted with $BF_3{\cdot}Et_2O$, only decomposition of the ketone **400** was observed.

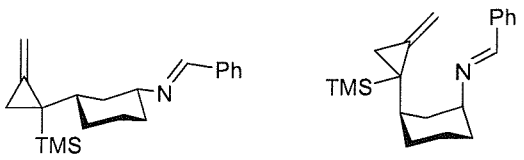
Cyclisation studies of imine **454** were carried out in DCM with either $TiCl_4$ or $BF_3{\cdot}Et_2O$ as catalyst. In either case no product was formed. When $TiCl_4$ was used as catalyst, amine **453** could be recovered almost quantitatively. When $BF_3{\cdot}Et_2O$ was used as catalyst, the starting materials decomposed almost completely, and only a small amount of amine **453** could be recovered (Scheme 166).



454

Scheme 166

These results were not surprising, as the cyclisation could only be expected to work if the methylenecyclopropane and the imine substituents on the cyclohexyl ring were *cis* to each other, as well as both substituents being in an axial position (Figure 10), and from the ^{13}C NMR of amine **453** it could be seen that more than one of the possible diastereomers of the amine had been formed. Therefore, even if the cyclisation reaction had been successful, the maximum expected yield would have been 50%.

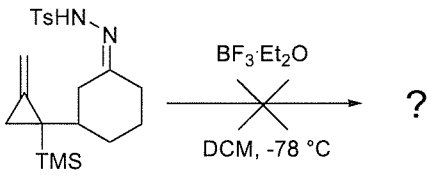


A **B**

Figure 10

Unfavourable (**A**) and favourable (**B**) conformations of *cis* - isomer of **454** for cyclisation reaction.

Cyclisation studies of hydrazone **455** were carried out in nitroethane at -78 °C with 1 equivalent of $BF_3{\cdot}Et_2O$ as catalyst, as these conditions had been found to give the best results in cyclisation studies by Patient.[114] No product was obtained, and only decomposition of the starting material was observed (Scheme 167).

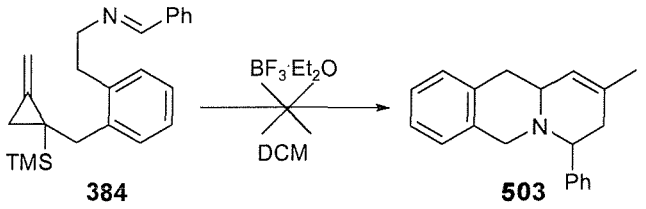


455

Scheme 167

4.3.4 Cyclisation studies of imines 384 and 386

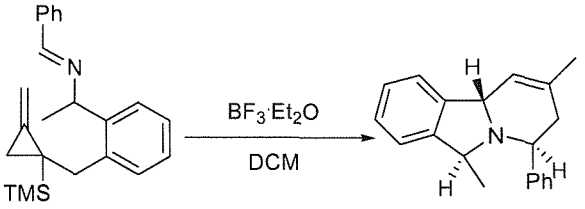
Cyclisation studies of imine **384** were carried out in DCM at -78 with 1 equivalent of $BF_3{\cdot}Et_2O$ as catalyst. No cyclised product was obtained, and the starting material decomposed completely (Scheme 168).



384 **503**

Scheme 168

Cyclisation studies of imine **386** were also carried out in DCM with 1 equivalent of $BF_3{\cdot}Et_2O$ as catalyst. Reaction proceeded at room temperature to give bicycle **504** in good yield as adjudged by ^1H NMR of the crude reaction material (Figure 11), but decomposition of the product during purification lowered the yield considerably (Scheme 169). In acidic media the double bond on the cyclohexene ring can move into conjugation with the aromatic ring. This gives raise to an enamine that in acidic media can be hydrolysed, causing decomposition of **504**.



386 **504**, 34%

Scheme 169

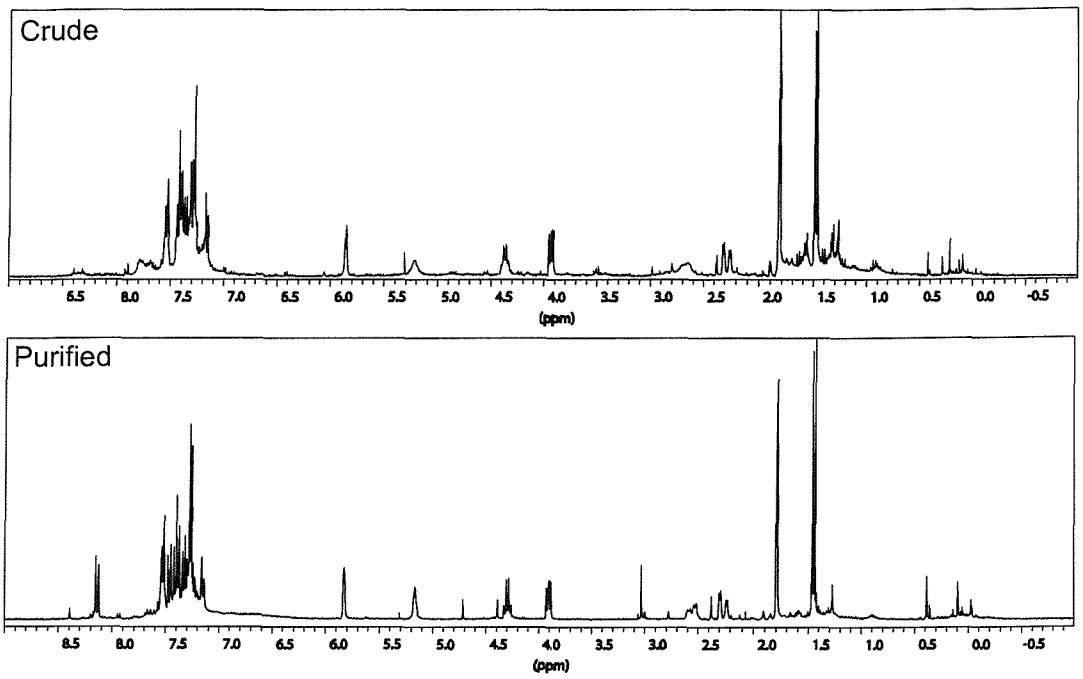


Figure 11

^{1}H NMR spectra of crude and purified **504**

To elucidate the stereochemistry of **504** GOESY studies were conducted. Irradiation of H_A caused 1.08% enhancement in H_C and no enhancement in H_B, or methyl group geminal to H_C. Irradiation of H_B caused 3.65% enhancement in Methyl group geminal to H_C, and no enhancement in either H_C or H_A. Irradiation of H_C caused 1.22% enhancement in H_A, and no enhancement in H_B. This result further supports the previous GOESY studies of **344** (Figure 3), **497** (Figure 5) and **501** (Figure 7) in showing that H_A and H_C are on the opposite side of the molecule **504** than H_B (Figure 12).

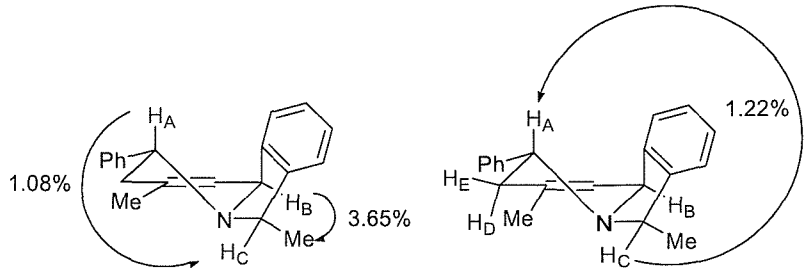


Figure 12

GOESY studies of **504**

The coupling pattern of H_A with a small axial-equatorial coupling to H_E and a bigger axial-axial coupling to H_D again supports the theory that H_A is in axial position and that the conformation of **504** is that shown in figure 13.

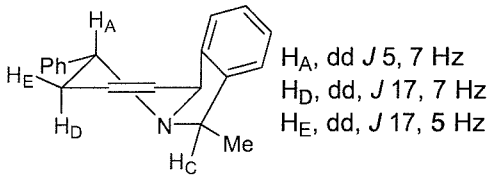


Figure 13

Coupling patterns of **504**

4.4 Conclusions

In conclusion, it was possible to make some substituted precursors for cyclisation, but synthesis of other compounds was not possible. Further examples of the basic cyclisation reaction were accomplished with the synthesised precursors, and these cyclisations were all observed to follow the same unexpected pathway as cyclisation of imine **315** (Chapter 3). Incorporation of substituents onto the alkyl chain was observed to have an effect on the cyclisation. Especially, incorporation of an aromatic ring greatly enhanced the cyclisation reaction, although the obtained product was not stable in the conditions used for purification.

4.5 Project conclusions

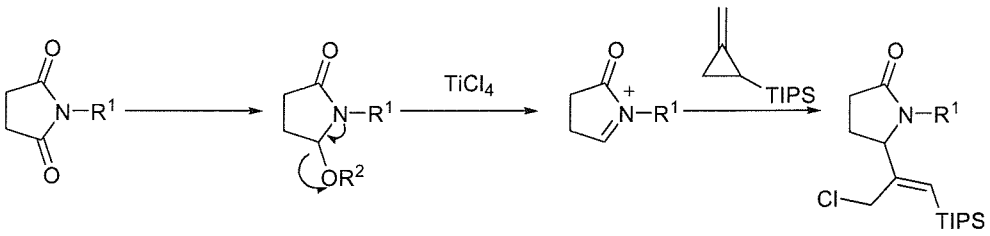
Many substrates for cyclisation studies were synthesised, but the synthesis of these substrates was in many cases problematic, which limits the synthetic usefulness of this methodology. Non-silylated methylenecyclopropyl imines failed to cyclise under the reaction conditions studied, but incorporation of a silyl group onto the methylenecyclopropane made imines with a 4-carbon alkyl chain reactive enough for cyclisation to occur. These imines did not give the expected product, but instead cyclised *via* an interesting novel pathway giving bicyclic compound as a single diastereomer in each case. Yields of these cyclisations were variable, but in all cases

significant amounts of the unreacted starting materials, amine and especially benzaldehyde, could be recovered. Substitution on the alkyl chain was shown to have an effect on the cyclisation, and especially incorporation of an aromatic ring onto the alkyl chain was shown to greatly enhance the cyclisation.

Methylenecyclopropyl cuprate was successfully synthesised from a silylated methylenecyclopropane, and Michael addition of this cuprate to ketones was shown to work, although this methodology was not as general as Michael additions of non-silylated methylenecyclopropyl cuprates.

4.6 Further work

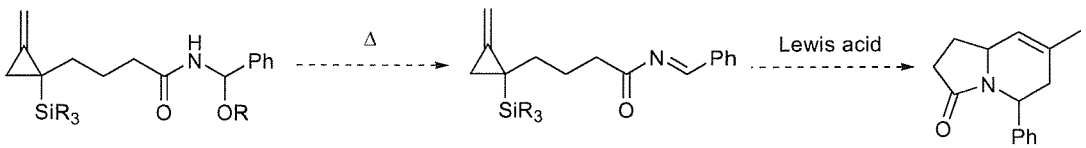
It can be concluded that imines are not reactive enough for Lewis acid catalysed cyclisation reactions with methylenecyclopropane. Recent work in the group shows that more reactive acyliminium ions formed in situ by a reaction with a Lewis acid instead can be reacted with methylenecyclopropane giving **508** in good yields (Scheme 170).[132]



505 **506**, 44-58% **507** **508**, 41-78%

Scheme 170

Further development of this methodology by tethering the acyliminium moiety onto methylenecyclopropane would provide a facile route to a variety of different functionalised lactams (Scheme 171).



509 **510** **511**

Scheme 171

EXPERIMENTAL

5.1 General experimental

Reactions requiring anhydrous conditions were conducted in oven-dried or flame-dried glassware. For reactions at low temperatures acetone-dry ice baths were used. Reagents used were of commercial grade and, when necessary, were purified prior to use as described by Perrin and Armarego.[169] Solvents used were distilled before use: THF was distilled from sodium and benzophenone under Ar, petroleum ether was distilled from calcium hydride at the fractional boiling point between 40 °C and 60 °C, DCM and triethylamine were was distilled from calcium hydride. Methylenecyclopropane was handled using the experimental methods as described by Thomas.[15]

Thin layer chromatography was performed on aluminium backed sheets coated with silica gel (0.25 mm) containing the fluorescent indicator UV_{254}. Flash chromatography was performed following the procedure outlined by Still,[170] on Sorbil C_{60}, 40-60 mesh Silica.

5.2 Instrumentation

^{1}H NMR spectra were obtained at 300 MHz on a Bruker AC 300 spectrometer, or at 400 MHz on a Bruker DPX 400 spectrometer. Peak positions are quoted against the δ scale relative to the residual chloroform signal (δ 7.27), using the following abbreviations; singlet (s), doublet (d), triplet (t), quartet (q), quintuplet (quint), multiplet (m). ^{13}C NMR spectra were obtained at 75.5 MHz on a Buker AC 300 spectrometer, or at 100 MHz on a Bruker DPX 400 Spectrometer. The multiplicities of the signals were determined by DEPT experiment at 135° and are quoted within the brackets using the following notation; quaternary (0), tertiary (1), secondary (2) and primary (3). Coupling constants are are reported in hertz (Hz).

All infrared spectra were obtained on a Bio-Rad Golden Gate A FT-IR spectrometer. The relative intensity of the peaks are quoted within the brackets using the following abbreviations; broad (br), strong (s), medium (m), weak (w).

Low resolution CI and EI spectra were obtained on a Thermoquest TraceMS gas chromatography mass spectrometer, and ES mass spectra were obtained on a Micromass platform with a quadrupole mass analyser. High resolution CI and EI mass spectra were obtained on a VG 70SE normal geometry double focusing mass spectrometer. High resolution ES mass spectra were obtained on a Bruker Apex III FT-ICR mass spectrometer, or on a Micromass Q-Tof 1 mass spectrometer.

X-Ray diffraction data was obtained on an Enraf Nonius KappaCCD diffractometer, and the structures were determined by direct methods using the program SHELXS97 and refined using SHELXL97.

5.3 Experimental for chapter 2

Methylenecyclopropane 2

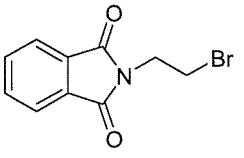
Following a method described by Binger.[13]

Methallyl chloride (280 ml, 2.84 mol) was added dropwise over 9 h to a rapidly stirred suspension of $NaNH_2$ (139 g, 3.36 mol) in dry di-*n*-butyl ether (400 ml) at 130-140 °C under a slow stream of nitrogen. The reaction mixture was refluxed for a further 10 h using a cold finger condenser at –40 °C. The products were collected in vessels at –78 °C. The upper layer of NH_3 was allowed to evaporate. The lower layer contained a mixture of methylenecyclopropane and methylcyclopropene (100 ml, 52%) in a 4.7:1 ratio.

The mixture was added to a solution of t-BuOH (10 g, 0.13 mol) and dimethylsulfoxide (25 ml) at 0 °C under a slow stream of nitrogen, and t-BuOK (8 g, 0,07 mol) in dimethylsulfoxide (25 ml) was added over 3 h. The reaction was allowed to warm to 45 °C over 14 h under a cold finger condenser at -60 °C. The cold finger was allowed to warm to 35 °C over 6 h. Methylenecyclopropane **2** (80 g, 100%) was trapped in vessels at -78 °C.

δ_H (300 MHz; $CDCl_3$) 1.09 (4H, t, J=2Hz, $2CH_2$); 5.43 (2H, q, J=2 Hz, $=CH_2$).

N-(2-Bromoethyl)-phthalimide 234



Following a method described by Quici.[115]

A mixture of 1,2-dibromoethane (5.05 g, 27 mmol), potassium phthalimide (2.0 g, 10.8 mmol) and tetrabutylammonium bromide (129 g, 0.4 mol) was stirred overnight at 81°C. The reaction mixture was allowed to cool to room temperature, filtered through

celite and washed with acetonitrile. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography (silica gel, DCM) to give **234** as white crystalline solid (1.7 g, 62%), m.p. 78-80 °C (lit.[171] m.p. 73-75 °C).

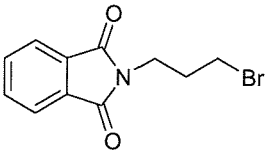
ν_{max} (liq. film) 1773 (s), 1711 (s), 1394 (s), 1082 (m), 973 (m), 716 (m).

δ_H (300 MHz; $CDCl_3$) 3.63(2H, t, J = 7 Hz, CH_2); 4.12(2H, t, J = 7 Hz, CH_2); 7.74-7.77(2H, m, Ar); 7.87-7.90(2H, m, Ar).

δ_C (75 MHz, $CDCl_3$) 28.3 (2), 39.4 (2), 123.7 (1), 132.0 (0), 134.4 (1), 168.0 (0).

LRMS (CI) *m/z* 254 (26%, $[M+H]^+$).

N-(3-Bromopropyl)-phthalimide 235



Following a method described by Quici.[115]

A mixture of 1,3-dibromopropane (5.44 g, 27.0 mmol), potassium phthalimide (2 g, 10.8 mmol) and tetrabutylammonium bromide (128 mg, 0.400 mmol) in acetonitrile (28 ml) was refluxed overnight. The reaction mixture was allowed to cool to room temperature and filtered through celite. The precipitate was washed with acetonitrile (50 ml) and filtrates were evaporated *in vacuo*. The residue was purified by chromatography (silica gel, DCM) to give bromopropylamine **235** as white solid (1.54 g, 54%), m.p. 72-74 °C (lit.[115] m.p. 74-76 °C).

ν_{max} (liq. film) 1765 (s), 1701(s), 1405 (s), 1374 (s), 1229 (s).

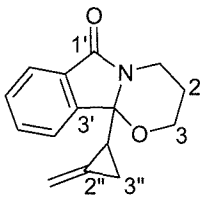
δ_H (300 MHz; $CDCl_3$) 2.27 (2H, quint, J = 7 Hz, CH_2); 3.43 (2H, t, J =7 Hz, CH_2); 3.85 (2H, t, J =7 Hz, CH_2); 7.72-7.84 (2H, m, Ar), 7.85-7.88 (2H, m, Ar).

δ_C (75 MHz, $CDCl_3$) 30.0 (2), 31.8 (2), 36.9 (2), 123.5 (1), 132.1 (0), 134.2 (1), 168.4 (0).

LRMS (CI) *m/z* 268 (8%, $[M+H]^+$).

^1H NMR data agrees with Quici.[115]

4a-(2-Methylenecyclopropyl)-2,3-dihydro-1*H*-4a*H*-4-oxa-9a-aza-fluoren-9-one 237



n-BuLi (2.4 M in hexane, 3.13 ml, 14.8 mmol) was added to a stirred solution of methylenecyclopropane (1.0 ml, 14.8 mmol) in THF (40 ml) under Ar at -50 °C. The reaction mixture was allowed to warm to 10 °C during 2 h and cooled to -50 °C. Bromide **235** (2.01 g, 14.8 mmol) in THF (10 ml) was added. The reaction mixture was allowed to warm to room temperature and was stirred ar room temperature overnight. The reaction mixture was quenched with aqueous NH_4Cl and extracted with ether. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 30-60% ethyl acetate in hexane) to give methylenecyclopropane derivative **237** as a white solid (315 mg, 9%), m.p. 116-118 °C.

ν_{max} (liq. film) 2962 (m), 2926 (m), 2874 (m), 1691 (s), 1401 (s), 1050 (s), 1025 (s), 1000 (s), 888 (s), 760 (s).

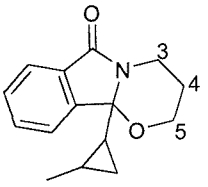
δ_H (300 MHz; $CDCl_3$) 0.81 (1H, ddt, J = 9, 6, 2 Hz, C(3")H_AH_B), 1.35 (1H, tt, J = 2, 9 Hz, C(3")H_AH_B), 1.68 (1H, m, C(2)H_AH_B), 1.82 (1H, m, C(2)H_AH_B), 2.39 (1H, ddt, J = 9, 6, 2 Hz, C(1")H), 3.47 (1H, ddd, J = 4, 12, 14 Hz, C(3)H_AH_B), 3.93 (1H, ddt, J = 12, 5, 2 Hz, C(1)H_AH_B), 4.42 (1H, tt, J = 3, 12 Hz, C(3)H_AH_B), 4.49 (1H, ddt, J = 13, 6, 2 Hz, C(1)H_AH_B), 5.53 (2H, m, $=CH_2$), 7.46-7.56 (3H, m, Ar H), 7.81 (1H, m, Ar H).

δ_C (75 MHz, $CDCl_3$) 7.9 (2), 17.6 (1), 24.8 (2), 35.6 (2), 62.0 (2), 89.4 (0), 106.3 (2), 122.2 (1), 123.6 (1), 129.7 (1), 130.7 (0), 131.5 (0), 131.6 (1), 144.5 (0),166.7 (0).

LRMS (CI) *m/z* 242 (100%, $[M+H]^+$).

HRMS (CI) $C_{15}H_{15}NO_2$ $[M+H]^+$ requires 242.1176, found 242.1167.

4a-(2-Methylcyclopropyl)-2,3-dihydro-1*H*-4a*H* 4-oxa-9a-aza-fluoren-9-one 238



Hydrazine monohydrate (0.1 ml, 1.87 mmol) was added to a stirred solution of **237** (75 mg, 0.31 mmol) in ethanol (10 ml). The reaction mixture was stirred in room temperature for 3 days, ethanol and hydrazine were removed *in vacuo*. The residue was taken up in a mixture of ethyl acetate and water (1:1), and the layers were separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 50% ethyl acetate in hexanes) to give **238** as yellow solid (32 mg, 42%), m.p 102-104 °C

ν_{max} 3003 (m), 2954 (m), 2931 (m), 2872 (m), 1697 (s), 1385 (s), 1286 (s), 1018 (s), 755 (s).

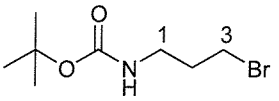
δ_H (300 MHz; $CDCl_3$) 0.29 (3H, d, J = 7 Hz, CH_3), 0.39 (1H, dt, J = 5, 6 Hz, cyclopropyl H), 0.77 (1H, m, cyclopropyl H), 1.15 (1H, dt, J = 5, 9 Hz, cyclopropyl H), 1.49 (1H, dt, J = 6, 9 Hz, cyclopropyl H), 1.63 (1H, m, C(4)H_AH_B), 1.81 (1H, m, C(4)H_AH_B), 3.44 (1H, td, J = 13, 4 Hz, C(3)H_AH_B), 3.94 (1H, ddt, J = 12, 4, 2 Hz, C(5)H_AH_B), 4.37-4.47 (2H, m, C(3)H_AH_B, C(5)H_AH_B), 7.48 (1H, m, Ar), 7.60-7.62 (2H, m, 2xAr), 7.78 (1H, m, Ar).

δ_C (75 MHz, $CDCl_3$) 8.9 (1), 12.2 (3), 13.5 (2), 19.2 (1), 25.1 (2), 37.1 (2), 62.2 (2), 122.0 (1), 123.6 (1), 129.4 (1), 130.5 (0), 132.3 (0), 132.6 (1), 148.3 (0), 168.5 (0).

LRMS (CI) *m/z* 244 (100%, $[M+H]^+$).

Crystal structure see appendix.

N-BOC-3-bromopropylamine 242



Following a method described by Siegel.[172]

3-Bromopropylamine hydrobromide (3.29 g, 15 mmol) and di-(*tert*-butyl) dicarbonate (3.6 g, 16.5 mmol) were slurried in THF (75 ml), and chilled to 5 °C. 1M NaOH (17 ml) was slowly added during 30 min. A solution formed. The reaction was stirred at room temperature overnight, and ethyl acetate and brine were added to the reaction mixture. The resulting layers were separated and the aqueous layer was again extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 25% diethyl ether in petroleum ether) to give protected amine **242** as a white solid (1.84 g, 52%), m.p. 38-39 °C (lit.[172] m.p. 39 °C).

ν_{max} (liq. film) 3347 (br m), 2976 (m), 2932 (m), 1685 (s), 1509 (s), 1365 (s), 1247 (s), 1162 (s).

δ_H (300 MHz; $CDCl_3$) 1.44 (9H, s, $3CH_3$); 2.04 (2H, quintet, J = 7 Hz, $C(2)H_2$); 3.27 (2H, t, J = 7 Hz, CH_2); 3.44 (2H, t, J = 7 Hz, CH_2), 4.70 (1H, br s, NH).

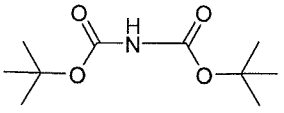
δ_C (75 MHz, $CDCl_3$) 28.5 (3), 31.0 (2), 32.8 (2), 39.2 (2), 79.6 (0), 156.1 (0).

LRMS (CI) *m/z* 238, (14%, $[M+H]^+$).

HRMS (ES) $C_{15}H_{17}NO_2$ $[2M+H]^+$ requires 509.2410, found 509.2416.

Mass spectroscopy data agrees with Siegel.[172]

tert-Butyl [(*tert*-butyloxycarbonyl)amino]methanoate 246



Following a method described by Grehn.[116]

Formamide (800 ml, 20 mmol) and Boc_2O (9.6 g, 44 mmol) in dry acetonitrile (8 ml) were slowly added to a stirred solution of DMAP (244 mg, 2 mmol) in dry acetonitrile

(2 ml) under Ar. The reaction mixture was heated to 35 °C to initiate the reaction and the reaction was stirred at room temperature for 5 h. The reaction mixture was cooled on ice and N,N-diethyl ethylenediamine (2.79 g, 24 mmol) was slowly added maintaining the reaction temperature below 25 °C. The reaction mixture was stirred at room temperature overnight and the solvent was removed *in vacuo* below 30 °C. The residual yellow oil was partitioned between diethyl ether (60 ml) and 1M $KHSO_4$ (40 ml). The organic layer was washed with 1M $KHSO_4$ (3x20 ml), 1M $NaHSO_4$ (3x20 ml) and saturated brine (3x20 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a white solid. The crude product was recrystallized from petroleum ether to give **246** as a white solid (3.0 g, 69%), m.p. 116-118 °C (lit.[116] m.p. 118-119 °C).

ν_{max} (liq. film) 2978 (m), 2932 (w), 2871 (w), 1788 (w), 1738 (s), 1692 (s), 1361 (s), 1123 (s), 848 (m), 767 (s).

δ_H (300 MHz, $CDCl_3$)1.48 (18H, s, CH_3), 6.81 (1H, br s, NH).

δ_C (75 MHz, $CDCl_3$) 28.2 (3), 82.1 (0), 149.9 (0).

LRMS (ES) *m/z* 240 (100%, $[M+Na]^+$), 457 (100%, $[2M+Na]^+$).

^1H NMR data agrees with Grehn.[116]

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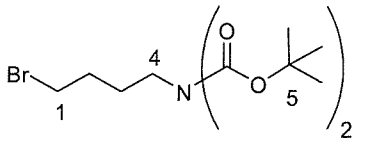
(15) *tert*-Butyl[(4-bromobutyl)(*tert*-butoxycarbonyl)amino]methanoate 248



Following a method described by Mutter.[173]

KOH (0.52 g, 9.22 mmol) in EtOH (4 ml) was added to a stirred solution of **246** (2.0 g, 9.22 mmol) in EtOH (4 ml) and was stirred at room temperature for 40 min. The potassium salt of **246** was precipitated with dry ether, filtered and dried under reduced pressure to give a white solid (1.44 g, 61%). The potassium salt of **246** was suspended in DMF (4 ml) and DCM (12 ml), and 1,4-dibromobutane (0.774 ml, 6.25 mmol) was added. The reaction mixture was stirred at 50 °C for 3.5 h, allowed to cool to room temperature, filtered and concentrated under reduced pressure. The residue was taken up in ethyl acetate (100 ml), washed with brine (3x30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel,

5-20% diethyl ether in petroleum ether) to give bromoamine **248** as a colourless oil (1.4 g, 43%).

ν_{max} (liq. film) 2978 (m), 2932 (m), 1738 (s), 1692 (s), 1361 (s), 1123 (s), 848 (s).

δ_H (300 MHz, $CDCl_3$) 1.51 (18H, s, CH_3), 1.73 (2H, m, CH_2), 1.87 (2H, m, CH_2), 3.43 (2H, t, $J = 7$ Hz, C(1)H_2), 3.60 (2H, t, $J = 7$ Hz, C(4)H_2).

δ_C (75 MHz, $CDCl_3$) 27.7 (2), 28.0 (3), 30.0 (2), 33.3 (2), 45.5 (2), 82.5 (0), 152.6 (0).

LRMS (ES) *m/z* 376 (58%, $[M+Na]^+$), 727 (100%, $[2M+Na]^+$).

^{1}H NMR data agrees with Mutter.[173]

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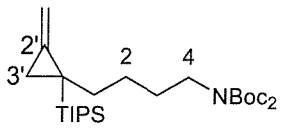
tert-Butyl((_tert_-butoxycarbonyl){4-[2-methylene-1-(1,1,1-triisopropylsilyl) cyclopropyl]butyl}amino)methanoate 251



n-BuLi (0.65 ml, 2.17 M in hexanes, 1.42 mmol) was added to a stirred solution of tri-isopropyl-(2-methylene-cyclopropyl)-silane (304 mg, 1.42 mmol) in THF (25 ml) at -78 °C under Ar. The reaction mixture was allowed to warm to 0 °C during 2 h, cooled to -60 °C and **248** (500 mg, 1.42 mmol) was added. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 5-20% ethyl acetate in petroleum ether) to give the protected amine **251** as colourless oil (128 mg, 19%).

ν_{max} (liq. film) 2970 (s), 2940 (s), 2865 (s), 2362 (s), 2337 (s), 1695 (s), 1117 (s), 876 (s).

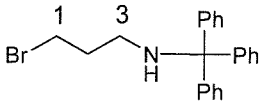
δ_H 0.87 (1H, m, C(3')H_AH$_B$), 1.03-1.28 (22H, m, C(3')H$_A$$H_B$, TIPS CH_3, TIPS CH), 1.44-1.71 (24H, m, Boc CH_3, C(1)H_2, C(2)H_2, C(3)H_2), 3.51 (2H, m, C(4)H_2), 5.21 (1H, m, =CH_AH$_B$), 5.33 (1H, m, =CH$_A$$H_B$).

δ_C (75 MHz, $CDCl_3$) 11.8 (2), 19.2 (1), 19.3 (3), 22.8 (0), 28.1 (3), 29.5 (2), 34.4 (2), 46.4 (2), 82.0 (2), 101.7 (2), 139.0 (0), 152.7 (0), 174.3 (0).

LRMS (ES) *m/z* 504 (100%, $[M+Na]^+$), 545 (50%, $[M+MeCN+Na]^+$), 986 (20%, $[2M+Na]^+$).

HRMS (ES) $C_{27}H_{51}NOSi$ [M+Na] requires 504.3480, found 504.3483.

***N*-(3-Bromopropyl)-*N*-tritylamine 253**



Following a method described by Meunier.[118]

Et_3N (1.3 ml, 4.56 mmol) was added to a stirred solution of 3-bromopropylamine (1 g, 4.56 mmol) and trityl bromide (1.47 g, 4.56 mmol) in DCM (19 ml). The reaction mixture was stirred at room temperature for 7 h, during which time a solid formed. DCM was added and the reaction mixture was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (0-2% MeOH in DCM) to give 2 products, bromoamine **253** (627 mg, 36%), m.p. 96-98 °C and trityl alcohol (613 mg), m.p. 158-160 °C.

Tritylbromide **253**

ν_{max} (liq. film) 3050 (w), 3020 (w), 2970 (w), 2940 (w), 2875 (w), 1594 (m), 1489 (s), 1248 (s), 766 (s), 741 (s), 696 (s).

δ_H (300 MHz, $CDCl_3$) 1.51 (1H, br s, NH), 2.04 (2H, quint, J = 7 Hz, C(2)H_2), 2.28 (2H, t, J = 7 Hz, C(3)H_2), 3.58 (2H, t, J = 7 Hz, C(1)H_2), 7.18-7.20 (3H, m, Ar), 7.27-7.32 (6H, m, Ar), 7.48-7.50 (6H, m, Ar).

δ_C (75 MHz, $CDCl_3$) 31.7 (2), 34.0 (2), 41.8 (2), 70.8 (0), 126.3 (1), 127.8 (1), 128.6 (1), 145.9 (0).

LRMS (ES) *m/z* 380 (2%, $[M+H]^+$), 797 (3%, $[2M+K]^+$).

^1H NMR and Mass spectroscopy data agrees with Meunier.[118]

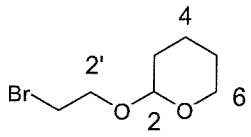
Trityl alcohol

ν_{max} (liq. film) 3467 (w), 1489 (m), 1444 (m), 1263 (s), 741 (s).

δ_H (300 MHz, $CDCl_3$) 2.82 (1H, s, OH), 7.27-7.30 (15H, m, Ar).

δ_C (75 MHz, $CDCl_3$) 82.0 (0), 127.2 (1), 127.9 (1x2), 146.8 (0).

2-Bromoethanol tetrahydropyranyl ether 260



Following a method described by Dado.[119]

3,4-dihydro-2-H-pyran (8.2 ml, 90 mmol) was slowly added to a stirred solution of 2-bromoethanol (3.75 g, 30 mmol) and *p*-toluenesulfonic acid monohydrate (0.57 g, 3mmol) in dioxane (60 ml) under Ar. After 2 h the solution was neutralised to pH 7 with saturated aqueous $NaHCO_3$ and partitioned between water (50 ml) and ethyl acetate (150 ml). The aqueous layer was further extracted with ethyl acetate (2x150 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 5-10% ethyl acetate in hexane) to give bromide **260** as a colourless oil (4.39 g, 70%).

ν_{max} (liq. film) 2933 (s), 2864 (m), 1365 (s), 1119 (s), 1019 (s), 867 (s), 813 (s).

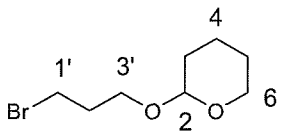
δ_H (300 MHz; $CDCl_3$) 1.51-1.75 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2), 3.51 (2H, dt, J = 2, 6 Hz, C(2')H_2), 3.54 (1H, m, C(1')H_AH$_B$), 3.76 (1H, dt, J = 11, 6 Hz, C(6)H_aH$_B$), 3.88 (1H, m, C(1')H$_A$$H_B$), 4.00 (1H, dt, J = 11, 6 Hz, C(6)H$_A$$H_B$), 4.66 (1H, t, J = 4Hz, C(2)H).

δ_C (75 MHz, $CDCl_3$) 19.2 (2), 25.3 (2), 30.4 (2), 30.8 (2), 62.2 (2), 67.5 (2), 98.9 (1).

LRMS (CI) *m/z* 207 (14%, $[M+H]^+$), 209 (15%, $[M+H]^+$).

Infrared data agrees with Menicagli.[174]

3-Bromopropanol tetrahydropyranyl ether 261



Following a method described by Dado.[119]

3,4-dihydro-2-H-pyran (8.2 ml, 90 mmol) was slowly added to a stirred solution of 3-bromo-1-propanol (4.17 g, 30 mmol) and *p*-toluenesulfonic acid monohydrate (0.57 g, 3 mmol) in dioxane (60 ml) under Ar. After 2 h the solution was neutralised to pH 7

with saturated aqueous $NaHCO_3$ and partitioned between water (50 ml) and ethyl acetate (150 ml). The aqueous layer was further extracted with ethyl acetate (2x150 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 10% ethyl acetate in hexanes) to give bromide **261** as colourless oil (6.37 g, 95%).

ν (liq. film) 2940 (s), 2869 (s), 1440 (m), 1352 (m), 1200 (m), 1132 (s), 1118 (s), 1074 (s), 1029 (s), 982 (s), 965 (s), 868 (s).

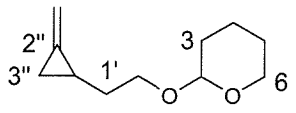
δ_H (300 MHz; $CDCl_3$) 1.49-1.88 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2), 2.12 (2H, quintet, J=6 Hz, C(2')H_2), 3.46-3.55 (4H, m, C(1')H_2, C(3')H_2), 3.81-3.90 (2H, m, C(6)H_2), 4.59 (1H, t, J = 3 Hz, C(2)H).

δ_C (75 MHz, $CDCl_3$) 19.6 (2), 25.6 (2), 30.7 (2), 30.9 (2), 33.0 (2), 62.4 (2), 65.0 (2), 98.8 (1).

LRMS (Cl) *m/z* 224 (20%, $[M+H]^+$).

^{1}H NMR data agrees with Dado.[119]

2-[(2'-Methylenecyclopropyl)ethoxy]tetrahydropyran 262



Following a method described by Destabel.[120]

n-BuLi (2.06 M in hexanes, 9.3 ml, 19.2 mmol) was added to a stirred solution of methylenecyclopropane (1.3 ml, 19.0 mmol) in THF (90 ml) at -50 °C under Ar. The reaction mixture was allowed to warm to 10 °C during 2 h and cooled to -50 °C. Bromide **260** (4 g, 19.0 mmol) in THF (16 ml) was added. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight, quenched with saturated aqueous NH_4Cl and extracted with diethyl ether (3x100 ml). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2-5 % ethyl acetate in hexane) to give methylenecyclopropane derivative **262** as colourless oil (2.35 g, 68%).

ν_{max} (liq. film) 2933 (br m), 2869 (m), 1119 (s), 1069 (s), 1030 (s), 882 (s).

δ_H (300 MHz; $CDCl_3$) 0.80 (1H, m, C(3")$H_A$$H_B$), 1.23 (1H, m, C(3")$H_A$$H_B$) 1.51-1.88 (9H, br m, C(3)H_2, C(4)H_2, C(5)H_2, C(1")H, C(1')H_2), 3.44-3.56, (2H, m, C(2')$H_A$$H_B$,

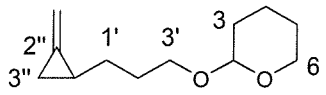
C(6)H_AH$_B$), 3.79-3.93 (2H, m, C(2')H$_A$$H_B$, C(6)H$_A$$H_B$), 4.63 (1H, t, J = 7 Hz C(2)H), 5.36 (1H, m, =CH_AH$_B$), 5.43 (1H, m, =CH$_A$$H_B$).

δ_C (75 MHz, $CDCl_3$) 9.3 (2), 12.9 (1), 19.5 (2), 25.5 (2), 30.7 (2), 33.2 (2), 62.2 (2), 67.2 (2), 98.8 (1), 102.8 (2), 136.3 (0).

LRMS (CIMS) m/z 183 (4%, $[M+H]^+$).

Spectroscopic data agrees with Destabel.[120]

2-[(3'-Methylenecyclopropyl)propoxy]tetrahydropyran 263



Following a method described by Destabel.[120]

n-BuLi (2.4 M in hexanes, 5.6 ml, 13.4 mmol) was added to a stirred solution of methylenecyclopropane (0.98 ml, 13.4 mmol) in THF (40 ml) under Ar at -50 °C. The reaction mixture was allowed to warm to 10 °C during 2 h and cooled to -50 °C. Bromide **261** (3 g, 13.4 mmol) in THF (12 ml) was added. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was quenched with aqueous NH_4Cl and extracted with diethyl ether (3x100 ml). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 4-6% ethyl acetate in hexane) to give protected alcohol **263** as colourless oil (2.22 g, 83%).

ν (liq. film) 2938 (s), 2868 (s), 1452 (w), 1351 (m), 1199 (m), 1120 (s), 1075 (s), 1021 (s), 882 (s), 869 (s), 814 (s).

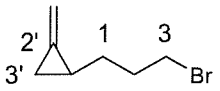
δ_H (300 MHz; $CDCl_3$) 0.75 (1H, m, C(3")H_AH$_B$), 1.25 (1H, m, C(3")H$_A$$H_B$), 1.45-1.90 (11H, br m, C(3)H_2, C(4)H_2, C(5)H_2, C(2')H_2, C(1')H_2, C(1")H), 3.38-3.53 (2H, m, C(3')H_AH$_B$, C(6)H_AH$_B$), 3.73-3.90 (2H, m, C(3')H$_A$$H_B$, C(6)H$_A$$H_B$), 4.58 (1H, m, C(2)H), 5.33 (1H, m, =CH_AH$_B$), 5.40 (1H, br s, =CH$_A$$H_B$).

δ_C (100 MHz, $CDCl_3$) 9.4 (2), 15.4 (1), 19.6 (2), 25.5 (2), 29.5 (2), 29.7 (2), 30.7 (2), 62.3 (2), 67.2 (2), 99.8 (1), 102.5 (2), 136.8 (0).

LRMS (CI) *m/z* 197 (10%, $[M+H]^+$).

Spectroscopic data agrees with Destabel.[120]

1-Bromo-3-methylenecyclopropyl propane 255



Following a method described by Pike.[121]

Ph_3P (1.18 g, 4.5 mmol) in DCM (10 ml) was slowly added to a stirred solution of THP-ether **263** (300 mg, 1.5 mmol) and CBr_4 (548 mg, 1.7 mmol) in DCM (30ml) under Ar at 0 °C. The reaction mixture was stirred overnight, concentrated *in vacuo* and purified by a short column (silica gel, DCM) to give the crude product as yellow oil (247 mg). The crude product was purified by column chromatography (silica gel, petroleum ether) to give bromide **255** as colourless oil (186 mg, 71%).

ν_{max} (liq. film) 2972 (m), 2931 (m), 2852 (m), 1438 (m), 1247 (s), 885 (s), 759 (s).

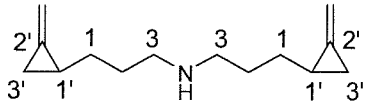
δ_H (300 MHz; $CDCl_3$) 0.79 (1H, m, C(3')H_AH_B), 1.27 (1H, tt, J = 2, 9 Hz, C(3') H_AH_B), 1.38-1.62 (3H, m, C(1')H, C(1)H_2), 2.00 (2H, quint, J = 7 Hz, C(2)H_2), 3.47 (2H, td, J = 7, 2 Hz, C(3)H_2), 5.38 (1H, m, =CH_AH_B), 5.43 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) 9.7 (2), 15.0 (1), 31.7 (2), 32.9 (2), 33.7 (2), 103.3 (2), 136.4 (0).

LRMS (CI) *m/z* 95 (100%, $[M-Br]^+$).

Spectroscopic data agrees with Pike.[121]

N,N-Bis[1-amino-3-methylenecyclopropyl propane] amine 265



Following a method described by Pillai.[117]

Bromide **255** was dissolved in saturated methanolic ammonia (14 ml) and stirred in room temperature for 3 days. The residual oil obtained after the removal of the solvent was taken up in ethyl acetate (15 ml) and neutralised with 1M HCl and saturated $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (6x15 ml). The combined organic phases were dried over anhydrous $NaSO_4$ and the solvent was removed *in vacuo*. The residue was purified by column

chromatography (silica gel, 5-10% MeOH in DCM) to give diamine **265** as a white solid (13 mg, 9%), m.p. 54-56 °C.

ν_{max} (liq. film) 2973 (br s), 2925 (br s), 2360 (m), 2341 (m), 1595 (m), 1474 (m), 886 (m).

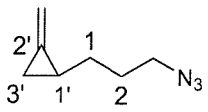
δ_H (300 MHz; $CDCl_3$) 0.76 (2H, tt, J = 2, 7 Hz, 2C(3')H_AH_B), 1.24 (2H, tt, J = 2, 9 Hz, 2C(3')H_AH_B), 1.34-1.53 (6H, m, 2C(1')H, 2C(1)H_2), 1.98-2.10 (4H, m, 2C(2)H_2), 2.99 (4H, t, J = 8 Hz, 2C(3)H_2), 5.36 (2H, br s, 2 =CH_AH_B), 5.43 (2H, m, 2 =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) 9.7 (2), 14.9 (1), 25.9 (2), 30.4 (2), 47.6 (2), 103.6 (2), 135.7 (0).

LRMS (ES) *m/z* 206 (100%, $[M+H]^+$).

HRMS (ES) $C_{14}H_{24}NO$ $[M+H]^+$ requires 206.1903, found 206.1895.

3-(2-Methylenecyclpropyl)-propylazide 257



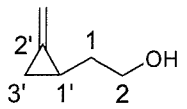
A solution of bromide **255** (800 mg, 4.21 mmol) and NaN_3 (547 mg, 8.42 mmol) in DMSO (20 ml) was stirred at 50 °C for 4 h, water (100 ml) was added and the reaction mixture was extracted with diethyl ether. The combined organic phases were washed with water, dried over $MgSO_4$ and concentrated *in vacuo* to give azide **257** as yellow oil (388 mg, 67%).

ν_{max} (liq. film) 3067 (w), 3038 (w), 2974 (m), 2929 (m), 2850 (m), 2091 (s), 1450 (m), 1282 (m), 1248 (s), 883 (s).

δ_H (300 MHz; $CDCl_3$) 0.76 (1H, tt, J = 6, 2 Hz, C(3')H_AH_B), 1.26 (1H, m, C(3')H_AH_B), 1.35-1.53 (3H, m, C(1')H, C(1)H_2), 1.74 (2H, m, C(2)H_2), 3.32 (2H, t, J = 7 Hz, C(3)H_2), 5.37 (1H, m, =CH_AH_B), 5.42 (1H, m =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) 9.4 (2), 15.0 (1), 28.6 (2), 30.1 (2), 51.0 (2), 102.9 (2), 136.2 (0).

2-Methylenecyclopropylethanol 266



Following a method described by Destabel.[120]

THP ether **262** (2.0 g, 10.99 mmol) was stirred with Amberlite IR-120 (+) resin (2.3 g) in methanol (100 ml) at 60 °C for 3 days. The reaction mixture was cooled to room temperature, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 5-20% ethyl acetate in petroleum ether) to give alcohol **266** as pale yellow oil (920 mg, 85%).

ν_{max} (liq. film) 3315 (br m), 2975 (m), 2930 (m), 2871 (m), 1038 (s), 884 (s), 732 (s).

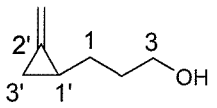
δ_H (400MHz; $CDCl_3$) 0.82 (1H, tt, J = 2, 7 Hz, C(3')H_AH$_B$), 1.29 (1H, m, C(3')H$_A$$H_B$), 1.48 (1H, quintuplet of triplets, J = 7, 2 Hz C(1')H), 1.59 (1H, dq, J = 14, 7 Hz C(1)H_AH$_B$), 1.69 (1H, dq, J = 14, 7Hz C(1)H$_A$$H_B$), 3.75 (2H, t, J = 7Hz, C(2)H_2), 5.40 (1H, br s, =CH_2 H_AH$_B$), 5.50 (1H, br s, =CH_2 H$_A$$H_B$).

δ_C (75 MHz, $CDCl_3$) 9.2 (2), 12.5 (1), 35.9 (2), 62.7 (2), 103.1 (2), 135.9 (0).

LRMS (CI) *m/z* 79 (15%, $[M-H_2O+H]^+$), 97 (8%, $[M-H]^+$), 99 (4%, $[M+H]^+$).

Spectroscopic data agrees with Destabel.[120]

3-Methylenecyclopropylpropan-1-ol 267



Following a method described by Destabel.[120]

THP ether **263** (380 mg, 1.9 mmol) was stirred with Amberlite IR-120 (+) resin (395 mg) in methanol (19 ml) under Ar at 60 °C for 2 days. The reaction mixture was cooled to room temperature, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 30% ethyl acetate in petrol) to give alcohol **267** as a colourless oil (126 mg, 59%).

ν (liq. film) 3308 (br s), 2932 (m), 2858 (m), 1149 (w), 1401 (w), 1051 (s), 883 (s).

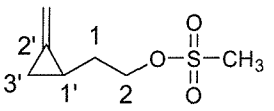
δ_H (300 MHz; $CDCl_3$) 0.72 (1H, m, C(3')CH_AH$_B$), 1.25 (1H, m, C(3')CH$_A$$H_B$), 1.42 (2H, m, C(1)$CH_2$), 1.70 (2H, C(2)$CH_2$), 1.80 (1H, m, C(1')CH), 3.67 (2H, dt, J = 1, 7 Hz, C(3)H_2), 5.34 (1H, br s, =CH_AH$_B$), 5.40 (1H, br s, =CH$_A$$H_B$).

δ_C (75 MHz, $CDCl_3$) 9.5 (2), 15.5 (1), 29.4 (2), 32.5 (2), 62.6 (2), 102.8 (2), 136.9 (0).

MS (CI) *m/z* 95 (100%, $[M-H_2O+H]^+$), 113 (35%, $[M+H)]^+$).

Spectroscopic data agrees with Destabel.[120]

Methanesulfonic acid 2-(2-methylenecyclopropyl)-ethyl ester 268



Mesyl chloride (701 mg, 6.12 mmol) was slowly added to a stirred solution of alcohol **266** (500 mg, 5.1 mmol) in DCM (13 ml) at -15 °C under Ar. The reaction mixture was allowed to warm to room temperature and was stirred for 2 h, during which time the reaction mixture turned yellow and a white solid formed. The reaction was quenched with cold water, washed with 2M H_2SO_4 and saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. The reaction mixture was concentrated *in vacuo* to give mesylate **268** as yellow oil (829 mg, 92%).

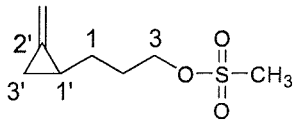
ν_{max} (liq. film) 2945 (w), 2938 (w), 1345 (s), 1168 (s), 951 (s), 906 (s), 803 (s), 729 (s).

δ_H (400MHz; $CDCl_3$) 0.85 (1H, tt, J = 2, 7Hz C(3')H_AH$_B$), 1.34 (1H, tt, J = 2, 9 Hz, C(3')H$_A$$H_B$), 1.51 (1H, quintuplet of triplets, J = 7, 2 Hz C(1')H), 1.75 (1H, dq, J = 14, 7 Hz, C(1)H_AH$_B$), 1.86 (1H, dq, J = 14, 7 Hz, C(1)H$_A$$H_B$), 3.03 (3H, s, SO_3CH_3), 4.31 (2H, t, J = 7Hz, C(2)H_2),5.42 (1H, br s, C=CH_AH$_B$); 5.48 (1H, br s, C=CH_AH$_B$).

δ_C (75 MHz, $CDCl_3$) 9.3 (2), 11.8 (1), 32.5 (3), 37.4 (2), 69.7 (2), 103.9 (2), 134.5(0).

LRMS (CIMS) *m/z* 194 (88%, $[M+NH_4]^+$).

Methanesulfonic acid 2-(2-methylenecyclopropyl)-propyl ester 269



Mesyl chloride (3.573 g, 31.18 mmol) was slowly added to a stirred solution of alcohol **267** (2.91 g, 25.98 mmol) in DCM (80 ml) at -15 °C under Ar. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 2 h, during which time the reaction mixture turned yellow and a white solid formed. The reaction was quenched with ice-cold water and washed with 2M H_2SO_4, saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. The reaction mixture was concentrated *in vacuo* to give mesylate **269** as yellow oil (4.63 g, 94%).

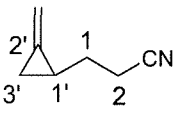
ν_{max} (liq. film) 3070(w), 3025 (w), 2971(w), 2939(w), 1342 (s), 1323 (s), 1166(s), 945 (s), 922 (s), 882 (s), 819 (s).

δ_H (300 MHz; $CDCl_3$) 0.77 (1H, m, C(3')H_AH$_B$), 1.27 (1H, tt, J = 2, 9 Hz, C(3')H$_A$$H_B$), 1.39-1.61 (3H, m, C(1')H, C(1)H_2), 1.89 (2H, m, C(2)H_2), 3.01 (3H, s, CH_3), 4.28 (2H, td, J = 7, 1 Hz, C(3)H_2),5.37 (1H, br s, =CH_AH$_B$); 5.42 (1H, br s, =CH$_A$$H_B$).

δ_C (75 MHz, $CDCl_3$) 9.4 (2), 14.7 (1), 28.8 (2), 28.9 (2), 37.4 (3), 69.6 (2), 103.1 (2), 135.9(0).

LRMS (Cl) m/z 208 (84%, $[M+NH]_4^+$).

4-(2-Methylenecyclpropyl)-propionitrile 270



Following a method described by Fish.[122]

A solution of mesyl ester **268** (800 mg, 4.55 mmol) and NaCN (445 mg, 9.1 mmol) was stirred in DMSO (20 ml) at 60 °C under Ar overnight. The reaction mixture was allowed to cool to room temperature, half-saturated brine was added and the reaction mixture was extracted with diethyl ether. The combined organic layers were washed

with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give nitrile **270** as yellow oil (226 mg, 46%).

ν_{max} (liq. film) 2983 (m), 2928 (m), 2243 (m), 1425 (m), 1133 (w), 1025 (w), 882 (s).

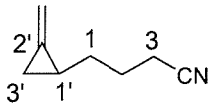
δ_H (300 MHz; $CDCl_3$) 0.87 (1H, tt, J = 2, 7 Hz C(3')H_AH_B), 1.36 (1H, tt, J = 2, 9 Hz, C(3')H_AH_B), 1.54(1H, quintuplet of triplets, J = 7, 2 Hz, C(1')H), 1.69 (1H, dq, J = 14, 7 Hz, C(1)H_AH_B), 1.76 (1H, dq, J = 14, 7 Hz, C(1)H_AH_B), 2.45 (2H, t, J = 7Hz, C(2)H_2), 5.43 (1H, br s, =CH_AH_B), 5.51 (1H, br s, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) 9.5 (2), 14.5 (1), 17.4 (2), 29.0 (2), 104.4 (2), 119.5 (0), 134.2 (0).

LRMS (CI) *m/z* 106 (35%, $[M-H]^+$), 108 (15%, [M+H]), 125 (5%, $[M+NH_4]^+$).

HRMS (CI) C_7H_9N $[M+H]^+$ requires 107.07350, found 107.07325.

4-(2-Methylenecyclpropyl)-butyronitrile 271



Following a method described by Fish.[122]

A solution of mesyl ester **269** (990 mg, 5.21 mmol) and NaCN (511 mg, 10.42 mmol) in DMSO (15 ml) was stirred at 60 °C overnight. The reaction mixture was allowed to cool to room temperature, half-saturated brine was added and the reaction mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give nitrile **271** as colourless oil (586 mg, 93%).

ν_{max} (liq. film) 2973 (m), 2933 (m), 2849 (m), 2238 (m), 1424 (m), 882 (s).

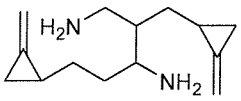
δ_H (300 MHz; $CDCl_3$) 0.79 (1H, tt, J = 2, 7 Hz C(3')H_AH_B), 1.28 (1H, tt, J = 2, 9 Hz, C(3')H_AH_B), 1.40(1H, quintuplet of triplets, J = 7, 2 Hz, C(1')H), 1.55 (2H, m, C(1)H_2), 1.81 (2H, quintuplet, J = 7 Hz, C(2)H_2), 2.41 (2H, t, J = 7 Hz, C(3)H_2), 5.39 (1H, m, =CH_AH_B), 5.42 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) 9.4 (2), 14.5 (1), 16.8 (2), 25.2 (2), 31.8 (2), 103.3 (2), 119.8 (0), 135.5 (0).

LRMS (CI) *m/z* 120 (50%, $[M-H]^+$), 122 (30%, $[M+H]^+$).

HRMS (EI) $C_8H_{11}N$ $[M]^+$ requires 121.08915, found 121.08890.

5-(2-Methylenecyclopropyl)-2-[(2-methylenecyclopropyl)methyl]-1,3-pentanediamine 273



A solution of nitrile **270** (300 mg, 2.8 mmol) in THF (5 ml) was added to a stirred solution of $LiAlH_4$ in THF (1.0M, 11 ml, 11 mmol) at -5 °C under N_2. The reaction mixture was allowed to warm to room temperature, and was stirred at room temperature overnight. 2M NaOH was added until all excess $LiAlH_4$ was consumed. The reaction mixture was filtered, dried over $MgSO_4$ and concentrate *in vacuo*. The residue was purified by column chromatography (silica gel, 20-40% MeOH in DCM) to give 2 products, amine **256** (8 mg, 25%) and amine **273** (42 mg, 75%).

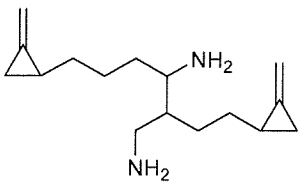
Data for amine **273**.

ν_{max} (liq. film) 3400 (w), 2973 (s), 2918 (s), 2854 (s), 1592 (m), 1439 (m), 878 (s).

δ_H (300 MHz; $CDCl_3$) 0.71-0.79 (2H, m, 2C(1')H), 1.21-1.60 (11H, m, $5CH_2$, CH), 2.87-3.05 (3H, m, CH, CH_2), 5.31-5.41 (4H, m, 2 $=CH_2$).

LRMS (CI) *m/z* 221 (100%, $[M+H]^+$).

6-(2-Methylenecyclopropyl)-2-[2-(2-methylenecyclopropyl)ethyl]-1,3-hexanediamine 274



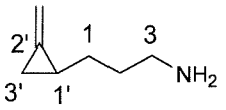
A solution of nitrile **271** (700 mg, 5.79 mmol) in THF (4 ml) was added to a stirred suspension of $LiAlH_4$ (440 mg, 11.57 mmol) in THF (20 ml) at 0 °C under N_2. The reaction mixture was allowed to warm to room temperature, and was stirred at room temperature overnight. 2M NaOH was added until all excess $LiAlH_4$ was consumed. The reaction mixture was filtered, dried over $MgSO_4$ and concentrate *in vacuo* to give a mixture of amine **272** and amine **274** (346 mg).

ν_{max} (liq. film) 3400 (w), 2968 (m), 2924 (s), 2854 (m), 1434 (s), 1360 (s), 1212 (s), 872 (s).

LRMS (GCCI) *m/z* Rt. 5.32 min, 126 (100%, $[M+H]^+$) amine **272**.

Rt. 8.70 min, 249 (100%, $[M+H]^+$) amine **274**.

3-(2-Methylenecyclpropyl)-propylamine 256



A solution of nitrile **270** (527 mg, 4.93 mmol) in diethyl ether (4 ml) was slowly added to a stirred solution of $LiAlH_4$ (1.0M in diethyl ether, 20 ml, 20 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight, cooled to 0 °C and diethyl ether and 2M NaOH were added until all excess $LiAlH_4$ was consumed. The reaction mixture was dried over $MgSO_4$ and concentrated *in vacuo* to give amine **256** as colourless oil (440 mg, 80%).

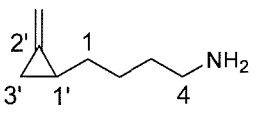
ν_{max} (liq. film) 3348 (br w), 3288 (br w), 3062 (w), 3042 (w), 2968 (m), 2924 (m), 2854 (m), 1562 (m), 1434 (m), 1015 (m), 882 (s), 798 (s).

δ_H (300 MHz; $CDCl_3$) 0.74 (1H, tt, J = 2, 7 Hz, C(3')$H_A$$H_B$), 1.23 (1H, m, C(3')$H_A$$H_B$), 1.32-1.50 (4H, m, C(2) H_2, C(1)H_2), 1.59 (1H, m, C(1')H), 2.74 (2H, t, J = 7 Hz, C(3)H_2), 5.35 (1H, br s, =C$H_A$$H_B$); 5.41 (1H, m, =C$H_A$$H_B$).

δ_C (75 MHz, $CDCl_3$) 9.4 (2), 15.5 (1), 30.4 (2), 33.4 (2), 41.8 (2), 102.5 (2), 136.9 (0).

LRMS (GC-CI) *m/z* 112 (72%, $[M+H]^+$).

4-(2-Methylenecyclpropyl)-butylamine 272



A solution of nitrile **271** in diethyl ether (2.5 ml) was slowly added to a stirred solution of $LiAlH_4$ in diethyl ether (19 ml, 1.0M, 19 mmol). The reaction mixture was allowed to warm to room temperature, stirred at room temperature overnight, and diethyl ether and 2M NaOH were added until all excess $LiAlH_4$ was consumed. The reaction mixture

was dried over $MgSO_4$ and concentrated *in vacuo* to give the amine **272** as colourless oil (430 mg, 72%).

ν_{max} (liq. film) 3367 (w), 2924 (s), 2849 (s), 1454 (w), 1306 (w), 881 (s).

δ_H (300 MHz; $CDCl_3$) 0.72 (1H, m, C(3')H_AH$_B$), 1.21 (1H, tt, J = 2, 9 Hz, C(3')H$_A$$H_B$), 1.33-1.50(7H, m, C(1)$H_2$, C(2)$H_2$, C(3)$H_2$, C(1')H), 2.70 (2H, t, J = 7 Hz, C(4)H_2), 5.33 (1H, m, =CH_AH$_B$), 5.39 (1H, m, =CH$_A$$H_B$).

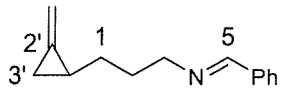
δ_C (75 MHz, $CDCl_3$) 9.3 (2), 15.6 (1), 26.7 (2), 32.9 (2), 33.4 (2), 42.2 (2),102.4 (2), 137.0 (0).

LRMS (CI) *m/z* 126 (100%, $[M+H]^+$).

HRMS (CI) $C_8H_{16}N$ $[M+H]^+$ requires 126.1283, found 126.1280.

Anal. Calcd for $C_8H_{15}N{\cdot}0.25(CH_3)_2CO$: C, 75.21; H, 11.90, N; 10.02. Found C, 75.08; H, 11.89; N, 10.02.

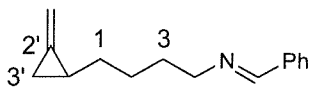
Benzylidene-[3-(2-methylene-cyclopropyl)-propyl]-amine 279



Benzaldehyde (182µl, 1.79mmol) was added to a stirred solution of propylamine **256** in DCM (4 ml) over 4Å molecular sieves under Ar. The reaction mixture was stirred at room temperature for 6 h, filtered and concentrated *in vacuo* to give imine **279** as colourless oil (305 mg, 86%).

δ_H (300 MHz; $CDCl_3$) 0.76 (1H, m, C(3')H_AH$_B$), 1.24 (1H, m, C(3')H$_A$$H_B$), 1.38-1.51 (3H, m, C(1')H, C(1)H_2), 1.85 (2H, quint., J = 7 Hz, C(2)H_2), 3.66 (2H, t, J = 7 Hz, C(3)H_2), 5.35 (1H, m, =CH_AH$_B$), 5.42 (1H, m, =CH$_A$$H_B$), 7.41-7.43 (3H, m, Ar), 7.72-7.75 (2H, m, Ar), 8.29 (1H, s, C(5)H).

Benzylidene-[4-(2-methylene-cyclopropyl)-butyl]-amine 280

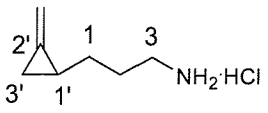


Benzaldehyde (85µl, 0.84mmol) was added to a stirred solution of butylamine **272** (105 mg, 0.84 mmol) in DCM (3 ml) on 4 Å molecular sieves at room temperature under Ar.

The reaction mixture was stirred at room temperature for 5 h, filtered and concentrated *in vacuo* to give imine **280** as colourless oil (200 mg, 70%).

δ_H (300 MHz; $CDCl_3$) 0.73 (1H, m, C(3')H_AH_B), 1.22 (1H, m, C(3')H_AH_B), 1.38-1.56 (5H,m, C(1')H, $C(1)H_2$, $C(2)H_2$), 1.76 (2H, quint., $J = 7$ Hz, $C(3)H_2$), 3.63 (2H, t, $J = 7$ Hz, $C(4)H_2$), 5.34 (1H, m, =CH_AH_B), 5.39 (1H, m, =CH_AH_B), 7.40-7.45 (3H, m, Ar), 7.72-7.75 (2H, m, Ar), 8.29 (1H, s, C(1)H).

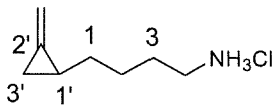
3-(2-Methylenecyclpropyl)-propylamine hydrochloride salt 288



Hydrochloric acid (37 % in water, 0.15 ml 1.80 mmol) was slowly added to a stirred solution of propylamine **256** (200 mg, 1.80 mmol) in diethyl ether (4 ml). A white solid was immediately formed that later dissolved. Toluene (5 ml) was added and the reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* to give the hydrochloride salt **288** as a brown solid (175 mg, 66%), m.p 122-126 °C.

δ_H (300 MHz; $CDCl_3$) 0.77 (1H, m, C(3')H_AH_B), 1.26 (1H, br s, C(3')H_AH_B), 1.42-1.50 (4H, m, $C(1)H_2$, $C(2)H_2$), 1.98 (1H, m, C(1')H), 3.11 (1H, m, C(3)H_AH_B), 5.37 (1H, br s, =CH_AH_B), 5.44 (1H, br s, =CH_AH_B).

4-(2-Methylenecyclpropyl)-butylamine hydrochloride salt 289

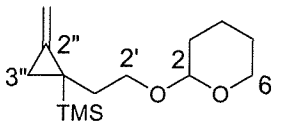


Hydrochloric acid (37 % in water, 0.19 ml 2.32 mmol) was slowly added to a stirred solution of butylamine **272** (290 mg, 2.32 mmol) in diethyl ether (5 ml). The reaction mixture was stirred at room temperature for 3 h, diethyl ether was removed *in vacuo*, toluene was added and removed *in vacuo*. The formed blue solid was triturated in petroleum ether and filtered to give hydrochloride salt **289** as light blue solid (295 mg, 79%), m.p. 128-132 °C.

δ_H (300 MHz; $CDCl_3$) 0.73 (1H, m, C(3')H_AH$_B$), 1.23 (1H, m, C(3')H$_A$$H_B$), 1.39-1.54 (5H, m, C(1')H, C(1)H_2, C(2)H_2), 1.85 (2H, m, C(3)H_2), 3.02 (2H, br s, C(4)H_2), 5.34 (1H, s, =CH_AH$_B$), 5.42 (1H, s, =CH$_A$$H_B$), 8.27 (3H, s, NH_3Cl).

5.4 Experimental for Chapter 3

Trimethyl-{2-methylene-1-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-cyclopropyl}-silane 297



n-BuLi (10 ml, 2.4M solution in hexanes, 24 mmol) was added to a stirred solution of methylenecyclopropane (1.6 ml, 24 mmol) in THF (90 ml) at -78 °C under Ar. The reaction mixture was allowed to warm to 10 °C during 2 h, cooled to -50 °C and TMSCl (3.03 ml, 24 mmol) was slowly added. The reaction mixture was allowed to warm to 10°C during 2 h, cooled to – 50 °C and *n*-BuLi (10 ml, 2.4 M in hexanes, 24 mmol) was added. The reaction mixture was allowed to warm to 10 °C during 2 h, cooled to -50 °C and **260** (5.0 g, 24 mmol) in THF (20 ml) was added. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 5-20% ethyl acetate in petroleum ether) to give the protected alcohol **297** as colourless oil (4.15 g, 68%).

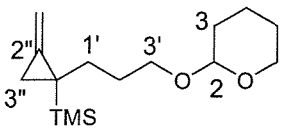
ν_{max} (liq. film) 2942 (m), 2898 (w), 2870 (w), 1248 (s), 1120 (s), 1032 (s), 833 (s).

δ_H (300 MHz; $CDCl_3$) 0.00 (9H, s, CH_3), 0.90 (1H, m, C(3")H_AH_B), 1.08 (1H, m, C(3")H_AH_B), 1.49-1.95 (8H, m, C(3)H_2, C(4)H_2, C(5)H_2, C(2')H_2), 3.38 (1H, m, C(2')CH_AH_B), 3.52 (1H, m, C(6)H_AH_B), 3.74 (1H, m, C(2')H_AH_B), 3.86 (1H, m, C(6)H_AH_B), 4.56 (1H, m, C(2)H), 5.22 (1H, m, =CH_AH_B), 5.28 (1H, br s, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –2.7 (3), 11.3 (0), 12.7 (2), 19.6 (2), 25.4 (2), 30.7 (2), 35.0 (2), 62.3 (2), 66.6 (2), 98.8 (1), 100.6 (2), 139.1 (0).

LRMS (CI) *m/z* 255, (4% $[M+H]^+$).

Trimethyl-{2-methylene-1-[3-(tetrahydro-pyran-2-yloxy)-propyl]-cyclopropyl}-silane 298



Following a method described by Destabel.[120]

N-Butyllithium (2.19 M in hexane, 6.14 ml, 13.4 mmol) was added to a stirred solution of methylenecyclopropane (0.98 ml, 13.45 mmol) in THF (40 ml) under Ar at -50 °C. The reaction mixture was allowed to warm to 10 °C during 2 h and cooled to -50 °C. TMSCl (1.71 ml, 13.45 mmol) was added and the reaction mixture was allowed to warm to 10 °C during 2 h, and then cooled to -50 °C. Bromide **261** (3 g, 13.45 mmol) in THF (12 ml) was added. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was quenched with aqueous NH_4Cl and extracted with diethyl ether (3x100 ml). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2-8% ethyl acetate in hexane) to give THP alcohol **298** as colourless oil (2.87 g, 79%).

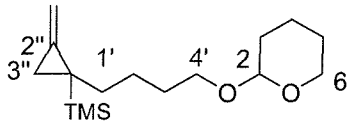
ν_{max} (liq. film) 2942 (m), 2869 (m), 1243 (s), 1120 (s), 1031 (s), 833 (s).

δ_H (300 MHz; $CDCl_3$) 0.00 (9H, s, $SiMe_3$), 0.82 (1H, ddd, J = 2, 4, 7 Hz, C(3")H_AH_B), 1.05 (1H, m, C(3")H_AH_B), 1.40-1.87 (10H, m, C(3)H_2, C(4)H_2, C(5)H_2, C(2')H_2, C(1')H_2), 3.34 (1H, m, C(3')H_AH_B), 3.50 (1H, m, C(6) H_AH_B), 3.68 (1H, m, C(3')H_AH_B), 3.86 (1H, m, C(6)H_AH_B) 4.56 (1H, m, C(2)H), 5.21 (1H, br s, =CH_AH_B), 5.26 (1H, br s, =CH_AH_B).

δ_C (100 MHz, $CDCl_3$) 0.0 (3), 15.0 (2), 16.3 (0), 22.3 (2), 28.1 (2), 31.0 (2), 33.4 (2), 34.6 (2), 64.9 (2), 70.3 (2), 101.4 (1), 102.8 (2), 142.4 (0).

Spectroscopic data agrees with Destabel.[120]

Trimethyl-2-methylene-1-[4-(tetrahydro-2*H*-2-pyranyloxy)butyl] cyclopropylsilane 299



Following a method described by Destabel.[120]

N-Butyllithium (2.30 M in hexane, 7.9 ml, 18.7 mmol) was added to a stirred solution of methylenecyclopropane (1.23 ml, 18.7 mmol) in THF (100 ml) at -50 °C under Ar. The reaction mixture was allowed to warm to 10 °C during 2 h and cooled to -50 °C. TMSCl (2.3 ml, 18.7 mmol) was added and the reaction mixture was allowed to warm to 10 °C during 2 h, and then cooled to -50 °C. Chloride **304** (3.5 g, 18.7 mmol) in THF (10 ml) was added. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was quenched with aqueous saturated NH_4Cl and extracted with diethyl ether (3x100 ml). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2% ethyl acetate in petroleum ether) to give THP ether **299** as colourless oil (3.45 g, 67%).

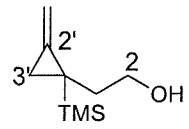
ν_{max} (liq. film) 2940 (m), 1351 (w), 1248 (s), 1120 (s), 1033 (s), 834 (s).

δ_H (300 MHz, $CDCl_3$) –0.01 (9H, s, CH_3), 0.81 (1H, dt, J = 8, 2 Hz, C(3'')H_AH_B), 1.03 (1H, ddd, J = 1.5, 2 Hz J_3 = 8 Hz, C(3'')H_AH_B), 1.09-1.87 (12H, m, C(1')H_2, C(2')H_2, C(3')H_2, C(3)H_2, C(4)H_2, C(5)H_2), 3.37 (1H, m, C(4')H_AH_B), 3.51 (1H, m, C(6)H_AH_B), 3.72 (1H, m, C(4')H_AH_B), 3.87 (1H, m, C(6)H_AH_B), 4.58 (1H, m, C(2)H), 5.19 (1H, m, =CH_AH_B), 5.24 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –2.6 (3), 12.5 (2), 14.0 (0), 19.6 (2), 24.9 (2), 25.5 (2), 30.0 (2), 30.7 (2), 35.5 (2), 62.2 (2), 67.3 (2), 98.7 (1), 99.9 (2), 140.0 (0).

LRMS (CI) *m/z* 283 (1%, $[M+H]^+$).

2-(2-Methylene-1-trimethylsilanyl-cyclopropyl)-ethan-1-ol 300



Following a method described by Destabel.[120]

A solution of the protected alcohol **297** in methanol (150 ml) was stirred with Amberlite IR 120+ ion exchange resin (6.10 g) at 60 °C for 3 days. The reaction mixture was allowed to cool to room temperature, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 5-20% ethyl acetate in petroleum ether) to give the alcohol **300** as a colourless oil (2.46 g, 45%).

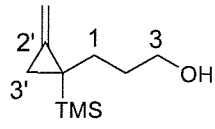
ν_{max} (liq. film) 3318 (br w), 2954 (w), 2897 (w), 1248 (s), 1037 (m), 833 (s).

δ_H (300 MHz; $CDCl_3$) 0.00 (9H, s, CH_3), 0.94 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.11 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.64 (1H, ddd, J = 14, 7, 7 Hz, C(2)H_AH_B), 1.91 (1H, ddd, J = 14, 7, 7 Hz, C(2)H_AH_B), 3.66 (2H, m, C(1)H_2), 5.27 (1H, dt, J = 1, 2 Hz, =CH_AH_B), 5.33 (1H, br s, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –2.8 (3), 11.3 (0), 12.5 (2), 37.8 (2), 62.0 (2), 101.1 (2), 139.4 (0).

LRMS (CI) *m/z* 169 (12%, $[M-H]^+$)171, (10%, $[M+H]^+$).

3-(2-Methylene-1-trimethylsilanyl-cyclopropyl)-propan-1-ol 301



Following a method described by Destabel.[120]

THP ether **298** (5.73 g, 21.3 mmol) was stirred with Amberlite IR-120 (+) resin (4.0 g) in methanol (110 ml) at 60 °C for 3 days. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2-15% ethyl acetate in petroleum ether) to give alcohol **301** as a colourless oil (2.59 g, 66%).

ν_{max} (liq. film) 3312 (br m), 2954 (m), 2800 (w), 1250 (s), 1059 (s), 838 (s).

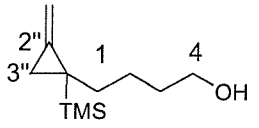
δ_H (300 MHz; $CDCl_3$) 0.00 (9H, s, $SiMe_3$), 0.82 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.06 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.39 (2H, m, C(1)H_2), 1.60 (2H, m, C(2) H_2), 3.61 (2H, t, J = 7 Hz, C(3)H_2), 5.22 (1H, br s, =CH_AH_B), 5.27 (1H, br s, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) -2.6 (3), 12.4 (2), 13.5 (0), 31.3 (2), 31.4 (2), 63.1 (2), 100.3 (2), 139.8 (0).

LRMS (CI) *m/z* 185 (4%, $[M+H]^+$).

Spectroscopic data agrees with Destabel.[120]

4-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-1-butanol 302



Following a method described by Destabel.[120]

THP ether **299** (3.38 g, 11.99 mmol) was stirred with Amberlite IR-120 (+) resin (2.24 g) in methanol (50 ml) at 60 °C for 3 days. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 4-8% ethyl acetate in petroleum ether) to give alcohol **302** as colourless oil (1.39 g, 59%).

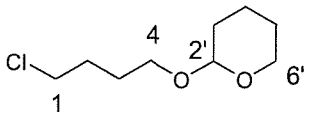
ν_{max} (liq. film) 3311 (br, m), 2935 (m), 1248 (s), 1034 (s), 832 (s).

δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, CH_3), 0.81 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.05 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.27-1.61 (6H, m, C(1)H_2, C(2)H_2, C(3)H_2), 3.63 (1H, t, J = 7 Hz, C(4)H_2), 5.20 (1H, m, =CH_AH_B), 5.25 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –2.6 (3), 12.4 (2), 13.9 (0), 24.4 (2), 33.1 (2), 35.4 (2), 62.9 (2), 100.1 (2), 139.0 (0).

LRMS (CI) *m/z* 183 (8% $[M-CH_3]^+$), 197 (14%, $[M-H]^+$), 199 (10%, M+H).

4-Chlorobutyl tetrahydro-2*H*-2-pyranyl ether 304



Following a method described by Dado.[119]

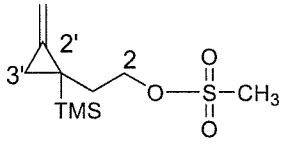
3,4-dihydro-2-H-pyran (16.4 ml, 180 mmol) was slowly added to a stirred solution of 4-chloro-1-butanol (5.99 ml, 60 mmol) and *p*-toluenesulfonic acid monohydrate (1.14 g, 6 mmol) in dioxane (80 ml) under Ar. After 2 h the solution was neutralised to pH 7 with saturated aqueous $NaHCO_3$ and partitioned between water (100 ml) and ethyl acetate (200 ml). The aqueous layer was further extracted with ethyl acetate (2x150 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2-5% ethyl acetate in petroleum ether) to give chloride **304** as a colourless oil (9.52 g, 82%).

δ_H (300 MHz, $CDCl_3$) 1.50-1.94 (12H, m, C(1)H_2, C(2)H_2, C(3)H_2, C(3')H_2, C(4')H_2, C(5')H_2), 3.43 (1H, m, C(4)$H_A$$H_B$), 3.54 (1H, m, C(6')$H_A$$H_B$), 3.77 (1H, m, C(4)$H_A$$H_B$), 3.85 (1H, m, C(6')$H_A$$H_B$), 4.58 (1H, m, C(2')H).

δ_C (75 MHz, $CDCl_3$) 19.6 (2), 25.4 (2), 27.1 (2), 29.6 (2), 30.7 (2), 45.0 (2), 62.3 (2), 66.6 (2), 98.8 (1).

Spectroscopic data agrees with Rumbero.[175]

Methanesulfonic acid 2-(2-methylene-1-trimethylsilanyl-cyclopropyl)-ethyl ester 305



Mesyl chloride (1.25 ml, 16.1 mmol) was slowly added to a stirred solution of alcohol **300** (2.28 g, 13.4 mmol) in DCM (25 ml) at -15 °C under Ar. The reaction mixture was allowed to warm to 10 °C during 2 h, washed with 2M sulfuric acid and saturated

aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo* to give mesylate **305** as a yellow oil (2.79 g, 84%).

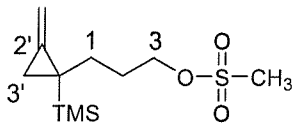
ν_{max} (liq. film) 2955 (w), 2900 (w), 1735(s), 1353(s), 1172(s), 952(s), 833(s), 751(s).

δ_H (300 MHz; $CDCl_3$) 0.02 (9H, s, CH_3), 0.94 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.16 (1H, ddd, J = 1.5, 2, 8 Hz, C(3')H_AH_B), 1.84 (1H, ddd, J = 14, 9, 6 Hz, C(2)H_AH_B), 2.01 (1H, ddd, J = 14, 9, 6 Hz, C(2)H_AH_B), 3.00 (3H, s, CH_3), 4.21 (2H, m, C(1)H_2), 5.28 (1H, td, J = 2, 1 Hz, =CH_AH_B), 5.35 (1H, br s, =CH_AH_B).

δ_C (75MHz; $CDCl_3$) –2.6 (3), 10.6 (0), 13.0 (2), 34.4 (2), 37.7 (3), 68.9 (2), 101.9 (2), 137.8 (0).

LRMS (CI) *m/z* 233 (1%, $[M\text{-}CH_3]^+$), 266 (6%, $[M+NH_4]^+$).

Methanesulfonic acid 3-(2-methylene-1-trimethylsilanyl-cyclopropyl)-propyl ester 306



Mesyl chloride (1.0 ml, 13.45 mmol) was slowly added to a stirred solution of alcohol **301** (2.13 g, 11.21 mmol) in DCM (35 ml) at -15 °C under Ar. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 2 h, during which time the reaction mixture turned yellow and a white solid formed. The reaction was quenched with cold water and washed with 2M H_2SO_4, saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the mesylate **306** as a yellow oil (2.91 g, 99%).

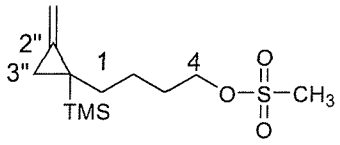
ν_{max} (liq. film) 2958(m), 2900(w), 2850 (W), 1353 (s), 1250 (s), 1176(s), 975 (s), 921 (s), 838 (s).

δ_H (300 MHz; $CDCl_3$) 0.00 (9H, s, CH_3), 0.83 (1H, dt, J = 9, 7 Hz, C(3')H_AH_B), 1.09 (1H, ddd, J = 2, 2, 8 Hz, C(3')H_AH_B), 1.47 (1H, m, C(1)H_AH_B), 1.63 (1H, m, C(1)H_AH_B) 1.78 (2H, m, C(2)H_2), 3.00 (3H, s, SO_3CH_3), 4.19 (2H, t, J = 7 Hz, C(3)H_2), 5.22 (1H, m, =CH_AH_B), 5.29 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) -2.7 (3), 12.4 (2), 13.1 (0), 27.8 (2), 31.1 (2), 37.3 (3), 70.1 (2), 100.8 (2), 139.0 (0).

LRMS (CI) *m/z* 280 (6%, $[M+NH_4]^+$).

4-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]butyl methanesulfonate 307



Mesyl chloride (0.62 ml, 8.06 mmol) was slowly added to a stirred solution of alcohol **302** (1.33 g, 6.72 mmol) in DCM (20 ml) at -15 °C under Ar. The reaction mixture was allowed to warm to room temperature and was stirred 2 h at room temperature, during which time the reaction mixture turned yellow and a white solid formed. The reaction was quenched with cold water and washed with 2M H_2SO_4, saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. The reaction mixture was concentrated *in vacuo* to give mesylate **307** as yellow oil (1.50 g, 81%).

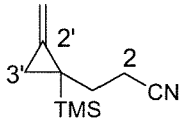
ν_{max} (liq. film) 1952 (w), 1352 (m), 1172 (s), 934 (s), 832 (m), 523 (m).

δ_H (300 MHz, $CDCl_3$) –0.01 (9H, s, CH_3), 0.80 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.06 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.34-1.76 (6H, m, C(1)H_2, C(2)H_2, C(3)H_2), 3.01 (3H, s, CH_3), 4.21 (2H, t, J = 7 Hz, C(4)H_2), 5.20 (1H, m, =CH_AH_B), 5.26 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –2.6 (3), 12.4 (2), 13.6 (0), 24.1 (2), 29.3 (2), 34.9 (2), 37.3 (3), 69.8 (2), 100.3 (2), 139.5 (0).

LRMS (CI) *m/z* 294 (6%, $[M+NH_4]^+$).

3-(2-Methylene-1-trimethylsilanyl-cyclopropyl)- propionitrile 308



Following a method described by Fish.[122]

A suspension of NaCN (1.10 g, 22.5 mmol) and mesylate **305** in DMSO (30 ml) was stirred at 60 °C overnight. The reaction mixture was then allowed to cool to room temperature, half-saturated brine (200 ml) was added and the reaction mixture was extracted with ethyl acetate. The combined organic phases were washed with brine,

dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 5-15% ethyl acetate in petroleum ether) to give nitrile **308** as colourless oil (1.57 g, 78%).

ν_{max} (liq. film) 2957 (w), 2861 (w), 2246 (w), 1250 (s), 833 (s), 751 (s).

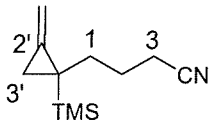
δ_H (300 MHz; $CDCl_3$) 0.02 (9H, s, CH_3), 0.94 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.15 (1H, ddd, J = 1.5, 2, 8 Hz, C(3')H_AH_B), 1.80 (1H, ddd, J = 14, 9, 7 Hz, C(1)H_AH_B), 1.93 (1H, ddd, J = 7, 9, 14 Hz, C(1)H_AH_B), 2.27 (1H, ddd, J = 7, 9, 17 Hz, C(2)H_AH_B), 2.34 (1H, ddd, J = 7, 9, 17 Hz, C(2)H_AH_B), 5.29 (1H, dt, J = 1, 2 Hz, =CH_AH_B), 5.37 (1H, m, =CH_AH_B).

δ_C (75MHz; $CDCl_3$) –2.8 (3), 12.2 (2), 12.8 (0), 15.5 (2), 30.5 (2), 102.2 (2), 119.8 (0), 137.1 (0).

LRMS (CI) *m/z* 180 (28%, $[M+H]^+$), 197 (44%, $[M+NH]_4^+$).

HRMS (EI) $C_{10}H_{16}NSi$ [M-H] requires 178.1052, found 178.1048.

4-(2-Methylene-1-trimethylsilanyl-cyclopropyl)-butyronitrile 309



Following a method described by Fish.[122]

A solution of mesyl ester **306** (2.82 g, 10.76 mmol) and NaCN (1.06 g, 21.53 mmol) in DMSO (30 ml) was stirred at 60 °C overnight. The reaction mixture was allowed to cool to room temperature, half-saturated brine was added and the reaction mixture was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give nitrile **309** as yellow oil (1.72 g, 83%).

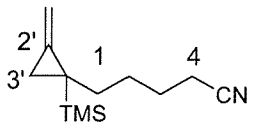
ν_{max} (liq. film) 3071 (w), 3042 (w), 2958 (m), 2900 (w), 2850 (w), 1461 (w), 1250 (s), 1117 (s), 838 (s), 754 (s).

δ_H (300 MHz; $CDCl_3$) 0.00 (9H, s, $SiMe_3$), 0.84 (1H, tt, J = 2, 8 Hz C(3')H_AH_B), 1.10 (1H, ddd, J = 2, 2, 8 Hz, C(3')H_AH_B), 1.49-1.78 (4H, m, C(1)H_2, C(2)H_2), 2.31 (2H, t, J = 7 Hz, C(3)H_2), 5.22 (1H, td, J = 2, J_2 = 1 Hz, C=CH_AH_B), 5.30 (1H, m, C=CH_AH_B).

δ_C (75 MHz, $CDCl_3$) -2.7 (3), 12.5 (2), 13.1 (0), 17.3 (2), 24.2 (2), 34.4 (2), 100.9 (2), 119.6 (0), 138.7 (0).

LRMS (CI) *m/z* 194 (48%, $[M+H]^+$), 211 (34%, $[M+NH_4]^+$).

5-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]pentanenitrile 310



Following a method described by Fish.[122]

A solution of mesylate **307** (1.40 g, 5.06 mmol) and NaCN (496 mg, 10.1 mmol) in DMSO (15 ml) was stirred at 60 °C overnight. The reaction mixture was allowed to cool to room temperature, half-saturated brine was added and the reaction mixture was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2-3% ethyl acetate in petroleum ether) to give nitrile **310** as colourless oil (780 mg, 74%).

ν_{max} (liq. film) 2953 (m), 2247 (w), 1248 (s), 833 (s).

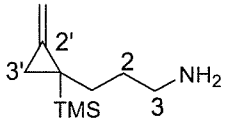
δ_H (300 MHz, $CDCl_3$) –0.00 (9H, s, CH_3), 0.81 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.07 (1H, ddd, J = 2, 2, 8 Hz, C(3')H_AH_B), 1.33-1.68 (6H, m, C(1)H_2, C(2)H_2, C(3)H_2), 2.33 (2H, t, J = 7 Hz, C(4)H_2), 5.20 (1H, m, =CH_AH_B), 5.27 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –2.6 (3), 12.5 (2), 13.5 (0), 17.0 (2), 25.6 (2), 27 3 (2), 34.7 (2), 100.5 (2), 119.7 (0), 139.4 (0).

LRMS (CI) *m/z* 208 (80%, $[M+H]^+$).

HRMS (EI) $C_{12}H_{20}NSi$ [M-H] requires 206.1365, found 206.1367.

3-(2-Methylene-1-trimethylsilanyl-cyclopropyl)-propylamine 311



Nitrile **308** (500 mg, 2.79 mmol) in diethyl ether (2 ml) was slowly added to a stirred solution of $LiAlH_4$ in diethyl ether (10 ml, 1.0M, 10 mmol). The reaction mixture was stirred at room temperature overnight, cooled to 5 °C and 2M NaOH was added. The

reaction mixture was dried over $MgSO_4$ and concentrated *in vacuo* to give the amine **311** as colourless oil (446 mg, 87%).

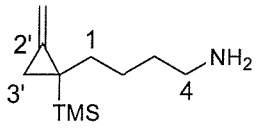
ν_{max} (liq. film) 2957 (m), 2840 (m), 1244 (s), 828 (s).

δ_H (300 MHz; $CDCl_3$) 0.01 (9H, s, CH_3), 0.80 (1H, dt, J = 7, 2 Hz, C(3')H_AH_B), 1.05 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.32-1.59 (4H, m, C(1)H_2, C(2)H_2), 2.64 (2H, t, J = 7 Hz, C(3)H_2), 5.20 (1H, br s, =CH_AH_B), 5.25 (1H, br s, =CH_AH_B)

δ_C (75 MHz, $CDCl_3$) –2.6 (3), 12.5 (2), 13.6 (0), 32.5 (2), 32.9 (2), 42.5 (2), 100.1 (2), 139.9 (0).

LRMS (ES) *m/z* 184, (100%, $[M+H]^+$).

4-(2-Methylene-1-trimethylsilanyl-cyclopropyl)-butylamine 312



A solution of nitrile **309** (200 mg, 1.04 mmol) in diethyl ether (2.0 ml) was slowly added to a stirred solution of $LiAlH_4$ in diethyl ether (4.0 ml, 1.0M, 4.0 mmol). The reaction mixture was stirred at room temperature overnight, and diethyl ether and 2M NaOH were added. The reaction mixture was dried over $MgSO_4$ and concentrated *in vacuo* to give amine **312** as colourless oil (185 mg, 91%).

ν_{max} (liq. film) 2928 (m), 2844 (m), 1247 (s), 827 (s), 748 (s).

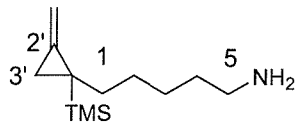
δ_H (300 MHz; $CDCl_3$) –0.01 (9H, s, CH_3), 0.80 (1H, tt, J = 2, 7 Hz, C(3')H_AH_B), 1.02 (1H, ddd, J = 2, 2, 8 Hz, C(3')H_AH_B), 1.29-1.65 (6H, m, C(1)H_2, C(2)H_2, C(3)H_2), 2.67 (2H, t, J = 7 Hz, C(4)H_2), 5.19 (1H, m, =CH_AH_B), 5.25 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –2.6 (3), 12.4 (2), 13.9 (0), 24.1 (2), 25.5 (2), 34.0 (2), 35.5 (2), 100.0 (2), 140.0 (0).

LRMS (ES) *m/z* 198 (100%, $[M+H]^+$), 239 (15%, $[M+H+MeCN]^+$).

HRMS (ES) $C_{11}H_{23}NSi$ $[M+H]^+$ requires 198.1673, found 198.1666.

5-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]pentylamine 313



A solution of nitrile **310** (720 mg, 3.48 mmol) in diethyl ether (5.0 ml) was slowly added to a stirred solution of $LiAlH_4$ in diethyl ether (14.0 ml, 1.0 M, 14.0 mmol). The reaction mixture was stirred at room temperature for 2 h, and diethyl ether and NaOH (2M) were added. The reaction mixture was dried over $MgSO_4$ and concentrated *in vacuo* to give amine **313** as colourless oil (560 mg, 77%).

ν_{max} (liq. film) 2925 (m), 2851 (m), 1460 (w), 1247 (s).

δ_H (300 MHz, $CDCl_3$) –0.02 (9H, s, CH_3), 0.79 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.03 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.22-1.51 (8H, m, C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2), 1.62 (2H, br s, NH_2), 2.68 (2H, t, J = 7 Hz, C(5)H_2), 5.18 (1H, m, =CH_AH_B), 5.24 (1H, m, =CH_AH_B).

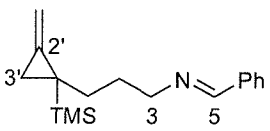
δ_C (75 MHz, $CDCl_3$) –2.6 (3), 12.4 (2), 13.9 (0), 27,2 (2), 28.1 (2), 33.5 (2), 35.7 (2), 42.1 (2), 99.9 (2), 140.0 (0).

LRMS (ES+) *m/z* 212 (60%, $[M+H]^+$).

HRMS $C_{12}H_{26}NSi$ $[M+H]^+$ requires 212.1829, found 212.1825.

Anal. Calcd for $C_{12}H_{25}NSi{\cdot}0.3(CH_3)_2CO$: C, 67.71; H, 11.8, N; 6.12. Found C, 67.69; H, 11.8; N, 6.12.

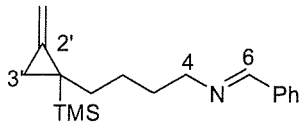
Benzylidene-[3-(2-methylene-1-trimethylsilanyl-cyclopropyl)-propyl]-amine 314



Benzaldehyde (111µl, 1.09mmol) was added to a stirred solution of propylamine **311** (200 mg, 1.09 mmol) in DCM (3 ml) over 4 Å molecular sieves under Ar. The reaction mixture was stirred at room temperature for 3 h, filtered and concentrated *in vacuo* to give imine **314** as colourless oil (272 mg, 92%).

δ_H (300 MHz; $CDCl_3$) 0.84 (1H, m, C(3')H_AH$_B$), 1.07 (1H, m, C(3')H$_A$$H_B$), 1.45 (1H, m, C(1)$H_AH_B$), 1.59 (1H, m, C(1)H$_A$$H_B$), 1.75 (2H, m, C(2)$H_2$), 3.57 (2H, t, J = 7 Hz, C(3)H_2), 5.22 (1H, m, =CH_AH$_B$), 5.27 (1H, m, =CH$_A$$H_B$), 7.43 (3H, m, Ar), 7.73 (2H, m, Ar), 8.27 (1H, br s, C(5)H).

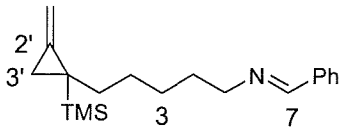
Benzylidene-[4-(2-methylene-1-trimethylsilanyl-cyclopropyl)-butyl]-amine 315



Benzaldehyde (103 µl, 1.02 mmol) was added to a stirred solution of butylamine **312** (200 mg, 1.02 mmol) in DCM (2 ml) on 4 Å molecular sieves at room temperature under Ar. The reaction mixture was stirred at room temperature for 3 h, filtered and concentrated en vacuo to give the imine **315** as a colourless oil (245 mg, 84%).

δ_H (300 MHz; $CDCl_3$) 0.81 (1H, dt, J = 8, 2, Hz, C(3')H_AH$_B$), 1.04 (1H, dt, J = 8, 2 Hz, C(3')H$_A$$H_B$), 1.36-1.71 (6H, m, C(1)H_2, C(2)H_2, C(3)H_2), 3.60 (2H, t, J = 7 Hz, C(4)H_2), 5.20 (1H, m, =CH_AH$_B$), 5.24 (1H, m, =CH$_A$$H_B$), 7.43-7.41 (3H, m, Ar), 7.71-7.74 (2H, m, Ar), 8.27 (1H, s, C(6)H).

***N*1-[(*E*)-1-Phenylmethylidene]-5-[2-methylene-1-(1,1,1-trimethylsilyl) cyclopropyl]-1-pentanamine 316**

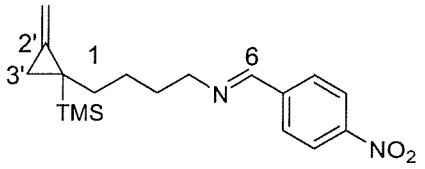


A solution of amine **313** (212 mg, 1.0 mmol) and benzaldehyde (102 µl, 1.00 mmol) in DCM (10 ml) was stirred at room temperature under Ar over 4 Å molecular sieves for 5 h, filtered and concentrated *in vacuo* to give the imine **316** as cloudy white oil (260 mg, 87%).

δ_H (300 MHz, $CDCl_3$) –0.02 (9H, s, CH_3), 0.79 (1H, dt, J = 8, 2 Hz, C(3')H_AH$_B$), 1.03 (1H, dt, J = 8, 2 Hz, C(3')H$_A$$H_B$), 1.26-1.74 (8H, m, C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2),

3.60 (2H, t, J = 7 Hz, C(5)H_2), 5.19 (1H, m, =CH_AH$_B$), 5.24 (1H, m, =CH$_A$$H_B$), 7.40-7.43 (3H, m, Ar), 7.71-7.74 (2H, m, Ar), 8.27 (1H, s, C(7)H).

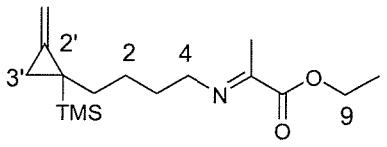
[4-(2-Methylene-1-trimethylsilanyl-cyclopropyl)-butyl]-(4-nitro-benzylidene)-amine 317



P-nitrobenzaldehyde (230 mg, 1.52 mmol) was added to a stirred solution of butylamine **312** (300 mg, 1.52 mmol) in DCM (3.5 ml) on 4 Å molecular sieves at room temperature under Ar. The reaction mixture was stirred at room temperature for 3 h, filtered and concentrated *in vacuo* to give imine **317** as colourless oil (414 mg, 83%).

δ_H (300 MHz; $CDCl_3$) –0.02 (9H, s, CH_3), 0.80 (1H, dt, J = 8, 2 Hz, C(3')H_AH$_B$), 1.05 (1H, dt, J = 8, 2 Hz, C(3')H$_A$$H_B$), 1.40-1.74 (6H, m, C(1)H_2, C(2)H_2, C(3)H_2), 3.66 (2H, t, J = 7 Hz, C(4)H_2), 5.19 (1H, m, =CH_AH$_B$), 5,25 (1H, m, =CH$_A$$H_B$), 7.88-7.91 (2H, m, Ar), 8.26-8.29 (2H, m, Ar), 8.35 (1H, s, C(6)H).

Ethyl 2-(4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]butylimino) propanoate 318

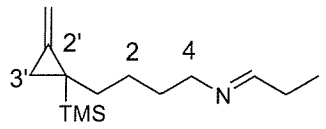


A solution of amine **312** (203 mg, 1.03 mmol) and ethyl pyruvate (120 mg, 1.03 mmol) in DCM (4 ml) was stirred over 4 Å mol. sieves under Ar for 1 h, filtered and concentrated *in vacuo* to give imine **318** with some impurities as yellow oil (250 mg, 82%).

δ_H (300 MHz; $CDCl_3$) -0.01 (9H, s, CH_3), 0.80 (1H, m, C(3')H_AH$_B$), 1.04 (1H, m, C(3')H$_A$$H_B$), 1.21-1.69 (9H, m, C(1)H_2, C(2)H_2, C(3)H_2, C(10)H_3), 2.09 (3H, s, CH_3),

3.46 (2H, t, J = 7 Hz, C(4)H_2), 4.32 (2H, q, J = 7 Hz, C(9)H_2), 5.20 (1H, m, =CH_AH$_B$), 5.25 (1H, m, =CH$_A$$H_B$).

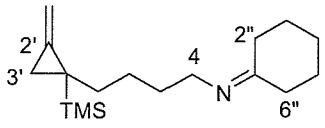
N1-[(*E*)-Propylidene]-4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-1-butanamine 319



A solution of amine **312** (130 mg, 0.66 mmol) and propionaldehyde (38 mg, 0.66 mmol) in DCM (3 ml) was stirred over 4 Å molecular sieves under Ar at room temperature for 2 h, filtered and concentrated *in vacuo* to give imine **319** as yellow oil (131 mg, 84%).

δ_H (300 MHz; $CDCl_3$) -0.02 (9H, s, CH_3), 0.80 (1H, m, C(3')H_AH$_B$), 0.92 (1H, m, C(3')H$_A$$H_B$), 1.02-1.61 (9H, m, C(1)H_2, C(2)H_2, C(3)H_2, C(7)H_2, C(8)H_3), 2.25 (2H, m, C(7)H_2), 3.33 (2H, t, J = 6 Hz, C(4)H_2), 5.18 (1H, m, =CH_AH$_B$), 5.24 (1H, m, =CH$_A$$H_B$), 7.65 (1H, t, J = 9 Hz, C(6)H).

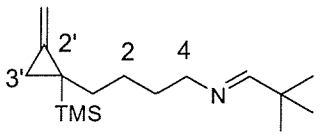
N1-Cyclohexyliden-4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-1-butanamine 320



A solution of amine **312** (202 mg, 1.03 mmol) and cyclohexanone (107 mg, 1.03 mmol) in DCM (3 ml) was stirred over 4 Å molecular sieves under Ar for 48 h, filtered and concentrated *in vacuo* to give a mixture of imine **320** and cyclohexanone as colourless oil (203 mg, 71%).

δ_H (300 MHz; $CDCl_3$) -0.01 (9H, s, CH_3), 0.81 (1H, dt, J = 8, 2 Hz, C(3')H_AH$_B$), 1.04 (1H, m, C(3')H$_A$$H_B$), 1.29-1.91 (12H, m, C(1)H_2, C(2)H_2, C(3)H_2, C(3")H_2, C(4")H_2, C(5")H_2), 2.28-2.37 (4H, m, C(2")H_2, C(6")H_2), 3.28 (2H, t, J = 7 Hz, C(4)H_4), 5.19 (1H, m, =CH_AH$_B$), 5.24 (1H, m, =CH$_A$$H_B$).

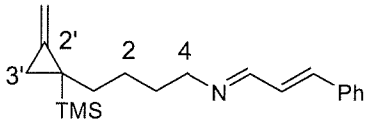
N1-[(E)-2,2-Dimethylpropylidene]-4-[2-methylene-1-(1,1,1-trimethylsilyl) cyclopropyl]-1-butanamine 321



A solution of amine **312** (102 mg, 0.520 mmol) and pivalaldehyde (56 µl, 0.520 mmol) in DCM (3 ml) was stirred over 4 Å mol. sieves under Ar for 4 h, filtered and concentrated *in vacuo* to give imine **321** as colourless oil (110 mg, 80%).

δ_H (300 MHz; $CDCl_3$) -0.02 (9H, s, CH_3), 0.79 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.00-1-10 (10H, m, C(3')H_AH_B, CH_3), 1.24-1.58 (6H, m, C(1)H_2, C(2)H_2, C(3)H_2), 3.34 (2H, t, J = 7 Hz,C(4)H_2), 5.18 (1H, m, =CH_AH_B), 5.24 (1H, m, =CH_AH_B), 7.48 (1H, t, J = 1 Hz, =CH).

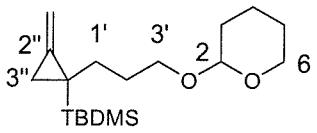
N1-[(E,2E)-3-Phenyl-2-propenylidene]-4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-1-butanamine 322



A solution of amine **312** (173 mg, 0.878 mmol) and cinnamaldehyde (114 µl, 0.878 mmol) in DCM (4 ml) was stirred over 4 Å molecular Sieves under Ar for 3 h, filtered and concentrated *in vacuo* to give imine **322** as colourless oil (260 mg, 95%).

δ_H (300 MHz; $CDCl_3$) -0.01 (9H, s, CH_3), 0.81 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.04 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.29-1.74 (6H, m, C(1)H_2, C(2)H_2, C(3)H_2), 3.50 (2H, t, J = 7 Hz, C(4)H_2), 5.20 (1H, m, =CH_AH_B), 5.25 (1H, m, =CH_AH_B), 6.93 (1H, m, =CH), 7.32-7-53 (5H, m, Ar), 7.57-7.61 (1H, m, =CH), 8.02 (1H, m, =CH).

3-1-[1-(*tert*-Butyl)-1,1-dimethylsilyl]-2-methylenecyclopropylpropyl tetrahydro-2*H*-2-pyranyl ether 325



Following a method described by Destabel.[120]

n-BuLi (2.30 M in hexanes, 5.9 ml, 13.5 mmol) was added to a stirred solution of methylenecyclopropane (0.9 ml, 13.5 mmol) in THF (100 ml) under Ar at -50 °C. The reaction mixture was allowed to warm to 10 °C during 2 h and cooled to -50 °C. TBDMSCl (2.0 g, 13.5 mmol) was added and the reaction mixture was allowed to warm to 10 °C during 2 h, and then cooled to -50 °C. Bromide **261** (3.0 g, 13.5 mmol) in THF (10 ml) was added. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction was quenched with aqueous saturated NH_4Cl and extracted with diethyl ether (3x100 ml). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2% ethyl acetate in petroleum ether) to give THP ether **325** as colourless oil (1.60 g, 38%).

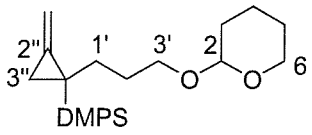
ν_{max} (liq. film) 2930 (m), 2855 (m), 1466 (w), 1251 (s), 1032 (s), 823 (s), 808 (s).

δ_H (300 MHz, $CDCl_3$) –0.09 (3H, s, CH_3), -0.08 (3H, s, CH_3), 0.84 (1H, m, C(3'')H_AH_B), 0.97 (9H, s, CH_3), 1.08 (1H, m, C(3'')H_AH_B), 1.49-1.89 (10H, m, C(1')H_2, C(2')H_2, C(3)H_2, C(4)H_2, C(5)H_2), 3.30 (1H, m, C(3')H_AH_B), 3.50 (1H, m, C(6)H_AH_B), 3.66 (1H, m, C(3')H_AH_B), 3.85 (1H, m, C(6)H_AH_B), 4.56 (1H, t, J = 3 Hz, C(2)H), 5.22 (1H, br s, =CH_AH_B), 5.29 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –6.6 (3), -6.3 (0), 12.7 (2), (18)3 (0), 19.6 (2), 25.5 (2), 27.4 (3), 27.8 (2), 30.7 (2), 32.5 (2), 62.2 (2), 67.7 (2), 98.7 (1), 100.9 (2), 139.6 (0).

LRMS (CI) *m/z* 311 (1%, $[M+H]^+$).

Dimethyl2-methylene-1-[3-(tetrahydro-2*H*-2-pyranyloxy)propyl]cyclopropyl phenylsilane 326



Following a method described by Destabel.[120]

n-BuLi (2.35 M in hexane, 5.7 ml, 13.5 mmol) was added to a stirred solution of methylenecyclopropane (0.9 ml, 13.5 mmol) in THF (100 ml) under Ar at -50 °C. The reaction mixture was allowed to warm to 10^0C during 2 h and cooled to -50 °C. DMPSCl (2.25 ml, 13.5 mmol) was added and the reaction mixture was allowed to warm to 10 °C during 2 h, and then cooled to -50 °C. Bromide **261** (3.0 g, 13.5 mmol) in THF (10 ml) was added. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight. The reaction was quenched with aqueous saturated NH_4Cl and extracted with diethyl ether (3x100 ml). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2% ethyl acetate in petroleum ether) to give THP ether **326** as colourless oil (2.35 g, 53%).

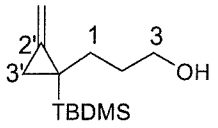
ν_{max} (liq. film) 2942 (m), 1427 (m), 1250 (s), 1113 (s), 812 (s).

δ_H (300 MHz, $CDCl_3$) 0.27 (6H, s, CH_3), 0.87 (1H, m, C(3'')H_AH$_B$), 1.12 (1H, dt, J = 8, 2 Hz, C(3'')H$_A$$H_B$), 1.35-1.86 (10H, m, C(3)H_2, C(4)H_2, C(5)H_2, C(1')H_2, C(2')H_2), 3.25 (1H, m, C(3')H_AH$_B$), 3.45 (1H, m, C(6)H_AH$_B$), 3.57 (1H, m, C(3')H$_A$$H_B$), 3.80 (1H, m, C(6)H$_A$$H_B$), 4.47 (1H, s, C(2)H), 5.30 (1H, m, =CH_AH$_B$), 5.32 (1H, br s, =CH$_A$$H_B$), 7.34-7.37 (3H, m, Ar), 7.53-7.57 (2H, m, Ar).

δ_C (75 MHz, $CDCl_3$) –4.8 (3), 12.5 (2), 13.1 (0), 19.6 (2), 25.4 (2), 28.0 (2), 30.7 (2), 31.7 (2), 62.2 (2), 67.5 (2), 98.6 (1), 101.1 (2), 127.6 (1), 129.0 (1), 133.9 (1), 137.9 (0), 138.9 (0).

LRMS (CI) *m/z* 311 (11%, $[M+H]^+$).

3-1-[1-(*tert*-Butyl)-1,1-dimethylsilyl]-2-methylenecyclopropyl-1-propanol 327



Following a method described by Destabel.[120]

THP ether **325** (1.56 g, 5.02 mmol) was stirred with Amberlite IR-120 (+) resin (940 mg) in methanol (50 ml) at 60 °C for 3 days. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 5-8% ethyl acetate in petroleum ether) to give alcohol **327** as colourless oil (747 mg, 66%).

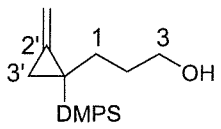
ν_{max} (liq. film) 3309 (br w), 2930 (m), 2856 (m), 1464 (w), 1251 (m), 823 (m), 807 (m).

δ_H (300 MHz, $CDCl_3$) –0.09 (3H, s, CH_3), -0.08 (3H, s, CH_3), 0.84 (1H, dt, J=8, 2 Hz, C(3')H_AH_B), 0.98 (9H, s, CH_3), 1.11 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.44 (1H, br s, OH), 1.48-1.71 (4H, m, C(1)H_2, C(2)H_2), 3.59 (2H, t, J = 6 Hz, C(3)H_2), 5.22 (1H, m, =CH_AH_B), 5.31 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –6.6 (3), -6.2 (3), 12.59 (2), 12.61 (0), 18.3 (0), 27.4 (3), 30.8 (2), 32.1 (2), 63.1 (2), 101.0 (2), 139.6 (0).

LRMS (CIMS): *m/z* 225 (70%, $[M-H]^+$), 227 (60%, $[M+H]^+$).

3-[1-(1,1-Dimethyl-1-phenylsilyl)-2-methylenecyclopropyl]-1-propanol 328



Following a method described by Destabel.[120]

THP ether **326** (2.26 g, 6.8 mmol) was stirred with Amberlite IR-120 (+) resin (1.20 g) in methanol (50 ml) at 60 °C for 3 days. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 5-10% ethyl acetate in petroleum ether) to give alcohol **328** as a colourless oil (1.12 g, 67%).

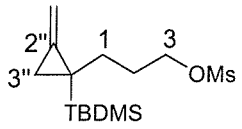
ν_{max} (liq. film) 3309 (br m), 2944 (m), 1427 (m), 1249 (s), 1112 (s), 811 (s).

δ_H (300 MHz, $CDCl_3$) 0.27 (3H, s, CH_3), 0.28 (3H, s, CH_3), 0.89 (1H, tt, J = 8, 2 Hz, C(3')H_AH_B), 1.14 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.25-1.65 (4H, m, C(1)H_2, C(2)H_2), 3.48 (2H, t, J = 6 Hz, C(3)H_2), 5.31 (1H, m, =CH_AH_B), 5.34 (1H, br s, =CH_AH_B), 7.36-7 38 (3H, m, Ar), 7.54-7.59 (2H, m, Ar).

δ_C (75 MHz, $CDCl_3$) –4.3 (3), -4.2 (3), 12.6 (2), 13.0 (0), 31.0 (2), 31.3 (2), 62.9 (2), 101.3 (2), 127.7 (1), 129.1 (1), 133.9 (1), 137.9 (0), 138.9 (0).

LRMS (CI) *m/z* 245 (16%, $[M-H]^+$), 247 (18%, $[M+H]^+$).

3-1-[1-(*tert*-Butyl)-1,1-dimethylsilyl]-2-methylenecyclopropylpropyl methanesulfonate 329



Mesyl chloride (0.29 ml, 3.77 mmol) was slowly added to a stirred solution of alcohol **327** (710 mg, 3.14 mmol) in DCM (10 ml) at -15 °C under Ar. The reaction mixture was allowed to warm to 10 °C over 1 h, during which time the reaction mixture turned yellow and a white solid formed. The reaction was quenched with cold water, washed with 2M H_2SO_4 and with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. The reaction mixture was concentrated *in vacuo* to give mesylate **329** as yellow oil (900 mg, 86%).

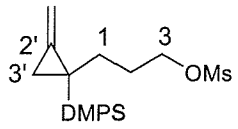
ν_{max} (liq. film) 2955 (m), 2930 (m), 2856 (m), 1469 (m), 1353 (s), 1173 (s).

δ_H (300 MHz, $CDCl_3$) –0.08 (6H, s, CH_3), 0.85 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 0.97 (9H, s, CH_3), 1.14 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.58-1.86 (4H, m, C(1)H_2, C(2)H_2), 3.00 (3H, s, CH_3), 4.19 (2H, m, C(3)H_2), 5.23 (1H, m, =CH_AH_B), 5.33 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –6.7 (3), -6.3 (3), 12.2 (0), 12.6 (2), 18.3 (0), 27.3 (2), 27.4 (3), 31.6 (2), 37.3 (3), 70.1 (2), 101.5 (2), 138.8 (0).

LRMS (CI) *m/z* 322 (6%, $[M+H]^+$).

3-[1-(1,1-Dimethyl-1-phenylsilyl)-2-methylenecyclopropyl]propyl methanesulfonate 330



Mesyl chloride (0.39 ml, 5.06 mmol) was slowly added to a stirred solution of alcohol **328** (1.04 g, 4.22 mmol) in DCM (10 ml) at -15 °C under Ar. The reaction mixture was allowed to warm to 10 °C over 1 h, during which time the reaction mixture turned yellow and a white solid formed. The reaction was quenched with cold water and washed with 2M H_2SO_4, with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. The reaction mixture was concentrated *in vacuo* to give mesylate **330** as yellow oil (1.16 g, 85%).

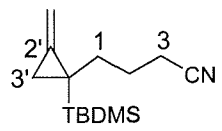
ν_{max} (liq. film) 2958 (w), 1732 (w), 1352 (m), 1172 (s), 811 (s).

δ_H (300 MHz, $CDCl_3$) 0.27 (3H, s, CH_3), 0.28 (3H, s, CH_3), 0.90 (1H, dt, J = 8, 2 Hz, C(3')$H_A$$H_B$), 1.18 (1H, dt, J = 8, 2 Hz, C(3')$H_A$$H_B$), 1.55-1.67 (4H, m, C(1)H_2, C(2)H_2), 2.91 (3H, s, CH_3), 4.05 (2H, m, C(3)H_2), 5.32 (1H, m, =C$H_A$$H_B$), 5.36 (1H, m, =C$H_A$$H_B$), 7.36-7.39 (3H, m, Ar), 7.53-7.57 (2H, m, Ar).

δ_C (75 MHz, $CDCl_3$) -4.4 (3), -4.36 (3), 12.7 (2), 12.7 (0), 27.5 (2), 31.0 (2), 37.3 (3), 70.0 (2), 101.7 (2), 127.8 (1), 129.2 (1), 133.9 (1), 137.6 (0), 138.3 (0).

LRMS (CI) *m/z* 342 (14%, $[M+NH_4]^+$).

4-1-[1-(*tert*-Butyl)-1,1-dimethylsilyl]-2-methylenecyclopropylbutanenitrile 331



Following a method described by Fish.[122]

A solution of mesylate **329** (826 mg, 2.72 mmol) and NaCN (266 mg, 5.43 mmol) in DMSO (10 ml) was stirred at 60 °C overnight. The reaction mixture was allowed to cool to room temperature, half-saturated brine was added and the reaction mixture was extracted with diethyl ether. The combined organic layers were washed with brine,

dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2-3% ethyl acetate in petroleum ether) to give nitrile **331** as colourless oil (459 mg, 72%).

ν_{max} (liq. film) 2956 (m), 2931 (m), 2856 (m), 2246 (w), 1646 (m), 1251 (m), 823 (s).

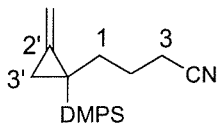
δ_H (300 MHz, $CDCl_3$) –0.09 (3H, s, CH_3), -0.08 (3H, s, CH_3), 0.86 (1H, dt, J = 8, 2 Hz, C(3')$H_A$$H_B$), 0.98 (9H, s, CH_3), 1.14 (1H, dt, J = 8, 2 Hz, C(3')$H_A$$H_B$), 1.57-1.79 (4H, m, C(1)H_2, C(2)H_2), 2.29 (2H, t, J = 7 Hz, C(3)H_2), 5.24 (1H, m, =C$H_A$$H_B$), 5.34 (1H, br s, =C$H_A$$H_B$).

δ_C (75 MHz, $CDCl_3$) –6.7 (3), -6.3 (3), 12.3 (0), 12.7 (2), 17.4 (2), 18.3 (0), 23.6 (2), 27.4 (3), 35.0 (2), 101.7 (2), 119.6 (0), 138.5 (0).

LRMS (CI) *m/z* 236 (80%, $[M+H]^+$), 253 (20%, $[M+NH_4]^+$).

HRMS (EI) $C_{14}H_{24}NSi$ [M-H] requires 234.1678, found 234.1674.

4-[1-(1,1-Dimethyl-1-phenylsilyl)-2-methylenecyclopropyl]butanenitrile 332



Following a method described by Fish.[122]

A solution of mesylate **330** (1.08 g, 3.33 mmol) and NaCN (326 mg, 6.66 mmol) was stirred in DMSO (10 ml) at 60 °C overnight. The reaction mixture was allowed to cool to room temperature, half-saturated brine was added and the reaction mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 5-6% ethyl acetate in petroleum ether) to give the nitrile **332** as colourless oil (669 mg, 79%).

ν_{max} (liq. film) 2957 (w), 2245 (w), 1426 (m), 1250 (s), 1112 (s), 811 (s).

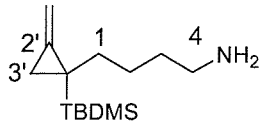
δ_H (300 MHz, $CDCl_3$) 0.27 (3H, s, CH_3), 0.29 (3H, s, CH_3), 0.92 (1H, dt, J = 8, 2 Hz, C(3')$H_A$$H_B$), 1.19 (1H, dt, J = 8, 2 Hz, C(3')$H_A$$H_B$), 1.39-1.71 (4H, m, C(1)H_2, C(2)H_2), 2.16 (2H, t, J = 7 Hz, C(3)H_2), 5.32 (1H, m, =C$H_A$$H_B$), 5.38 (1H, m, =C$H_A$$H_B$), 7.36-7.40 (3H, m, Ar), 7.54-7.57 (2H, m, Ar).

δ_C (75 MHz, $CDCl_3$) –4.5 (3), -4.4 (3), 12.7 (2), 12.8 (0), 17.1 (2), 23.8 (2), 34.3 (2), 101.9 (2), 119.5 (0), 127.8 (1), 129.3 (1), 133.8 (1), 137.5 (0), 138.0 (0).

LRMS (CI) *m/z* 256 (95%, $[M+H]^+$), 273 (70%, $[M+NH_4]^+$).

HRMS (EI) $C_{16}H_{20}NSi$ [M-H] requires 254.1365, found 254.1364.

4-1-[1-(*tert*-Butyl)-1,1-dimethylsilyl]-2-methylenecyclopropylbutylamine 333



A solution of nitrile **331** (420 mg, 1.78 mmol) in diethyl ether (10.0 ml) was slowly added to a stirred solution of $LiAlH_4$ in diethyl ether (7.0 ml, 1.0M, 7.0 mmol). The reaction mixture was stirred at room temperature for 2 h, and diethyl ether and 2M NaOH were added until excess $LiAlH_4$ was consumed. The reaction mixture was dried over $MgSO_4$ and concentrated under reduced pressure to give amine **333** as colourless oil (320 mg, 76%).

ν_{max} (liq. film) 2926 (m), 2853 (m), 1462 (m), 1248 (s), 871 (s).

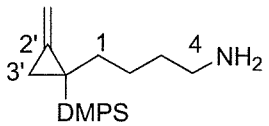
δ_H (300 MHz, $CDCl_3$) –0.11 (3H, s, CH_3), -0.10 (3H, s, CH_3), 0.81 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 0.96 (9H, s, CH_3), 1.07 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.22-1.62 (6H, m, $C(1)H_2$, $C(2)H_2$, $C(3)H_2$),1.72 (2H, br s,NH_2), 2.66 (2H, 2H, t, J = 7 Hz, $C(4)H_2$), 5.20 (1H, m, =CH_AH_B), 5.28 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –6.6 (3), -6.2 (3), 12.6 (2), 13.1 (0), 18.3 (0), 24.9 (2), 27.4 (3), 33.9 (2), 35.9 (2), 42.0 (2), 100.7 (2), 137.8 (0).

LRMS (ES) *m/z* 240 (70%, $[M+H]^+$), 253 (10%, $[M+MeCN+H]^+$).

HRMS (ES) $C_{14}H_{30}NSi$ $[M+H]^+$ requires 240.2142, found 240.2138.

4-[1-(1,1-Dimethyl-1-phenylsilyl)-2-methylenecyclopropyl]butylamine 334



A solution of nitrile **332** (618 mg, 2.42 mmol) in diethyl ether (6.0 ml) was slowly added to a stirred solution of $LiAlH_4$ in diethyl ether (10.0 ml, 1.0M, 10.0 mmol). The reaction mixture was stirred at room temperature for 20 h, and diethyl ether and 2M NaOH were added until excess $LiAlH_4$ was consumed. The reaction mixture was dried

over $MgSO_4$ and concentrated *in vacuo* to give the amine **334** as colourless oil (585 mg, 93%).

ν_{max} (liq. film) 2927 (m), 2848 (m), 1426 (m), 1248 (m), 1110 (m), 811 (s).

δ_H (300 MHz, $CDCl_3$) 0.257 (3H, s, CH_3), 0.262 (3H, s, CH_3), 0.88 (1H, dt, J = 8, 2 Hz, C(3')$H_A$$H_B$), 1.19 (1H, dt, J = 8, 2 Hz, C(3')$H_A$$H_B$), 1.14-1.58 (8H, m, C(1)H_2, C(2)H_2, C(3)H_2, NH_2), 2.54 (2H, t, J = 7 Hz, C(4)H_2), 5.29 (1H, m, =C$H_A$$H_B$), 5.23 (1H, m, =C$H_A$$H_B$), 7.34-7.37 (3H, m, Ar), 7.54-7.57 (2H, m, Ar).

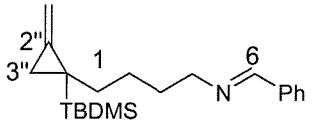
δ_C (75 MHz, $CDCl_3$) –4.3 (3), -4.2 (3), 12.7 (2), 13.5 (0), 25.1 (2), 33.8 (2), 35.2 (2), 41.9 (2), 101.0 (2), 127.6 (1), 129.0 (1), 133.9 (1), 138.1 (0), 139.2 (0).

LRMS (ES) *m/z* 260 (100%, $[M+H]^+$), 301 (10%, $[M+MeCN+H]^+$).

HRMS (ES) $C_{16}H_{26}NSi$ [M+H] requires 260.1829, found 260.1826.

Anal. Calcd for $C_{16}H_{25}NSi$·0.5MeOH: C, 71.94; H, 9.88; N, 5.08. Found C, 72.04; H, 9.72; N, 4.80.

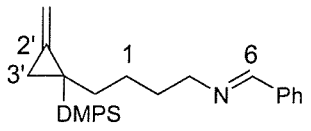
N1-[(*E*)-1-Phenylmethylidene]-4-1-[1-(*tert*-butyl)-1,1-dimethylsilyl]-2-methylenecyclopropyl-1-butanamine 335



A solution of amine **333** (131 mg, 0.55 mmol) and benzaldehyde (56 µl, 0.55 mmol) in DCM (10 ml) was stirred at room temperature under Ar over 4 Å molecular sieves for 5 h, filtered and concentrated under reduced pressure to give the imine **335** as white cloudy oil (166 mg, 92%).

δ_H (300 MHz, $CDCl_3$) –0.01 (3H, s, CH_3), -0.01 (3H, s, CH_3), 0.82 (1H, dt, J = 8, 2 Hz, C(3')$H_A$$H_B$), 0.96 (9H, s, CH_3), 1.07 (1H, dt, J = 8, 2 Hz, C(3')$H_A$$H_B$), 1.26-1.69 (6H, m, C(1)H_2, C(2)H_2, C(3)H_2), 3.59 (2H, t, J = 7 Hz, C(4)H_2), 5.20 (=C$H_A$$H_B$), 5.27 (1H, m, =C$H_A$$H_B$), 7.40 (3H, m, Ar), 7.68-7.74 (2H, m, Ar), 8.27 (1H, s, C(6)H).

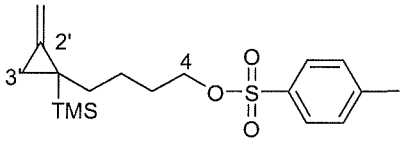
N1-[(*E*)-1-Phenylmethylidene]-4-[1-(1,1-dimethyl-1-phenylsilyl)-2-methylenecyclopropyl]-1-butanamine 336



A solution of amine **334** (118 mg, 0.46 mmol) and benzaldehyde (47 μl, 0.46 mmol) in DCM (10 ml) was stirred at room temperature under Ar over 4 Å molecular sieves for 5 h, filtered and concentrated under reduced pressure to give imine **336** as colourless oil (149 mg, 94%).

δ_H (300 MHz, $CDCl_3$) 0.25 (6H, s, CH_3), 0.89 (1H, dt, J = 8, 2 Hz, C(3')H_AH$_B$), 1.11 (1H, dt, J = 8, 2 Hz, C(3')H$_A H_B$), 1.22-1.60 (6H, m, $3CH_2$), 3.48 (2H, dt, J = 2, 7 Hz, C(4)H_2), 5.28 (1H, m, =CH_AH$_B$), 5.30 (1H, m, =CH$_A H_B$), 7.31-7.34 (2H, m, Ar), 7.41-7.43 (3H, m, Ar), 7.52-7.58 (2H, m, Ar), 7.68-7.71 (2H, m, Ar), 7.89-7.92 (1H, m, Ar), 8.18 (1H, s, C(6)H), 10.04 (1H, s, =CH).

4-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]butyl 4-methyl-1-benzenesulfonate 340



Following a procedure described by Nicolaou.[126]

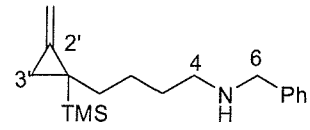
TsCl (1.143 g, 5.98 mmol) and DMAP (100 mg, 0.82 mmol), were added to a stirred solution of alcohol **302** in Et_3N (1 ml) and DCM (20 ml) at 0 °C under Ar. The reaction mixture was stirred at 0 °C for 4 h, quenched with ice-cold water, washed with 1M $KHSO_4$ and aqueous saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (2-10% ethyl acetate in petroleum ether) to give tosylate **340** as white solid (394 mg, 58%), m.p. 80-82 °C.

δ_H (300 MHz, $CDCl_3$) -0.04 (9H, s, CH_3), 0.75 (1H, dt, J = 8, 2 Hz, C(3')H_AH$_B$), 1.02 (1H, dt, J = 8,, 2 Hz, C(3')H$_A H_B$), 1.24-1.46 (4H, m, $2CH_2$), 1.56 (2H, m, CH_2), 2.46

(3H, s, CH_3), 4.00 (2H, t, J = 7 Hz, C(4)H_2), 5.15 (1H, m, =CH_AH$_B$), 5.24 (1H, m, =CH$_A$$H_B$), 7.35 (2H, d, J = 8 Hz, Ar), 7.77-7.78 (2H, m, Ar).

δ_C (75 MHz, $CDCl_3$) -2.6 (3), 12.4 (2), 13.6 (0), 21.6 (3), 24.1 (2), 29.0 (2), 34.9 (2), 70.4 (2), 100.3 (2), 127.9 (1), 129.8 (1), 139.55 (0), 139.56 (0), 144.6 (0).

N1-Benzyl-4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-1-butanamine 337



Following a procedure described by Overman.[127]

A solution of tosylate **340** (215 mg, 0.61 mmol) and benzyl amine (333µl, 3.05 mmol) in ethanol was refluxed overnight. The reaction mixture was allowed to cool to room temperature and was partitioned between DCM (25 ml) and 1M KOH (25 ml). The aqueous phase was extracted with DCM, and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (Silica gel, 10-50% ethyl acetate in petroleum ether) to give amine **337** as colourless oil (106 mg, 90%).

ν_{max} (liq. film) 2926 (m), 2844 (m), 2811 (m), 1453 (s), 1247 (s), 1119 (m), 833 (s).

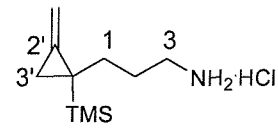
δ_H (300 MHz, $CDCl_3$) -0.02 (9H, s, CH_3), 0.79 (1H, dt, J = 8,, 2 Hz, C(3')H_AH$_B$), 1.03 (1H, dt, J = 8,, 2 Hz, C(3')H$_A$$H_B$), 1.27-1.55 (6H, m, C(1)H_2, C(2)H_2, C(3)H_2), 1.76 (1H, br s, NH), 2.61 (2H, t, J = 7 Hz, C(4)H_2), 3.79 (2H, s, C(6)H_2), 5.19 (1H, m, =CH_AH$_B$), 5.24 (1H, m, =CH$_A$$H_B$), 7.33-7.34 (5H, m, Ar).

δ_C (75 MHz, $CDCl_3$) -2.57 (3), 12.4 (2), 13.9 (0), 26.0 (2), 30.3 (2), 35.5 (2), 49.2 (2), 53.9 (2), 100.0 (2), 126.9 (1), 128.2 (1), 128.4 (1), 140.0 (0), 140.5 (0).

LRMS (ES) *m/z* 288 (100%, $[M+H]^+$).

HRMS (ES) $C_{18}H_{29}NSi$ $[M+H]^+$ requires 288.2142, found 288.2146.

3-[2-Methylene-1-(1,1,1,-trimethylsilyl)cyclopropyl]propylamine hydrochloride salt 341

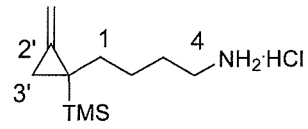


HCl (37%, w/v in H_2O, 0.07 ml, 0.8 mmol) was added to a stirred solution of amine **311** (150 mg, 0.8 mmol) in diethyl ether (4 ml). The reaction mixture was stirred at room temperature for 2 h, during which time a white solid was formed. Toluene was added, and the solvents were removed under reduced pressure to give hydrochloride salt **341** as pale brown solid (178 mg, 99%), m.p. 138-142 °C.

ν_{max} (liq. film) 2955 (m), 2895 (w), 2362 (w), 1574 (w), 1499 (w), 1248 (m), 831 (s), 746 (s).

δ_H (300 MHz, $CDCl_3$) 0.01 (9H, s, CH_3), 0.87 (1H, d, J = 7 Hz, C(3')H_AH_B), 1.07 (1H, d, J = 7 Hz, C(3')H_AH_B), 1.50 (1H, m, C(1)H_AH_B), 1.61 (1H, m, C(1)H_AH_B), 1.78 (2H, m, C(2)H_2), 2.94 (2H, br s, C(3)H_2), 5.24 (1H, m, =CH_AH_B), 5.29 (1H, m, =CH_AH_B), 8.30 (3H, NH_3).

4-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]butylamine hydrochloride salt 342



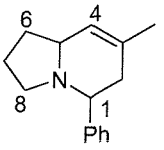
HCl (37%, w/v in H_2O, 0.08 ml, 1.05 mmol) was added to a stirred solution of amine **312** (207 mg, 1.05 mmol) in diethyl ether (3 ml). The reaction mixture was stirred at room temperature for 2 h, during which time a white solid was formed. Toluene was added, and the solvents were removed *in vacuo* to give hydrochloride salt **342** as pale brown solid (235 mg, 96%), m.p. 144-148 °C.

δ_H (300 MHz, $CDCl_3$) –0.02 (9H, s, CH_3), 0.81 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.05 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.38 (2H, m, CH_2), 1.53-1.96 (4H, m, 2CH_2), 2.94

(2H, br s, C(4)H_2), 5.21 (1H, br s, =CH_AH$_B$), 5.26 (1H, br s, =CH$_A$$H_B$), 8.26 (3H, br s, NH_3).

δ_C (100 MHz, $CDCl_3$) -2.3 (3), 12.6 (2), 13.7 (0), 25.3 (2), 28.2 (2), 34.9 (2), 40.1 (2), 100.7 (2), 139.5 (0).

7-Methyl-5-phenyl-1,2,3,5,6,8a-hexahydro-indolizine 344



General method from imine **315**

$BF_3{\cdot}Et_2O$ (89 µl, 0.70 mmol) was added to a stirred solution of imine **315** (100 mg, 0.35 mmol) in DCM (4 ml) at -78 °C under Ar. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight. The reaction was quenched with water and extracted with DCM. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 1-10% MeOH in DCM) to give bicycle **344** as dense brown oil (30 mg, 40%). For yields and conditions see table 4.

ν_{max} (liq. film) 2970 (w), 2918 (w), 1458 (m), 1055 (s), 1033 (s), 758 (s), 701 (s).

δ_H (400MHz; $CDCl_3$) 1.83 (3H, s, CH_3), 1.90 (1H, m, C(6)H_AH$_B$), 2.07 (2H, m, C(7)H_2), 2.31-2.42 (2H, m, C(2)H$_A$$H_B$, C(6)H$_A$$H_B$), 2.77 (1H, dd, J = 14, 8 Hz, C(2)H_AH$_B$), 3.04 (1H, dt, J = 9, 6 Hz, C(8)H_AH$_B$), 3.47 (1H, dt, J = 9, 6 Hz, C(8)H$_A$$H_B$), 4.02 (1H, dd, J = 8, 3 Hz, C(1)H), 4.27 (1H, br s, C(5)H), 5.57 (1H, s, C(4)H), 7,40-7.50 (5H, m, Ar).

δ_C (100 MHz, $CDCl_3$) 21.8(2), 22.7 (3), 29.8 (2), 36.0 (2), 52.7 (2), 61.7 (1), 62.7 (1), 117.6 (1), 127.8 (1), 129.7 (1), 129.8 (1), 133.6 (0), 135.0 (0).

LRMS (ES) *m/z* 214 (100%, $[M+H]^+$).

HRMS (ES) $C_{15}H_{19}N$ $[M+H]^+$ requires 213.1517, found 213.1513.

Lewis Acid	Solvent	Yield (%)
$BF_3{\cdot}Et_2O$	DCM	40
$BF_3{\cdot}Et_2O$	$EtNO_2$	36
$In(OTf)_3$	$EtNO_2$	37

Table 4

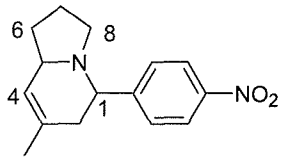
From imine **335**

$BF_3{\cdot}Et_2O$ (38 μl, 0.30 mmol) was added to a stirred solution of imine **335** (97 mg, 0.30 mmol) in DCE (10 ml) at room temperature under Ar. The reaction mixture was slowly heated to 80 °C and was stirred at 80 °C overnight. The reaction was quenched with water and extracted with DCM. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 1-10% MeOH in DCM) to give the bicycle **x** as a dense brown oil (8 mg, 13%).

δ_H (400MHz; $CDCl_3$) 1.83 (3H, s, CH_3), 1.90 (1H, m, C(6)H_AH_B), 2.07 (2H, m, C(7)H_2), 2.31-2.42 (2H, m, C(2)H_AH_B, C(6)H_AH_B), 2.77 (1H, dd, J = 14, 8 Hz, C(2)H_AH_B), 3.04 (1H, dt, J = 9, 6 Hz, C(8)H_AH_B), 3.47 (1H, dt, J = 9, 6 Hz, C(8)H_AH_B), 4.02 (1H, dd, J = 8, 3 Hz, C(1)H), 4.27 (1H, br s, C(5)H), 5.57 (1H, s, C(4)H), 7,40-7.50 (5H, m, Ar).

^{1}H NMR data agrees with previous.

7-Methyl-5-(nitro-phenyl)-1,2,3,5,6,8a-hexahydro-indolizine 356



General method

$In(OTf)_3$ (218 mg, 0.388 mmol) was added to a stirred solution of Imine **317** (100 mg, 0.303 mmol) in DCM (2 ml) at -78 °C under Ar. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight, quenched with water and extracted with DCM. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column

chromatography (silica gel, 1-10% MeOH in DCM) to give the indolizine **356** as brown solid (28 mg, 36%). For yields and conditions see table 5.

ν_{max} (liq. film) 2962 (m), 2911 (m), 2876 (m), 1600 (m), 1514 (s), 1341 (s), 1260 (s), 848 (s), 746 (s).

δ_H (300 MHz; $CDCl_3$) 1.60 (1H, m, C(6)H_AH$_B$), 1.75 (3H, s, CH_3), 1.77 (2H, m, C(7)H_2), 1.95 (1H, m, C(6)H$_A$$H_B$), 2.19 (2H, m, C(2)$H_2$), 2.63 (1H, ddd, J = 11, 8, 5 Hz, C(8)H_AH$_B$), 2.79 (1H, ddd, J = 11, 8, 7 Hz, C(8)H$_A$$H_B$), 3.43 (1H, m, C(5)H), 3.82 (1H, dd, J = 7, 5 Hz, C(1)H), 5.58 (1H, m, C(4)H), 7.53-7.56 (2H, m, Ar), 8.17-8.20 (2H, m, Ar).

δ_C (100 MHz, $CDCl_3$ 22.8 (2), 22.9 (3), 30.8 (2), 37.8 (2), 52.0 (2), 58.9 (1), 59.2 (1), 123.1 (1), 123.6 (1), 128.5 (1), 131.0 (0), 147.0 (0), 151.6 (0).

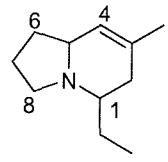
LRMS (ES) *m/z* 259 (100%, $[M+H]^+$).

HRMS (ES) $C_{15}H_{18}N_2O_2$ $[M+H]^+$ requires 259.1441, found 259.1440.

Lewis Acid	Solvent	Yield (%)
$BF_3{\cdot}Et_2O$	DCM	32
$In(OTf)_3$	$EtNO_2$	36

Table 5

5-Ethyl-7-methyl-1,2,3,5,6,8a-hexahydro-indolizine 358



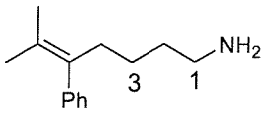
$BF_3{\cdot}Et_2O$ (34 µl, 0.27 mmol) was added to a stirred solution of imine **319** (63 mg, 0.27 mmol) in DCM (3 ml) at -78 °C under Ar. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight. The reaction was quenched with water and extracted with DCM. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 1-10% MeOH in DCM) to give bicycle **358** as dense brown oil (4.7 mg, 10%).

δ_H (300 MHz; $CDCl_3$) 1.05 (3H, t, J = 8 Hz, CH_3), 1.65-1.89 (4H, m, CH_2, C(2)H_2), 1.81 (3H, s, CH_3), 2.01 (1H, m, C(7)H_AH$_B$), 2.18 (1H, m, C(7)H$_A$$H_B$), 2.41 (2H, m,

$C(6)H_2$), 3.12 (1H, m $C(8)H_AH_B$), 3.32 (1H, m, C(1)H), 3.82 (1H, m, $C(8)H_AH_B$), 4.31 (1H, m, C(5)H), 5.30 (1H, m, C(4)H).

δ_C (100 MHz, $CDCl_3$) 10.4 (3), 21.6 (2), 23.3 (3), 24.2 (2), 25.3 (2), 29.6 (2), 51.9 (2), 58.0 (1), 58.3 (1), 116.6 (1), 131.8 (0).

6-Methyl-5-phenyl-5-hepten-1-amine 362



$BF_3{\cdot}Et_2O$ (38 μL, 0.30 mmol) was added to a stirred solution of imine **344** (97 mg, 0.30 mmol) in DCE (10 ml) at room temperature under Ar. The reaction mixture was slowly heated to 80 °C and was stirred at 80 °C overnight. The reaction was quenched with water and extracted with DCM. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 1-10% MeOH in DCM) to give the bicycle **344** as a dense brown oil (4 mg, 5%) and **362** as a dense brown oil (38 mg, 29%).

Data for **362**:

δ_H (300 MHz; $CDCl_3$) 1.27 (2H, m, CH_2), 1.42 (2H, m, CH_2), 1.53 (3H, s, CH_3), 1.80 (3H, s, CH_3), 1.88 (2H, br s, NH_2), 2.36 (2H, t, J = 8 Hz, $C(4)H_2$), 2.62 (2H, t, J = 7 Hz, $C(1)H_2$), 7.04-7.10 (2H, m, Ar), 7.20 (1H, m, Ar), 7.26-7.35 (2H, m, Ar).

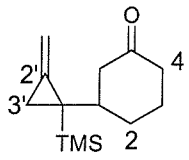
δ_C (100 MHz, $CDCl_3$) 20.1 (3), 22.1 (3), 25.4 (2), 33.3 (2), 34.0 (2), 42.0 (2), 125.7 (1), 127.8 (0), 127.8 (1), 128.9 (1), 135.1 (0), 144.0 (0).

LRMS (ES) *m/z* 204 (100%, $[M+H]^+$).

HRMS (ES) $C_{14}H_{22}N_1$ [M+H]+ requires 204.1747, found 204.1744.

5.5 Experimental for chapter 4

3-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-1-cyclohexanone 400



By a method modified from the method described by Peron.[17]

n-BuLi (2.4M in hexanes, 2.16 ml, 5.25 mmol) was added to a stirred solution of methylenecyclopropane (0.35 ml, 5.25 mmol) in THF (5 ml) at -78 °C under Ar. The reaction mixture was allowed to warm slowly to 10 °C, cooled to -78 °C and TMSCl (0.67 ml, 5.25 mmol) was added. The reaction mixture was allowed to warm slowly to 10 °C, cooled to -78 °C and *n*-BuLi (2.4M in hexanes, 2.16 ml, 5.25 mmol) was added. The reaction mixture was allowed to warm to 10 °C, cooled to -30 °C and cannulated to a stirred suspension of CuI (500 mg, 2.6 mmol) in THF (10 ml). The reaction mixture was stirred at -30 °C for 30 min, cooled to -78 °C and 2-cyclohexen-1-one (0.190 ml, 1.97 mmol) in THF (2.5 ml) and TMSCl (0.67 ml, 5.25 mmol) in THF (2.5 ml) were added over 30 min. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight. Reaction was quenched with aqueous saturated NH_4Cl and extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in diethyl ether (10 ml) and 2M HCl (10 ml) was added. The reaction mixture was stirred at room temperature for 48 h, extracted with diethyl ether, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 0-3% Ethyl acetate in petroleum ether) to give ketone **400** as colourless oil (380 mg, 87%).

ν_{max} (liq. film) 2951 (m), 1708 (s), 1247 (s), 832 (s).

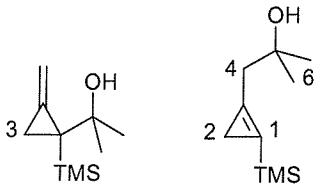
δ_H (300 MHz, $CDCl_3$) 0.03 (9H, s, CH_3), 0.92 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.03 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.41 (1H, m, CH_AH_B), 1.53 (1H, ddd, J = 3, 5, 13 Hz, CH_AH_B), 1.72 (1H, tt, J = 4, 13 Hz, CH), 1.93 (1H, m, CH_AH_B), 2.05 (1H, m, CH_AH_B), 2.18 (2H, m, CH_2), 2.36 (2H, m, CH_2).5.25 (1H, m, =CH_AH_B), 5.32 (=CH_AH_B).

δ_C (75 MHz, $CDCl_3$) -1.5 (3), 10.8 (2), 18.1 (0), 25.4 (2), 29.9 (2), 41.2 (2), 43.8 (1), 46.8 (2), 101.5 (2), 137.5 (0), 211.8 (0).

LRMS (CI) *m/z* 223 (10%, $[M+H]^+$), 73 (100%, $[SiMe_3]^+$).

HRMS (EI) $[M-H]^+$ $C_{13}H_{21}OSi$ requires 221.13617, found 221.13628.

2-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-propanol 401 and 2-methyl-1-[2-(1,1,1-trimethylsilyl)-1-cyclopropenyl]-2-propanol 407



401 **407**

Following a procedure by Binger.[14]

n-BuLi (2.4M in hexanes, 11.2 ml, 26.9 mmol) was added to a stirred solution of methylenecyclopropane (1.8 ml, 26.9 mmol) in THF (65 ml) at –78 °C under Ar. The reaction mixture was allowed to warm to 0 °C, cooled to –78 °C and TMSCl (3.41 ml, 26.9 mmol) was added. The reaction mixture was allowed to warm to 0 °C, cooled to –78 °C and *n*-BuLi (2.4M in hexanes, 11.2 ml, 26.9 mmol) was added. The reaction mixture was allowed to warm to 0 °C, cooled to –78 °C and acetone (1.97 ml, 26.9 mmol) was added. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 20 h, quenched with aqueous saturated NH_4Cl and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography to give alcohol **401** as yellow oil (2.02 g, 41%) and alcohol **407** as colourless oil (1.14 g, 23%).

Data for alcohol 401

ν_{max} (liq. film) 3459 (w), 2967 (m), 1461 (w), 1365 (m), 1326 (m), 1247 (s), 1177 (s), 1132 (s), 832 (s).

δ_H (300 MHz, $CDCl_3$) – 0.06 (9H, s, CH_3), 0.86 (1H, m, C(3)H_AH_B), 0.99 (1H, dt, J = 8, 2 Hz, C(3)H_AH_B), 1.26 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.45 (1H, br s, OH), 5.30 (1H, m, =CH_AH_B), 5.41 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) -0.6 (3), 9.4 (2), 24.6 (0), 28.0 (3), 30.6 (3), 71.1 (0), 101.9 (2), 137.4 (0).

LRMS (EI) *m/z* 169 (28%, $[M-CH_3]^+$), 184 (2%, $[M-H]^+$).

HRMS (EI) $C_9H_{17}OSi$ $[M-CH_3]^+$ requires 169.1049, found 169.1046.

Data for alcohol 407

ν_{max} (liq. film) 3370 (br, m), 2956 (s), 2847 (s), 1247 (s), 832 (s).

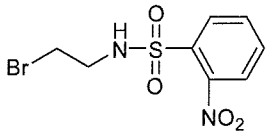
δ_H (300 MHz, $CDCl_3$) 0.19 (9H, m, CH_3), 0.87 (2H, m, C(2)H_2), 1.29 (6H, s, CH_3), 2.78 (2H, s, C(4)H_2).

δ_C (75 MHz, $CDCl_3$) -1.5 (3), 12.6 (2), 29.3 (3), 42.1 (2), 70.9 (0), 108.0 (0), 130.7 (0).

LRMS (CI) *m/z* 169 (56%, $[M-CH_3]^+$), 185 (M+H, 100%).

HRMS (EI) $C_9H_{17}OSi$ $[M-CH_3]^+$ requires 169.1049, found 169.1049.

***N*1-(2-Bromoethyl)-2-nitro-1-benzenesulfonamide 410**



Following a method described by Nagle.[133]

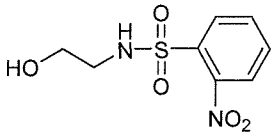
2-Nitrobenzene sulphonyl chloride (811 mg, 3.66 mmol) was added to a stirred solution of 2-bromoethylamine hydrochloride (500 mg, 2,44 mmol) and Et_3N (0.85 mmol, 6.1 mmol) in toluene (100 ml) at 0 °C under Ar. The reaction mixture was stirred at room temperature for 2 h, washed with aqueous saturated $NaHCO_3$, 2M $KHSO_4$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 4-10% ethyl acetate in petroleum ether) to give bromide **410** as pale brown solid (429 mg, 57%), m.p. 49-52 °C.

ν_{max} (liq. film) 3099 (m), 2358 (w), 1535 (s), 1358 (s), 1183 (s), 1158 (s), 1123 (s), 779 (s).

δ_H (300 MHz, $CDCl_3$) 3.45-3.59 (4H, m, CH_2), 5.87 (1H, t, J = 5 Hz, NH), 7.75-7.84 (2H, m, Ar), 8.15 (1H, m, Ar), 8.28 (1H, m, Ar).

δ_C (75 MHz, $CDCl_3$) 31.0 (2), 45.2 (2), 125.7 (1), 130.7 (1), 133.0 (1), 133.8 (1), 133.9 (0), 147.9 (0).

N1-(2-Hydroxyethyl)-2-nitro-1-benzenesulfonamide 413



Pyridine (1.26 ml, 14.32 mmol) was added to a stirred solution of 2-aminoethanol (0.86 ml, 14.32 mmol) and 2-nitrobenzene sulphonyl chloride (1.44 g, 6.51 mmol) in DCM (25 ml) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 2 h, quenched with water, washed with 2M sulphuric acid and saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 10-60% ethyl acetate in petroleum ether) to give alcohol **413** as white solid (732 mg, 58%), m.p. 78-80 °C.

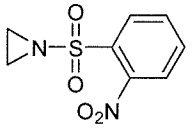
ν_{max} (liq. film) 2955 (m), 2922 (m), 2853 (m), 1727 (s), 1535 (m), 1358 (m), 1269 (s), 1121 (s).

δ_H (300 MHz, $CDCl_3$) 2.68 (1H, br s, OH), 3.23 (2H, m, CH_2), 3.71 (2H, m, CH_2), 7.71-7.77 (2H, m, Ar), 7.85 (1H, m, Ar), 8.11 (1H, m, Ar).

δ_C (75 MHz, $CDCl_3$) 45.6 (2), 61.0 (2), 125.3 (1), 130.9 (1), 132.8 (1), 133.3 (0), 133.7 (1), 147.9 (0).

LRMS (ES) *m/z* 247 (20%, M+H), 515 (100%, 2M+Na), 761 (50%, 3M+Na).

1-[(2-Nitrophenyl)sulfonyl]azirane 414



Following a method described by Berry.[136]

Toluenesulphonyl chloride (1.13 g, 5.95 mmol) and freshly ground KOH (1.21 g, 21.6 mmol) were added to a stirred solution of alcohol **413** (1.33 g, 5.41 mmol) in THF/diethyl ether (1:1, 30 ml) and the reaction mixture was heated to reflux for 45 min, cooled to room temperature and water was added. The reaction mixture was extracted with diethyl ether and the combined organic phases were dried over $MgSO_4$,

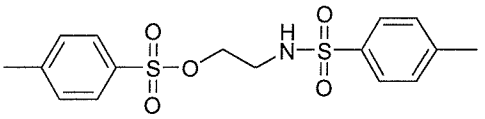
concentrated *in vacuo* and purified by column chromatography (silica gel, 20-80% ethyl acetate in petroleum ether) to give aziridine **414** as a yellow solid (484 mg, 39%), m.p. 98-100 °C and starting material (683 mg, 51%).

ν_{max} (liq. film) 3026 (m), 2698 (m), 2358 (m), 1365 (s), 1216 (s).

δ_H (300 MHz, $CDCl_3$) 2.63 (4H, s, CH_2), 7.67-7.84 (3H, m, Ar), 8.22 (1H, m, Ar).

δ_C (75 MHz, $CDCl_3$) 29.5 (2), 127.9 (1), 128.6 (0), 129.9 (0), 131.1 (1), 132.1 (1), 134.6 (1).

2-[(4-Methylphenyl)sulfonyl]aminoethyl 4-methyl-1-benzenesulfonate 417



Following a method described by McAuley.[138]

Ethanolamine was slowly added to a stirred suspension of tosyl chloride (13.27 g, 69.6 mmol) in pyridine (10 ml) at -50 °C under N_2. The reaction mixture was stirred at 0 °C for 24 h, ice was added and the yellow solid was filtered, washed with water and dissolved in DCM (200 ml). The organic layer was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure to give a pale yellow solid that was recrystallised from CCl_4 to give the tosylated ethanolamine **417** as pale yellow solid (11.58 g, 95%), m.p. 84-86 °C (lit.[176] m.p 82 °C).

ν_{max} (liq. film) 3274 (m), 2357 (w), 1737 (m), 1598 (m), 1357 (s), 1174 (s), 1150 (s), 909 (s).

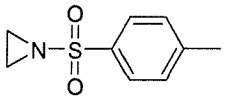
δ_H (300 MHz, $CDCl_3$) 2.44 (3H, s, CH_3), 2.47 (3H, s, CH_3), 3.22 (2H, "q", J = 5 Hz, CH_2), 4.05 (2H, t, J = 5Hz, CH_2), 4.91 (1H, t, J = 6 Hz, NH), 7.29-7.32 (2H, d, J = 8 Hz, Ar), 7.34-7.38 (2H, d, J = 7 Hz, Ar), 7.69-7.71 (2H, d, J = 8 Hz, Ar), 7.74-7.77 (2H, d, J = 8 Hz, Ar).

δ_C (75 MHz, $CDCl_3$) 21.5 (3), 21.7 (3), 42.1 (2), 68.7 (2), 127.0 (1), 127.9 (1), 129.8 (1), 130.0 (1), 132.1 (0), 136.5 (0), 143.8 (0), 145.4 (0).

LRMS (ES) *m/z* 370 (5%, $[M+H]^+$), 392 (70%, $[M+Na]^+$).

^1H NMR agrees with Herges.[176]

1-[(4-Methylphenyl)sulfonyl]azirane 418



Following a method described by Martin.[139]

KOH (3.42 g, 61.07 mmol) in water (18 ml) was added to a stirred suspension of **417** in toluene (45 ml) at room temperature. A pink solution and a white solid were formed immediately. The reaction mixture was stirred at room temperature for 3 h, shaken with water and the toluene layer was dried over $MgSO_4$ and concentrated under reduced pressure to give tosylaziridine **418** as pale yellow solid (1.74 g, 65 %), m.p 52-54 °C (lit, m.p. 52 °C[176] and 63-64 °C[139]).

ν_{max} (liq. film) 2923 (w), 2357 (w), 1737 (s), 1592 (m), 1489 (m), 1317 (s), 1231 (s), 1155 (s).

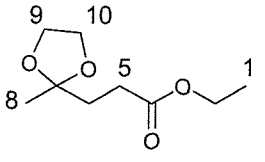
δ_H (300 MHz, $CDCl_3$) 2.36 (4H, s, CH_2), 2.45 (6H, s, CH_3), 7.33-7.36 (2H, d, J = 8 Hz, Ar), 7.81-7.84 (2H, d, J = 8 Hz, Ar).

δ_C (75 MHz, $CDCl_3$) 21.6 (3), 27.3 (2), 127.9 (1), 129.7 (1), 134.7 (0), 144.6 (0).

LRMS (ES) *m/z* 198 (30%, M+H), 220 (30%, M+Na), 413 (20%, M+H+H_2O).

^{1}H NMR agrees with Martin.[139]

Ethyl-3-(2-methyl-1,3-dioxolan-2-yl)propanoate 426



Following a method described by Peron.[17]

A solution of ethyl levulinate (28.0 g, 144 mmol), ethylene glycol (28.0 g, 451 mmol) and toluenesulphonic acid (350 mg, 2 mmol) in toluene (210 ml) was refluxed for 24 h. Water formed in the reaction was removed with a Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo*, taken up in diethyl ether, washed with aqueous saturated $NaHCO_3$ and dried oven $MgSO_4$. Ether was removed *in vacuo* and the residue

was purified by distillation under reduced pressure to give the protected ketone **426** as colourless oil (42.1 g, 66%).

ν_{max} (liq. film) 2940 (m), 2880 (m), 2362 (m), 2337 (m), 1730 (s), 1373 (m), 1092 (s), 1037 (s), 856 (s).

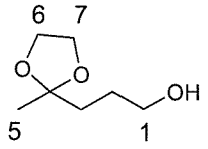
δ_H (300 MHz, $CDCl_3$) 1.26 (3H, t, J = 7 Hz, $C(1)H_3$), 1.33 (3H, s, $C(8)H_3$), 2.02 (2H, t, J = 8 Hz, $C(6)H_2$), 2.39 (2H, t, J = 8 Hz, $C(5)H_2$), 3.92-3.97 (4H, m, $C(9)H_2$, $C(10)H_2$), 4.13 (2H, q, J = 7 Hz, $C(2)H_2$).

δ_C (75 MHz, $CDCl_3$) 14.2 (3), 24.0 (3), 29.1 (2), 33.9 (2), 60.3 (2), 64.8 (2), 109.1 (0), 173.6 (0).

LRMS (CI) *m/z* 189 (100%, $[M+H]^+$).

Spectroscopic data agrees with Peron.[17]

3-(2-Methyl-1,3-dioxolan-2-yl)1-propanol 427



Following a method described by Peron.[17]

Ester **426** in THF (10 ml) was added to a stirred suspension of $LiAlH_4$ (1.14 g, 29 mmol) in THF (50 ml) at 0 °C. The reaction mixture was stirred at room temperature for 4 h, and diethyl ether and 2M NaOH were added. The reaction mixture was dried over $MgSO_4$ and concentrated *in vacuo* to give the alcohol **427** as colourless oil (2.15 g, 100 %).

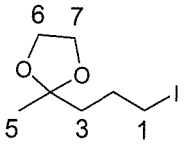
ν_{max} (liq. film) 3392 (m), 2950 (m), 2875 (m), 2367 (m), 2337 (m), 1378 (m), 1208 (m), 1052 (s), 846 (s).

δ_H (300 MHz, $CDCl_3$) 1.35 (3H, s, $C(5)H_3$), 1.64-1.81 (4H, m, $C(2)H_2$, $C(3)H_2$), 3.65 (2H, q, J = 6 Hz, $C(1)H_2$), 3.94-3.99 (4H, m, $C(6)H_2$, $C(7)H_2$).

δ_C (75 MHz, $CDCl_3$) 23.7 (3), 25.5 (2), 35.2 (2), 63.0 (2), 64.6 (2), 110 (0).

Spectroscopic data agrees with Peron.[17]

2-(3-Iodopropyl)-2-methyl-1,3-dioxolane 428



Following a method described by Peron.[17]

Triphenylphosphine (5.4 g, 13.7 mmol), imidazole (1.6 g, 20.6 mmol) and iodine (5.57 g, 13.7 mmol) were added to a stirred solution of alcohol **427** (2.0 g, 13.7 mmol) in a mixture of diethyl ether (120 ml) and acetonitrile (40 ml). The reaction mixture was stirred at room temperature for 10 min and then diluted with diethyl ether (100 ml). The reaction mixture was washed with aqueous saturated $Na_2S_2O_3$ (100 ml) and water (100ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 1-30% ethyl acetate in petroleum ether) to give **428** as pale yellow oil (2.76 g, 79%).

ν_{max} (liq. film) 2980 (m), 2950 (m), 2874 (m), 1373 (s), 1223 (s), 1112 (s), 1037 (s), 861 (s).

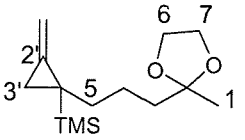
δ_H (300 MHz, $CDCl_3$) 1.32 (3H, s, $C(5)H_2$), 1.75 (2H, m, $C(3)H_2$), 1.95 (2H, m, $C(2)H_2$), 3.22 (2H, t, J = 7 Hz, $C(1)H_2$), 3.94-3.95 (4H, m, $C(6)H_2$, $C(7)H_2$).

δ_C (75 MHz, $CDCl_3$) 7.0 (2), 24.0 (3), 28.2 (2), 39.8 (2), 64.7 (2), 109.4 (0).

LRMS (CI) *m/z* 257 (100%, $[M+H]^+$).

Spectroscopic data agrees with Peron.[17]

Trimethyl{1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-2-methylenecyclopropyl} silane 429



Following a method described by Peron.[17]

n-BuLi (1.63 ml, 2.4M solution in hexanes, 3.91 mmol) was added to a stirred solution of methylenecyclopropane (0.264 ml, 3.91 mmol) in THF (40 ml) at -50 °C under Ar.

The reaction mixture was allowed to warm to 10 °C during 2 h, cooled to -78 °C and TMSCl (0.48 ml, 3.91 mmol) was added. The reaction mixture was allowed to warm to 0 °C during 1 h, cooled to –78 °C and *n*-BuLi (1.63 ml, 2.4M solution in hexanes, 3.91 mmol) was added. The reaction mixture was allowed to warm to 0 °C during 1 h, cooled to -78 °C and iodide **428** (1.0 g, 3.91 mmol) in THF (5 ml) was added. The reaction mixture was allowed to warm to room temperature and stirred at room temperature overnight. The reaction mixture was quenched with aqueous saturated NH_4Cl and extracted with diethyl ether. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2-5% ethyl acetate in petroleum ether) to give the protected ketone **429** as colourless oil (810 mg, 82%).

ν_{max} (liq. film) 2950 (m), 2880 (m), 2367 (m), 1248 (s), 1067 (s), 831 (s).

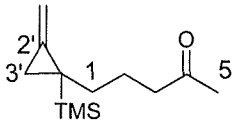
δ_H (300 MHz, $CDCl_3$) -0.00 (9H, s, CH_3), 0.82 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.15 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.31 (3H, s, C(1)H_2), 1.40-1.61 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2), 3.89-3.99 (4H, m, C(6)H_2, C(7)H_2), 5.20 (1H, m, =CH_AH_B), 5.25 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –2.6 (3), 12.4 (2), 14.0 (0), 22.8 (2), 23.8 (3), 35.8 (2), 39.4 (2), 64.6 (2), 100.2 (2), 110 (0), 139.8 (0).

LRMS (CI) *m/z* 255 (4%, $[M+H]^+$).

Spectroscopic data agrees with Peron[17]

5-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanoate 422



Following a method described by Peron.[17]

Concentrated aqueous HCl (1.5 ml) was added to a stirred solution of **429** (760 mg, 4.2 mmol) in acetone (90 ml) and water (10 ml). The reaction mixture was stirred at room temperature overnight and concentrated *in vacuo*. Diethyl ether was added and the reaction mixture was washed with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with diethyl ether, and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica

gel, 2-5% ethyl acetate in petroleum ether) to give ketone **422** as pale yellow oil (479 mg, 83%).

ν_{max} (liq. film) 2955 (w), 2895 (w), 1715 (s), 1408 (w), 1358 (w), 1248 (s), 831 (s).

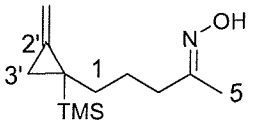
δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, CH_3), 0.81 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.05 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.32 (1H, m, CH_AH_B), 1.46 (1H, m, CH_AH_B), 1.59 (2H, m, CH_2), 2.12 (3H, s, CH_3), 2.38 (2H, t, J = 7 Hz, C(2)H_2), 5.20 (1H, m, =CH_AH_B), 5.26 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –2.6 (3), 12.5 (2), 13.7 (0), 22.5 (2), 29.9 (3), 35.1 (2), 43.9 (2), 100.3 (2), 139.6 (0), 208.9 (0).

LRMS (CI) *m/z* 211 (45%, $[M+H]^+$).

Spectroscopic data agrees with Peron.[17]

5-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanone oxime 424



Following a method described by Fowler.[143]

Ketone **422** (3.0 g, 14.3 mmol) in water/ethanol (1:1, 2 ml) was added to a stirred solution of K_2CO_3 (3.95 g, 28.6 mmol) and $H_2NOH{\cdot}HCl$ (1.99 g, 28.6 mmol) in water/ethanol (1:1, 11 ml). The suspension was refluxed for 3 h and then allowed to warm to room temperature. The reaction mixture was extracted with diethyl ether and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 5-10% ethyl acetate in petroleum ether) to give oxime **424** as a colourless oil (2.70 g, 84%).

ν_{max} (liq. film) 3231 (br w), 2952 (m), 2898 (m), 1244 (m), 867 (m), 830 (s).

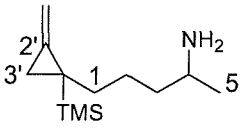
δ_H (300 MHz, $CDCl_3$) –0.01 (9H, s, CH_3), 0.81 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.05 (1H, ddd, J = 8, 2, 2 Hz, C(3')H_AH_B), 1.26-1.60 (4H, m, C(1)H_2, C(2)H_2), 1.86 (3H, s, C(5)H_3), 2.14 (2H, t, J = 7 Hz, C(3)H_2), 5.20 (1H, m, =CH_AH_B), 5.25 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) –2.6 (3), 12.5 (2), 13.2 (3), 13.7 (0), 24.9 (2), 35.2 (2), 36.1 (2), 100.2 (2), 139.7 (0), 158.6 (0).

LRMS (ES) *m/z* 226 (20%, $[M+H]^+$).

HRMS (ES) $C_{12}H_{24}NOSi$ $[M+H]^+$ requires 226.1622, found 226.1624.

5-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanamine 423



Following a method described by Liu.[144]

Oxime **424** (2.68 g, 11.9 mmol) in diethyl ether (10 ml) was added dropwise to a stirred solution of $LiAlH_4$ in diethyl ether (1.0 M, 36 ml, 36 mmol). The reaction mixture was refluxed for 20 h, diluted with diethyl ether, cooled to 0 °C and 2M NaOH was added. The reaction mixture was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2-10% MeOH, 0.2% Et_3N in DCM) to give amine **423** as a pale yellow oil (2.10 g, 84%).

ν_{max} (liq. film) 2957(m), 2925 (m), 2944 (w), 1249 (s), 835 (s).

δ_H (300 MHz, $CDCl_3$) – 0.01 (9H, s, CH_3), 0.81 (1H, m, C(3')H_AH_B), 1-02-1.07 (4H, m, C(3')H_AH_B, C(5)H_3), 1.25-1.51 (6H, m, C(1)H_2, C(2)H_2, C(3)H_2), 1.55 (2H, br s, NH_2), 2.86 (1H, sext, J = 6 Hz, C(4)H), 5.19 (1H, m, =CH_AH_B), 5.25 (1H, m, =CH_AH_B).

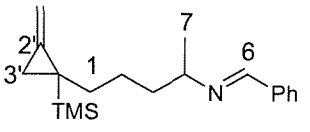
δ_C (75 MHz, $CDCl_3$) –2.6 (3), 12.4 (2), 14.0 (0), 23.7 (3), 25.1 (2), 35.6 (2), 40.4 (2), 46.8 (1), 100.0 (2), 140.0 (0).

LRMS (ES) *m/z* 212 (100%, $[M+H]^+$).

HRMS (ES) $C_{12}H_{26}Nsi$ $[M+H]^+$ requires 212.1829, found 212.1826.

Anal. Calcd for $C_{12}H_{25}NSi{\cdot}0.4CH_3OH$: C, 66.42; H, 11.96, N; 6.25. Found C, 66.65; H, 11.74; N, 6.43.

*N*2-[(*E*)-1-Phenylmethylidene]-5-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanamine 380

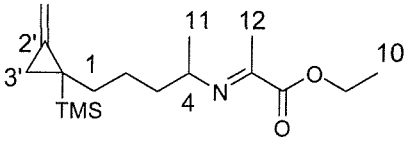


A solution of amine **423** (222 mg, 1.05 mmol) and benzaldehyde (107 µl, 1.05 mmol) in DCM (5 ml) was stirred at room temperature under Ar over 4 Å molecular sieves for

2 h, filtered and concentrated under reduced pressure to give the imine **380** as pale yellow oil (281 mg, 89%).

δ_H (300 MHz, $CDCl_3$) –0.06 (9H, s, CH_3), 0.78 (1H, ddd, J = 1.5,4, 8 Hz, C(3')H_AH_B), 1.02 (1H, ddd, J = 2.5, 4, 8 Hz, C(3')H_AH_B), 1.22-1.63 (9H, m, C(1)H_2, C(2)H_2, C(3)H_2, C(7)H_3), 3.29 (1H, m, C(4)H), 5.15 (1H, m, =CH_AH_B), 5.21 (1H, m, =CH_AH_B), 7.40-7.44 (3H, m, Ar), 7.74 (2H, br s, Ar), 8.27 (1H, s, C(6)H).

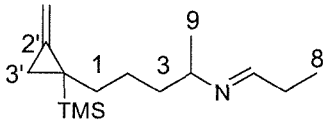
Ethyl 2-(1-methyl-4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl] butylimino)propanoate 430



A solution of amine **423** (205 mg, 0.97 mmol) and benzaldehyde (108 µl, 0.97 mmol) in DCM (3 ml) was stirred at room temperature under Ar over 4 Å molecular sieves for 2 h, filtered and concentrated *in vacuo* to give the imine **430** with some impurities as yellow oil (258 mg, 86%).

δ_H (300 MHz, $CDCl_3$) –0.02 (9H, m, CH_3), 0.77 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.04 (1H, m, C(3')H_AH_B), 1.10-1.62 (14H, m, C(1)H_2, C(2)H_2, C(3)H_2, C(9)H_2, C(10)H_3, C(11)H_3), 3.58 (1H, m, C(4)H), 4.18-4.39 (3H, m, C(12)H_3), 5.20 (1H, m, =CH_AH_B), 5.23 (1H, m, =CH_AH_B).

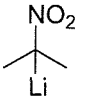
***N*2-[(*E*)-Propylidene]-5-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanamine 431**



A solution of amine **423** (200 mg, 0.95 mmol) and benzaldehyde (68 µl, 0.95 mmol) in DCM (3 ml) was stirred at room temperature under Ar over 4 Å molecular sieves for 4 h, filtered and concentrated *in vacuo* to give the imine **431** with some impurities as a yellow oil (173 mg, 73%).

δ_H (300 MHz, $CDCl_3$) –0.03 (9H, s, CH_3), 0.77 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 0.94-1.52 (15H, C(3')H_AH_B, C(1)H_2, C(2)H_2, C(3)H_2, C(7)H_2, C(8)H_3, C(9)H_3), 2.24 (1H, ddt, J = 8, 5,5 Hz, C(4)H), 5.17 (1H, m, =CH_AH_B), 5.23 (1H, m, =CH_AH_B), 7.60 (1H, t, J = 5 Hz, C(6)H).

19. Lithium salt of 2-nitropropane 433



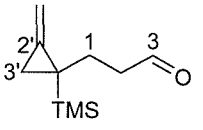
Following a method described by Linton.[145]

Lithium pieces (0.36 g, 51.9 mmol) were added to methanol (250 ml) at 0 °C under Ar, and the reaction mixture was stirred at room temperature until all lithium was consumed. 2-Nitropropane (9.30 g, 104.5 mmol) was added and the reaction mixture was stirred at 5 °C for 12 h, concentrated under reduced pressure to 25 ml and freshly distilled and degassed diethyl ether (200 ml) was added, which caused the product to precipitate. The solid was collected by filtration and dried under reduced pressure to give **433** as white solid (4.90 g, 100%).

δ_H (300 MHz, DMSO) 1.83 (6H, s, CH_3).

Spectroscopic data agrees with Linton.[145]

3-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]propanal 441



Following a method described by Patient.[114]

Dimethylsulphoxide (2.11 ml, 39.8 mmol) in DCM (13 ml) was added to a stirred solution of oxalyl chloride (1.35 ml, 19.9 mmol) in DCM (38 ml) under N_2 keeping the temperature of the reaction mixture under -60 °C. The reaction mixture was stirred for 5 min and alcohol **302** (3.18 g, 17.3 mmol) was added keeping the temperature of the reaction mixture below -60 °C. The reaction mixture was stirred for 45 min and Et_3N

(11.1 ml, 79.5 mmol) was added. The reaction mixture was allowed to warm to –10 °C over 2 h and was quenched with water. The reaction mixture was extracted with DCM and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 1-3% ethyl acetate in petroleum ether) to give aldehyde **441** as colourless oil (2.16 g, 68%).

ν_{max} (liq. film) 2953 (w), 2717 (w), 1724 (s), 1409 (w), 1248 (s), 832 (s).

δ_H (300 MHz, $CDCl_3$) 0.01 (9H, s, CH_3), 0.83 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.08 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.73 (1H, ddd, J = 7, 10, 14 Hz, C(1)H_AH_B), 1.94 (1H, ddd, J = 7, 9, 14 Hz, C(1)H_AH_B), 2.42 (2H, m, C(2)H_2), 5.21 (1H, m, =CH_AH_B), 5.31 (1H, m, =CH_AH_B), 9.74 (1H, t, J = 2 Hz, C(3)H).

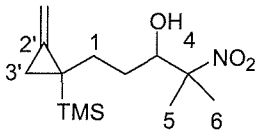
δ_C (75 MHz, $CDCl_3$) -2.9 (3), 12.0 (2), 12.8 (0), 26.6 (2), 42.0 (2), 101.4 (2), 138.5 (0), 202.5 (1).

LRMS (EI) 182 (10%,$[M]^+$), 167 (22%, $[M\text{-}CH_3]^+$), 110 (20%, $[M\text{-}SiMe_3]^+$), 73 (100%, $[SiMe_3]^+$).

HRMS (EI) $C_{10}H_{17}Osi$ $[M\text{-}H]^+$ requires 181.10487, found 181.10464.

NMR data agrees with Patient.[114]

4-Methyl-1-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-4-nitro-3-pentanol 442



Following a method described by Hamilton.[145]

DBU (0.12 ml, 0.87 mmol) was added to a stirred solution of aldehyde **441** (720 mg, 3.96 mmol) and 2-nitropropane (0.71 ml, 7.91 mmol) in THF. The solution turned immediately yellow. The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo* and partitioned between DCM and 10% HCl. The organic layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 0-1% ethyl acetate in petroleum ether) to give nitroalcohol **442** as a mixture of isomers in approximately 1:1 ratio as a colourless oil (663 mg, 62%).

ν_{max} (liq. film) 3469 (br w), 2952 (m), 1536 (s), 1455 (m), 1347 (s), 1116 (m), 1079 (m).

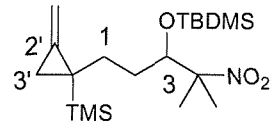
δ_H (300 MHz, $CDCl_3$) -0.09, 0.02 (9H, 2s, CH_3), 0.84 (1H, m, C(3')H_AH_B), 1.08 (1H, m, C(3')H_AH_B), 1.05-2.16 (10H, m, C(1)H_2, C(2)H_2, C(5)H_3, C(6)H_3), 4.00 (1H, m, C(3)H), 5.22 (1H, m, =CH_AH_B), 5.30 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) -2.7, -2.6 (3), 12.0, 12.7 (2), 13.4 (0), 20.1, 20.3 (3), 23.8, 23.9 (3), 29.6, 29.8 (2), 31.6, 32.2 (2), 75.7, 76.2 (1), 92.1 (0), 100.7, 100.8 (2), 139.1, 139.4 (0).

LRMS (CI) *m/z* 272 (6%, $[M+H]^+$), 73 (100%, $[SiMe_3]^+$).

HRMS (EI) $C_{13}H_{25}NO_3Si$ $[M]^+$ requires 271.16037, found 271.16103.

[1-(3-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-4-methyl-4-nitropentyl)-2-methylenecyclopropyl](trimethyl)silane 447



Following a method described by Williams.[148]

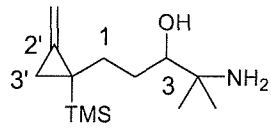
2,6-Lutidine (0.54 ml, 4.79 mmol) and TBDMSOTf (2.20 ml, 9.58 mmol) were added to a stirred solution of nitroalcohol **442** (650 mg, 2.39 mmol) in DCM (70 ml) at room temperature under N_2. The reaction mixture was stirred at room temperature for 24 h, diluted with DCM, washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 0-1% ethyl acetate in petroleum ether) to give the protected alcohol **447** as a mixture of isomers in approximately 1:1 ratio, as a colourless oil (727 mg, 79%).

ν_{max} (liq. film) 2952 (m), 2855 (m), 2365 (w), 1734 (w), 1542 (s), 1470 (m), 1249 (s), 1106 (s), 1052 (s), 833 (s).

δ_H (300 MHz, $CDCl_3$) -0.03 - -0.01 (15H, overlapping singlets, CH_3), 0.80 (1H, m, C(3')H_AH_B), 0.85-0.87 (9H, m, CH_3), 1.03-1.07 (1H, m, C(3')H_AH_B), 1.23-1.88 (4H, m, C(1)H_2, C(2)H_2), 1.47 (3H, s, CH_3), 1.53 (3H, s, CH_3), 4.10 (1H, m, C(3)H), 5.20 (1H, m, =CH_AH_B), 5.28 (1H, br s, =CH_AH_B).

δ_C (100 MHz, $CDCl_3$) -4.9 (3), -3.9 (0), -3.0 (3), -2.7 (3), 11.9, 12.2 (2), 19.8, 19.9 (0), 23.6, 23.7 (3), 25.7 , 25.8 (3), 31.5, 31.6 (2), 32.3, 32.5 (2), 77.7, 77.8 (1), 92.4, 92.5 (0), 100.6, 100.7 (2), 139.0 (0).

4-Amino-4-methyl-1-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-3-pentanol 443



Following a method described by Seebach.[149]

Nitroalcohol **447** (728 mg, 1.89 mmol) in diethyl ether (5 ml) was slowly added to a stirred solution of $LiAlH_4$ in diethyl ether (7.6 ml, 1.0 M, 7.6 mmol) at room temperature under N_2, and the reaction mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature, diluted with diethyl ether and 2M NaOH was added until all excess $LiAlH_4$ was consumed. The reaction mixture was dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (silica gel, 2-10% of 50% saturated NH_3 in MeOH in DCM) to give amine **443** as a mixture of isomers in approximately 1:1 ratio, as colourless oil (200 mg, 44%).

ν_{max} (liq. film) 3500 (br, m), 2958 (m), 1247 (s), 833 (s).

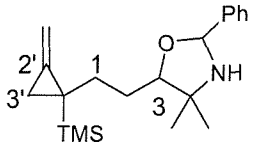
δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, CH_3), 0.85 (1H, m, C(3')H_AH_B), 0.96-2.00 (5H, m, C(1)H_2, C(2)H_2, C(3')H_AH_B), 1.02 (6H, s, CH_3), 1.11 (6H, s, CH_3), 3.10 (1H, m, C(3)H), 5.20 (1H, m, =CH_AH_B), 5.27 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) -2.6 (3), 11.9, 12.4 (2), 13.79, 13.84, 13.85 (0), 28.65, 28.69 (2), 29.48, 29.75 (2), 32.3 (3), 32.8 (3), 52.9 (0), 78.3, 78.5 (1), 100.2 (2), 139.9 (0).

MS (ES) *m/z* 242 (100%, $[M+H]^+$), 283 (10%, $[M+MeCN+H]^+$).

HRMS (ES) $C_{13}H_{27}NOSi$ $[M+H]^+$ requires 242.1935, found 242.1936.

4,4-Dimethyl-5-2-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]ethyl-2-phenyl-1,3-oxazolane 448

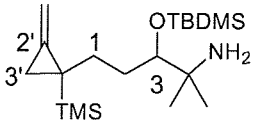


Following a method described by Kadouri-Puchot.[150]

A solution of benzaldehyde (80 μl, 0.79 mmol) and aminoalcohol **443** (190 mg, 0.79 mmol) in THF (5 ml) was stirred under N_2 over 4 Å molecular sieves at room temperature for 4 h, filtered and concentrated *in vacuo* to give the oxazolane **448** as a colourless oil (205 mg, 79%).

δ_H (300 MHz, $CDCl_3$) 0.02 (9H, s, CH_3), 0.89 (1H, m, C(3')H_AH_B), 1.07-1.40 (11H, m, C(1)H_2, C(2)H_2, C(3')H_AH_B, 2CH_3), 3.43 (1H, m, C(3)H), 3.57 (1H, m, C(3)H), 3.75 (1H, m, C(3)H), 5.23 (1H, m, =CH_AH_B), 5.28 (1H, m, =CH_AH_B), 5.45 (1H, s, C(6)H), 5.63 (1H, s, C(6)H), 7.30-7.68 (4H, m, Ar), 7.89 (1H, m, Ar).

2-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1,1-dimethyl-4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]butylamine 445



Following a method described by Boger.[151]

2,6-Lutidine (0.40 ml, 3.55 mmol) and TBDMSOTf (0.723 ml, 3.15 mmol) were added to a stirred solution of aminoalcohol **443** (190 mg, 0.788 mmol) in DCM (15 ml) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 18 h, washed twice with aqueous saturated $NaHCO_3$ and twice with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 0-10% MeOH in DCM), to give the protected alcohol **445** as a mixture of isomers as a yellow oil (211 mg, 75%).

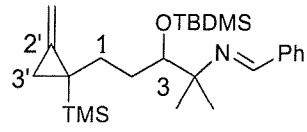
ν_{max} (liq. film) 2956 (m), 2930 (m), 2857 (m), 1248 (s), 1088 (s), 832 (s).

δ_H (300 MHz, $CDCl_3$) -0.01 (6H, s, CH_3), 0.07 (9H, s, CH_3), 0.90-0.92 (10H, m, $3CH_3$, C(3')H_AH_B), 1.02-1.06 (7H, m, $2CH_3$, C(3')H_AH_B), 1.26-1.83 (4H, m, $2CH_2$), 2.23 (2H, m, NH_2), 3.22 (1H, m, CHO, isomer a), 3.47 (1H, m, CHO, isomer b), 4.41 (1H, m, $=CH_AH_B$, isomer a), 4.47 (1H, m, $=CH_AH_B$, isomer b), 4.67 (1H, m, $=CH_AH_B$, isomer b), 4.87 (1H, m, $=CH_AH_B$, isomer a), 5.19 (1H, m, $=CH_AH_B$, isomer c), 5.25 (1H, m, $=CH_AH_B$, isomer c).

LRMS (ES) *m/z* 356.4 (100%, $[M+H]^+$), 397.4 (8%, $[M+K]^+$).

HRMS (ES) $C_{19}H_{41}NOSi_2$ $[M+H]^+$ requires 356.2800, found 356.2800.

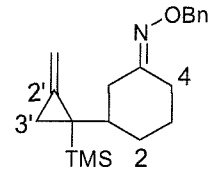
_N_2-[(_E_)-1-Phenylmethylidene]-3-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-2-methyl-5-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanamine 449



A solution of amine **445** (183 mg, 0.514 mmol) and benzaldehyde (52 µl, 0.514 mmol) in DCM (10 ml) was stirred over 4 Å molecular sieves under N_2 for 2 h, filtered and concentrated *in vacuo* to give imine **449** as yellow oil (192 mg, 84%).

δ_H (300 MHz, $CDCl_3$) -0.06-0.12 (15H, m, CH_3), 0.88 (10H, m, C(3')H_AH_B, CH_3), 1.19-1.21 (3H, C(3')H_AH_B, CH_2), 1.59 (1H, m, CH_AH_B), 1.74 (1H, m, CH_AH_B), 3.60 (1H, m, C(3)H, isomer a), 3.85 (1H, m, C(3)H, isomer b), 4.56 (2H, m, $=CH_2$, isomer a), 5.15 (1H, m, $=CH_AH_B$, isomer b), 5.20 (1H, m, $=CH_AH_B$, isomer b), 7.40 (3H, br s, Ar), 7.72-7.75 (2H, m, Ar), 8.25 (1H, m, N=CH).

3-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-1-cyclohexanone *O*1-benzyloxime 452



Following a method described by Booth.[152]

A solution of ketone **400** (78 mg, 0.351 mmol) and O-benzylhydroxylamine hydrochloride (224 mg, 1.41 mmol) in pyridine (4 ml) was stirred at room temperature for 48 h. Pyridine was removed *in vacuo* and the residue was diluted with DCM. The solution was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2-10% ethyl acetate in petroleum ether) to give benzyl oxime **452** as a mixture of isomers in approximately 1:1 ratio, as colourless oil (99 mg, 86%).

ν_{max} (liq. film) 2952 (w), 2930 (w), 1452 (m), 1248 (s).

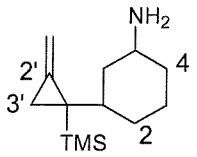
δ_H (300 MHz, $CDCl_3$) 0.02 (9H, s, CH_3), 0.92 (1H, m, C(3')H_AH_B), 1.02 (1H, m, C(3')H_AH_B), 1.14-1.98 (7H, m, C(1)H, C(2)H_2, C(3)H_2, C(4)H_AH_B, C(6)H_AH_B), 2.37 (1H, m, CH_AH_B), 3.36 (1H, m, CH_AH_B), 5.06 (2H, s, CH_2, isomer a), 5.07 (2H, s, CH_2, isomer b), 5.25 (1H, m, =CH_AH_B), 5.30 (1H, m, =CH_AH_B), 7.29-7.36 (5H, m, Ar).

δ_C (75 MHz, $CDCl_3$) -1.7, -1.4 (3), 10.44, 11.0 (2), 18.3, 18.5 (0), 24.9, 25.0 (2), 30.3, 30.4 (2), 30.9, 31.8 (2), 42.0, 44.0 (1), 75.0, 75.2 (2), 101.0, 101.1 (2), 127.4, 127.5 (1), 127.7, 127.9 (1), 128.2, 128.3 (1), 137.9, 137.93 (0), 138.2, 138.3 (0), 160.6, 160.7 (0).

LRMS (ES) *m/z* 328 (40%, $[M+H]^+$).

HRMS (ES) $C_{20}H_{30}NOSi$ $[M+H]^+$ requires 328.2091, found 328.2094.

3-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]cyclohexylamine 453



Benzyl oxime **452** (99 mg, 0.303 mmol) in diethyl ether (2 ml) was slowly added to a stirred solution $LiAlH_4$ in diethyl ether (1.0 M, 0.50 ml, 0.50 mmol) and diethyl ether (2 ml), and the reaction mixture was stirred at room temperature overnight. Reaction mixture was diluted with diethyl ether, excess $LiAlH_4$ was quenched with 2M NaOH and the reaction mixture was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **453** as a mixture of isomers in approximately 1:1 ratio, as pale yellow oil (61 mg, 90%).

ν_{max} (liq. film) 3064 (w), 2923 (m), 2853 (m), 1448 (w), 1247 (s), 833 (s).

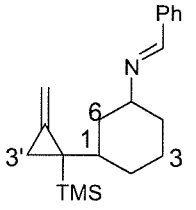
δ_H (300 MHz, $CDCl_3$) 0.03 (9H, s, CH_3), 0.86 (1H, m, C(3')H_AH_B), 0.96-1.25 (4H, m, C(3')H_AH_B), C(1)H, CH_2), 1.39-1.89 (6H, m, $3CH_2$), 2.28 (2H, s, NH_2), 3.32 (1H, m, C(5)H), 5.18 (1H, m, =CH_AH_B), 5.24 (1H, m, =CH_AH_B).

δ_C (75 MHz, $CDCl_3$) -1.3 (3), 10.9, 11.3 (2), 18.4, 18.5 (0), 20.3 (2), 25.0 (2), 30.4, 31.0 (2), 37.9 (2), 46.6 (1), 50.9 (1), 100.2, 100.3 (2), 138.9, 139.0 (0).

LRMS (ES) *m/z* 224 (70%, $[M+H]^+$), 265 (100%, $[M+MeCN+H]^+$).

HRMS (ES) $C_{13}H_{25}NSi$ $[M+H]^+$ requires 224.1829, found 224.1829.

***N*1-[(*Z*)-1-Phenylmethylidene]-3-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-1-cyclohexanamine 454**

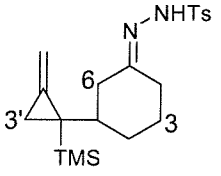


A solution of amine **453** (127 mg, 0.57 mmol) and benzaldehyde (58 µl, 0.57 mmol) in DCM (10 ml) was stirred at room temperature over 4 Å molecular sieves under N_2 for 2

h, filtered and concentrated *in vacuo* to give imine **454** with residual benzaldehyde as colourless oil (174 mg, 98%).

δ_H (300 MHz, $CDCl_3$) 0.02 (9H, s, CH_3), 0.86-1.89 (11H, m, C(1)H, C(3')H_2, C(2)H_2, C(3)H_2, C(4)H_2, C(6)H_2), 3.16 (1H, m, C(5)H), 5.21 (1H, m,=CH_AH$_B$), 5.25 (=C$H_A$$H_B$), 7.40-7.41 (3H, m, Ar), 7.72-7.77 (2H, m, Ar), 8.31 (1H, s, N=CH).

N'1-3-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]cyclohexyliden-4-methyl-1-benzenesulfonohydrazide 455

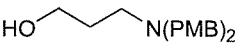


Following a method described by Patient.[114]

A solution of ketone **400** (120 mg, 0.541 mmol) and tosyl hydrazide (100.5 mg, 0.541 mmol) in hexane (5 ml) was refluxed for 1 h during which time a white precipitate was formed. Hexane was removed *in vacuo* and the residue was purified by column chromatography (2-5% ethyl acetate in petroleum ether) to give **455** as a mixture of isomers in approximately 1:1 ratio, as pale yellow solid (99 mg, 47%)., m.p 92-94 °C.

δ_H (300 MHz, $CDCl_3$) -0.01 (3H, s, CH_3), 0.94 (2H, m, C(3')H_2), 1.15-2.38 (9H, m, C(1)H, C(2)H_2, C(3)H_2, C(4)H_2, C(6)H_2), 2.43 (3H, s, CH_3),2.61 (2H, s, NH, isomer a), 2.65 (1H, s, NH, isomer b), 5.26 (2H, m, =CH_2), 7.30-7.33 (2H, d, J = 8 Hz, Ar), 7.83-7.85 (2H, d, J = 8 Hz, Ar).

3-[di-(4-Methoxybenzyl)amino]-1-propanol 463

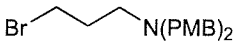


Et_3N (1.85 ml, 13.27 mmol) was added to a stirred solution of 3-bromo-1-propanol (1 ml, 11.06 mmol) in toluene (75 ml) at room temperature under N_2. The reaction mixture was heated to 80 °C overnight and the solvent was removed *in vacuo*. The residue was taken up in diethyl ether and aqueous saturated Na_2CO_3. The organic phase was washed with 2M HCl, and the combined aqueous phase was basified with aqueous saturated

$NaHCO_3$ and extracted with diethyl ether. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 5-50% ethyl acetate in petroleum ether) to give amine **463** as a dense colourless oil (746 mg, 26%).

δ_H (300 MHz, $CDCl_3$) 1.76 (2H, quint, J = 6 Hz, CH_2), 2.64 (2H, t, J = 6 Hz, CH_2), 3.52 (4H, s, $2CH_2$), 3.65 (2H, t, J = 6 Hz, CH_2), 3.81 (6H, s, $2CH_3$), 6.86-6.89 (4H, d, J = 7 Hz, Ar), 7.22-7.25 (4H, d, J = 7 Hz, Ar).

_N_-(3-Bromopropyl)-_N_,_N_-di(4-methoxybenzyl)amine 464

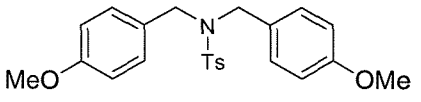


DMF (21 μl, 0.290 mmol) and thionyl bromide (0.270 ml, 3.48 mmol) were added sequentially to a stirred solution of alcohol **463** (740 mg, 2.90 mmol) in cyclohexane (15 ml) under N_2. The reaction mixture was stirred vigorously for 3 h, diluted with DCM until homogenous, washed with aqueous saturated $NaHCO_3$ and H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give bromide **464** as a yellow oil (700 mg, 64%).

δ_H (300 MHz, $CDCl_3$) 2.02 (2H, quint, J = 7 Hz, CH_2), 2.55 (2H, t, J = 7 Hz, CH_2), 3.40 (2H, t, J = 7 Hz, CH_2), 3.50 (4H, s, $2CH_2$), 3.81 (6H, s, $2CH_3$), 6.85-6.88 (4H, d, J = 9 Hz, Ar), 7.24-7.27 (4H, d, J = 9 Hz, Ar).

δ_C (75 MHz, $CDCl_3$) 30.6 (2), 31.9 (2), 51.4 (2), 55.2 (3), 57.5 (2), 113.6 (1), 129.9 (1), 131.6 (0), 158.6 (0).

_N_1,_N_1-Di(4-methoxybenzyl)-4-methyl-1-benzenesulfonamide 467



Following a method described by Lee.[155]

p-Methoxybenzyl chloride (3.17 ml, 23.4 mmol) in acetone (50 ml) was added drop wise over 3 h to a stirred suspension of *p*-toluenesulfonamide (2.0 g, 11.68 mmol) and K_2CO_3 (3.23 g, 23.4 mmol) in acetone (100 ml). The reaction mixture was refluxed for 72 h, cooled to room temperature, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, 0 - 50 % ethyl acetate in

petroleum ether) to give protected tosylamide **467** as white solid (4.4 g, 92%), m.p. 96–98 °C.

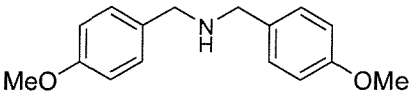
ν_{max} (liq. film) 2932 (w), 1609 (s), 1510 (s), 1250 (s), 1157 (s), 1031 (s).

δ_H (300 MHz, $CDCl_3$) 2.45 (3H, s, CH_3), 3.78 (6H, s, CH_3), 4.24 (4H, s, CH_2), 6.75-6.78 (2H, d, J = 9 Hz, Ar), 6.97-6.99 (2H, d, J = 9 Hz, Ar), 7.31 (1H, d, J = 8 Hz, Ar), 7.74 (1H, d, J = 8 Hz, Ar).

δ_C (75 MHz, $CDCl_3$) 21.5 (3), 49.5 (2), 55.2 (3), 113.7 (1), 127.2 (1), 127.7 (0), 129.6 (1), 129.9 (1), 137.8 (0), 143.1 (0), 159.0 (0).

LRMS (ES) *m/z* 429 (50%, $[M+NH_4]^+$), 450 (100%, $[M+K]^+$), 485 (90%, $[M+MeCN+MeOH+H]^+$).

_N,N_-Di(4-methoxybenzyl)amine 462



Following a method described by Johnson.[156]

$LiAlH_4$ (2.39 g, 62.8 mmol) was added portion wise to a stirred solution of amide **467** (3.80 g, 9.23 mmol) in THF (90 ml), and the reaction mixture was refluxed for 72 h. Reaction mixture was cooled to 0 °C, diluted with diethyl ether and excess $LiAlH_4$ was destroyed by drop wise addition of aq. 2M NaOH. Reaction mixture was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to give amine **462** as yellow oil (1.55 g, 65%).

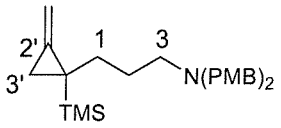
ν_{max} (liq. film) 2952 (w), 2933 (w), 2909 (w), 2833 (m), 1611 (m), 1509 (s), 1303 (s), 1240 (s).

δ_H (300 MHz, $CDCl_3$) 1.82 (2H, br s, NH_2), 3.75 (4H, s, CH_2), 3.82 (6H, s, CH_3), 6.87 – 6.90 (4H, d, J = 9 Hz, Ar), 7.26 – 7.29 (4H, d, J = 9 Hz, Ar).

δ_C (75 MHz, $CDCl_3$) 52.3 (2), 55.2 (3), 113.7 (1), 129.3 (1), 132.3 (0), 158.5 (0).

LRMS (ES) *m/z* 258 (100%, $[M+H]^+$), 299 (20%, $[M+MeCN+H]^+$), 515 (25%, $[2M+H]^+$).

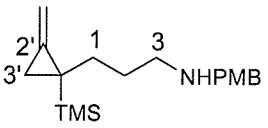
_N,N_-Di(4-methoxybenzyl)-_N_-3-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl] propylamine 468



n-BuLi (2.32 ml, 2.4M solution in hexanes, 5.56 mmol) was added to a stirred solution of methylenecyclopropane (2.8 ml, 2M solution in THF, 5.56 mmol) in THF (10 ml) at -78 °C under Ar. The reaction mixture was allowed to warm to 10 °C during 2 h, cooled to -50 °C and TMSCl (0.71 ml, 5.56 mmol) was slowly added. The reaction mixture was allowed to warm to 10°C during 2 h, cooled to – 50 °C and *n*-BuLi (2.32 ml, 2.4 M in hexanes, 5.56 mmol) was added. The reaction mixture was allowed to warm to 10 °C during 2 h, cooled to -50 °C and **464** (2.10 g, 5.56 mmol) in THF (20 ml) was added. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 1-20% ethyl acetate in petroleum ether) to give the protected amine **468** as colourless oil (692 mg, 31%).

δ_H (300 MHz, $CDCl_3$) -0.03 (9H, s, CH_3), 0.77 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.01 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.27-1.49 (4H, m, $2CH_2$), 2.32 (2H, t, J = 7 Hz, CH_2), 3.46 (4H, s, $2CH_2$), 3.81 (6H, s, $2CH_3$), 5.16 (1H, br s, =CH_AH_B), 5.23 (1H, br s, =CH_AH_B), 6.84-6.87 (4H, d, J = 9 Hz, Ar), 7.24-7.27 (4H, d, J = 9 Hz, Ar).

_N_-(4-Methoxybenzyl)-_N_-3-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl] propylamine 469



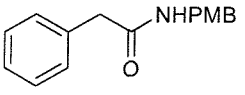
CAN (3.57 g, 6.51 mmol) was added to a stirred solution of amine **468** (690 mg, 1.63 mmol) in a mixture of THF (9 ml), MeCN (9 ml) and water (2 ml). The reaction

mixture was stirred at room temperature for 3 h, quenched with aqueous saturated $NaHCO_3$ and extracted with diethyl ether. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 0-2% MeOH in DCM) to give amine **469** as a colourless oil (271 mg, 75%).

δ_H (300 MHz, $CDCl_3$) -0.02 (9H, s, CH_3), 0.79 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.04 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.33-1.63 (4H, m, $2CH_2$), 2.59 (2H, t, J = 7 Hz, C(3)H_2), 2.75 (1H, br s, NH), 3.74 (2H, s, CH_2), 3.80 (3H, s, CH_3), 5.18 (1H, m, =CH_AH_B), 5.24 (1H, m, =CH_AH_B), 6.85-6.88 (2H, d, J = 9 Hz, Ar), 7.24-7.26 (2H, d, J = 9 Hz, Ar).

δ_C (75 MHz, $CDCl_3$) -2.6 (3), 12.4 (2), 13.6 (0), 28.2 (2), 33.2 (2), 49.2 (2), 53.0 (2), 55.2 (3), 100.2 (2), 113.8 (1), 129.6 (1), 131.3 (0), 139.7 (0), 158.7 (0).

N1-(4-Methoxybenzyl)-2-phenylacetamide 473

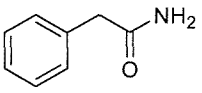


Phenylacetic acid (1.04 g, 7.65 mmol) was refluxed in thionyl chloride (10 ml) for 1 h, thionyl chloride was removed *in vacuo* and replaced with DCM (5 ml). The acid chloride solution was added to a stirred solution of *p*-methoxybenzyl amine (0.90 ml, 6.88 mmol) and Et_3N (2 ml) in DCM (10 ml), and the reaction mixture was stirred at room temperature under N_2 for 1 h. The reaction mixture was diluted with DCM, washed with aqueous saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (0-5% MeOH in DCM) to give amide **473** as a white solid (1.36 g, 77%).

δ_H (300 MHz, $CDCl_3$) 3.62 (2H, s, CH_2), 3.79 (3H, s, CH_3), 4.34 (1H, s, CH_AH_B), 4.36 (1H, s, CH_AH_B), 5.65 (1H, br s, NH), 6.81-6.85 (2H, m, Ar), 7.10-7.13 (2H, m, Ar), 7.26-7.38 (5H, m, Ar).

δ_C (75 MHz, $CDCl_3$) 43.1 (2), 43.8 (2), 55.3 (3), 114.0 (1), 127.4 (1), 128.9 (1), 129.0 (1), 129.4 (1), 130.1 (0), 134.7 (0), 158.9 (0), 170.7 (0).

2-Phenylacetamide 474

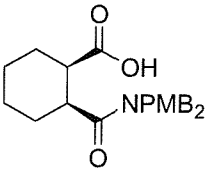


Following a method described by Davies.[153]

CAN (1.42 g, 2.59 mmol) in water (5 ml) was added to a stirred solution of amide **473** (220 mg, 0.862 mmol) in a mixture of MeCN (15 ml) and THF (5 ml). The reaction mixture was stirred at room temperature for 20 min, the solvent was removed *in vacuo* and replaced with DCM and half-saturated aqueous $NaHCO_3$. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a 1:1 mixture of *p*-methoxybenzaldehyde and **474** (177 mg, 76%).

δ_H (300 MHz, $CDCl_3$) 3.60 (2H, s, CH_2), 3.89 (3H, s, CH_3), 5.42 (1H, br s, NH_AH_B), 5.57 (1H, br s, NH_AH_B), 6.99-7.02 (2H, d, J = 9 Hz), 7.26-7.37 (5H, m, Ar), 7.83-7.85 (2H, d, J = 9 Hz, Ar), 9.89 (1H, s, CHO).

2-[Di(4-methoxybenzyl)amino]carbonyl-1-cyclohexanecarboxylic acid 459



Following a method described by Ling.[157]

DMAP (75 mg, 0.615 mmol) was added to a stirred solution of cis-1,2-cyclohexanedicarboxylic anhydride (95%, 1.396 g, 8.60 mmol) and amine **462** (1.58 g, 6.15 mmol) in a mixture of Et_3N and THF (1:1, 5.0 ml) and the reaction mixture was stirred at 70 °C overnight. The reaction was diluted with 10 % HCl (10 ml), extracted with ethyl acetate, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 10 % ethyl acetate in DCM) to give **459** as beige solid (2.50 g, 100%), m.p 158 -160 °C.

ν_{max} (liq. film) 3012 (w), 2943 (m), 2361 (w), 2432 (w), 1693 (s), 1645 (s), 1510 (s), 1240 (s), 1173 (s).

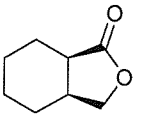
δ_H (300 MHz, $CDCl_3$) 1.36-1.99 (7H, m, $3CH_2$, CH_AH_B), 2.48 (1H, m, CH_AH_B), 2.64 (1H, CH), 3.30 (1H, m, CH), 3.78 (3H, s, CH_3), 3.80 (3H, s, CH_3), 4.14 (1H, d, J = 16 Hz, CH_AH_BN), 4.27 (1H, d, J = 16 Hz, CH_AH_BN), 4.52 (1H, d, J = 16 Hz, CH_AH_BN), 4.86 (1H, d, J = 16 Hz, CH_AH_BN), 6.84 (2H, d, J = 9 Hz, Ar), 6.90 (2H, d, J = 9 Hz, Ar), 7.10 (2H, d, J = 9 Hz, Ar), 7.15 (2H, d, J = 9 Hz, Ar).

δ_C (75 MHz, $CDCl_3$) 22.9 (2), 23.8 (2), 26.1 (2), 27.6 (2), 39.5 (1), 42.3 (1), 46.7 (2), 49.2 (2), 55.1 (3), 55.2 (3), 113.9 (1), 114.2 (1), 127.8 (1), 129.1 (0), 129.3 (1), 129.8 (0), 158.8 (0), 159.0 (0), 175.3 (0), 178.3 (0).

LRMS (ES) *m/z* 412 (20%, $[M+H]^+$), 424 (100%, $[M+Na]^+$), 845 (100%, $[2M+Na]^+$).

HRMS (ES) $C_{24}H_{29}NO_5$ $[M+H]^+$ requires 412.2119, found 412.2130.

(3a*S*, 7a*R*)Perhydro-1-isobenzofuranone 476



Following a procedure described by Mevellec.[159]

$NaBH_4$ (1.69 g, 44.6 mmol) was added to a stirred solution of cis-1,2-cyclohexanedicarboxylic anhydride (95%, 4.58 g, 29.7 mmol) in THF (60 ml) under N_2 and the reaction mixture was cooled to –78 °C. MeOH (8 ml) was added drop wise over 30 min, reaction mixture was stirred ad -78 °C for further 30 min, quenched with 1M HCl (25 ml) and 6M HCl (7 ml) and stirred at room temperature for 30 min. Solvent was removed *in vacuo*, and the residue was extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. The crude product was purified by column chromatography (silica gel, 0 – 2% ethyl acetate in DCM) to give lactone **476** as colourless oil (3.67 g, 88%).

ν_{max} (liq. film) 2931 (m), 2856 (m), 1767 (s), 1159 (s), 1127 (s), 1039 (s).

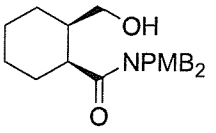
δ_H (300 MHz, $CDCl_3$) 1.17-1.32 (3H, m, CH_2, CH_AH_B), 1.55-1.68 (3H, m, CH_2, CH_AH_B), 1.82 (1H, m, CH_AH_B), 2.12 (1H, m, CH_AH_B), 2.45 (1H, m, CH), 2.65 (1H, m, CH), 3.96 (1H, dd, J = 1, 5 Hz, CH_AH_BO), 4.20 (1H, dd, J = 5, 9 Hz, CH_AH_BO).

δ_C (75 MHz, $CDCl_3$) 22.5 (2), 22.9 (2), 23.4 (2), 27.2 (2), 35.4 (1), 39.5 (1), 71.7 (2), 178.5 (0).

LRMS (CI) *m/z* 141 (86%, $[M+H]^+$), 158 (100%, $[M+NH_4]^+$).

HRMS (EI) $C_8H_{12}O_2$ $[M-H]^+$ requires 140.08373, found 140.08374.

***N*1,*N*1-Di(4-methoxybenzyl)-2-(hydroxymethyl)-1-cyclohexanecarboxamide 475**



Method A;

Following a procedure described by Nakajima.[158]

Et_3N (0.947 ml, 6.80 mmol) and ethyl chloroformate (0.604 ml, 6.32 mmol) were added to a stirred solution of acid **459** (2.0 g, 4.86 mmol) in THF (5 ml) at 0 °C under N_2. A solid was formed instantly. The reaction mixture was stirred for 1 h and the precipitate was filtered off. $NaBH_4$ (552 mg, 14.58 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with 10% HCl (10 ml) and extracted with ethyl acetate. The organic layers were washed with 10% HCl, 2M NaOH and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 5-20% ethyl acetate in petroleum ether) to give alcohol **475** as off white solid (374 mg, 19%).

Method B;

Following a procedure by Martin.[160]

$AlMe_3$ (2.0 M in hexanes, 0.58 ml, 1.167 mmol) was added to a stirred solution of amine **462** (300 mg, 1.167 mmol) in DCE (3 ml) at room temperature under N_2. Reaction mixture was stirred for 30 min, and lactone **476** (82 mg, 0.584 mmol) in DCE (1 ml) was added. The reaction mixture was refluxed for 24 h, cooled to 0 °C and 1M HCl (2 ml) was added drop wise. The reaction mixture was extracted with DCM and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 10-40% ethyl acetate in petroleum ether) to give alcohol **x** as off white solid (120 mg, 52%), m.p 95-98 °C.

ν_{max} (liq. film) 3456 (br w), 2930 (m), 2856 (m), 2361 (w), 1612 (s), 1511 (s), 1245 (s).

δ_H (300 MHz, $CDCl_3$) 1.26 (2H, m, CH_2), 1.42 (2H, m, CH_2), 1.56 (1H, m, C*H*CH2OH), 1.77 (2H, m, CH_2), 2.00 (2H, m, CH_2), 2.72 (1H, br s, OH), 2.91 (1H, dt, J = 4, 10 Hz, C*H*C=O), 3.56 (1H, dd, J = 4, 12 Hz, CH_AH_BOH), 3.80 (3H, s, CH_3), 3.83 (3H, s, CH_3), 4.13 (1H, m, CH_AH_BOH), 4.39 (1H, d, J = 17 Hz, CH_AH_BN), 4.43

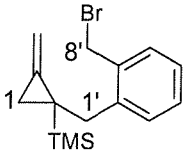
(1H, d, J = 14 Hz, CH_AH$_B$N), 4.47 (1H, d, J = 17 Hz, CH$_A$$H_B$N), 4.60 (1H, d, J = 14 Hz, CH$_A$$H_B$N), 6.85 (2H, d, J = 9 Hz, Ar), 6.92 (2H, d, J = 9 Hz, Ar), 7.10 (2H, d, J = 9 Hz, Ar), 7.15 (2H, d, J = 9 Hz, Ar).

δ_C (75 MHz, $CDCl_3$) 22.1 (2), 24.9 (2), 25.7 (2), 29.3 (2), 39.6 (1), 41.3 (1), 47.2 (2), 49.3 (2), 55.2 (3), 55.3 (3), 114.0 (1), 114.3 (1), 127.6 (1), 128.3 (0), 129.2 (0), 129.4 (1), 158.9 (0), 159.1 (0), 177.3 (0).

LRMS (ES) *m/z* 398 (20%, $[M+H]^+$), 420 (100%, $[M+Na]^+$), 817 (70%, $[2M+Na]^+$).

HRMS (ES) $C_{24}H_{31}NO_4$ $[M+H]^+$ requires 420.2145, found 420.2153.

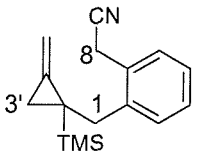
1-[2-(Bromomethyl)benzyl]-2-methylenecyclopropyl(trimethyl)silane 480



n-BuLi (2.4M in hexanes, 1.05 ml, 2.53 mmol) was added to a stirred solution of methylenecyclopropane (2M in THF, 1.26 ml, 2.53 mmol) in THF (10 ml) at -78 °C under N_2. The reaction mixture was allowed to warm to 10 °C, cooled to -78 °C and TMSCl (0.320 ml, 2.53 mmol) was added. The reaction mixture was allowed to warm to 10 °C, cooled to -78 °C and *n*-BuLi (2.4M in hexanes, 1.05 ml, 2.53 mmol) was added. The reaction mixture was allowed to warm to 10 °C, cooled to -78 °C and slowly cannulated to a stirred solution of dibromo-*o*-xylene (2.0 g, 7.58 mmol) in THF (20 ml) at -78 °C under N_2. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight, quenched with aqueous saturated NH_4Cl and extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (0-1% diethyl ether in petroleum ether) to give bromide **480** as a mixture of two isomers, a colourless oil with impurities (183 mg, 23%).

δ_H (300 MHz, $CDCl_3$) 0.047 (9H, s, CH_3, isomer a), 0.049 (9H, s, CH_3, isomer b), 0.58 (1H, dt, J = 2, 8 Hz, C(1)H_AH$_B$), 1.03 (1H, m, C(1)H$_A$$H_B$), 3.05 (2H, C(1')$H_2$, isomer a), 3.06 (2H, s, C(1')H_2, isomer b), 4.51 (2H, dd, J = 10, 17 Hz, C(8)H_2, isomer b), 4.61 (2H, dd, J = 11, 19 Hz, C(8)H_2, isomer a), 5.25 (2H, m, =CH_2), 7.13-7.33 (4H, m, Ar).

2-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]methylbenzyl cyanide 481



Following a method described by Fish.[122]

A solution of bromide **480** (180 mg, 0.582 mmol) and NaCN (60 mg, 1.22 mmol) in DMSO (3 ml) was stirred at 60 °C for 24 h. Half-saturated brine (40 ml) was added and the reaction mixture was extracted with diethyl ether (4x40 ml). The combined organic fractions were washed with brine (3x30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 0–2% ethyl acetate in petroleum ether) to give nitrile **481** as colourless oil (69 mg, 46%).

ν_{max} (liq. film) 2954 (m), 2362 (w), 2332 (w), 1729 (w), 1493 (w), 1454 (w), 1418 (w), 1250 (s), 839 (s).

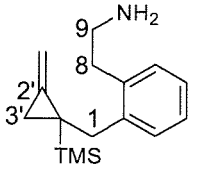
δ_H (300 MHz, $CDCl_3$) 0.02 (9H, s, CH_3), 0.54 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.03 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 2.88 (1H, d, J = 14 Hz, C(1)H_AH_B), 2.95 (1H, d, J = 14 Hz, C(1)H_AH_B), 3.70 (1H, s, C(8)H_2), 5.26 (2H, m =CH_2), 7.15 (1H, m, Ar), 7.22-7.27 (2H, m, Ar), 7.37 (1H, m, Ar).

δ_C (75 MHz, $CDCl_3$) -3.2 (3), 10.2 (2), 13.3 (0), 21.7 (2), 34.3 (2), 102.0 (2), 127.2 (1), 127.7 (1), 128.6 (1), 128.9 (0), 131.4 (1), 136.2 (0), 136.8 (0), 181.2 (0).

LRMS (EI) *m/z* 254 (50%, $[M-H]^+$), 73 (100%, $[SiMe_3]^+$).

HRMS (EI) $C_{16}H_{20}NSi$ $[M-H]^+$ requires 254.1365, found 254.1368.

2-(2-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]methylphenyl)-1-ethanamine 482



Nitrile **481** (100 mg, 0.39 mmol) in diethyl ether (1 ml) was added to a stirred suspension of $LiAlH_4$ (60 mg, 1.57 mmol) in diethyl ether (2 ml), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with diethyl ether and excess $LiAlH_4$ was quenched with 2M NaOH. The reaction mixture was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 0-5% MeOH in DCM) to give amine **482** as a colourless oil (48 mg, 48%).

ν_{max} (liq. film) 2953 (m), 1488 (w), 1452 (w), 1248 (s), 834 (s).

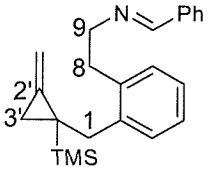
δ_H (400MHz, $CDCl_3$) -0.01 (9H, s, CH_3), 0.61 (1H, m, C(3')H_AH_B), 1.02 (1H, m, C(3')H_AH_B), 2.13 (2H, br s, NH_2), 2.79 (2H, m, CH_2), 2.90-2.99 (4H, m, $2CH_2$), 5.24 (1H, m, =CH_AH_B), 5.27 (1H, m, =CH_AH_B), 7.10-7.16 (4H, m, Ar).

δ_C (100 MHz, $CDCl_3$) -3.1 (3), 10.4 (2), 13.8 (0), 34.2 (2), 36.7 (2), 42.7 (2), 101.6 (2), 125.7 (1), 126.3 (1), 129.2 (1), 130.9 (1), 136.6 (0), 137.5 (0), 137.5 (0).

LRMS (ES) *m/z* 260 (100%, $[M+H]^+$).

HRMS (ES) $C_{16}H_{25}NSi$ $[M+H]^+$ requires 260.1829, found 260.1827.

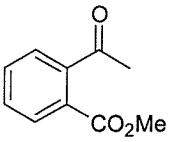
_N_1-[(_Z_)-1-Phenylmethylidene]-2-(2-[2-methylene-1-(1,1,1-trimethylsilyl) cyclopropyl]methylphenyl)-1-ethanamine 384



A solution of amine **482** (50 mg, 0.193 mmol) and benzaldehyde (19 µl, 0.193 mmol) in DCM (5 ml) was stirred for 2 h at room temperature under N_2, filtered and concentrated *in vacuo* to give a 1:1 mixture of imine **384** and benzaldehyde (70 mg, 80%).

δ_H (300 MHz, $CDCl_3$) -0.04 (9H, s, CH_3), 0.61 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.01 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 2.96 (2H, s, C(1)H_2), 2.99 (2H, dt, J = 1, 7 Hz, C(8)H_2), 3.82 (2H, t, J = 7 Hz, C(9)H_2), 5.22 (1H, m, =CH_AH_B), 5.26 (1H, m, =CH_AH_B), 7.09-7.19 (4H, m, Ar), 7.41-7.43 (3H, m, Ar), 7.68-7.73 (2H, m, Ar), 8.16 (1H, s, C(11)H).

Methyl 2-acetylbenzoate 488



Following a method described by Newman.[162]

2-Acetylbenzoic acid (10 g, 61.0 mmol), K_2CO_3 (12.6 g, 92 mmol) and methyl iodide (3.8 ml, 61.0 mmol) were refluxed in acetone (500 ml) for 24 h, the reaction mixture was filtered and concentrated *in vacuo*. The residue was taken up in DCM, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure to give ester **488** as pale yellow oil (10.28 g, 81%).

ν_{max} (liq. film) 2951 (w), 1718 (s), 1696 (s), 1432 (m), 1355 (m), 1265 (s), 1011 (s), 1064 (s).

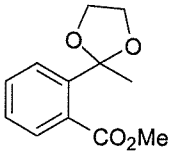
δ_H (300 MHz, $CDCl_3$) 2.55 (3H, s, CH_3), 3.91 (3H, s, CH_3), 7.42-7.61 (3H, m, Ar), 7.86 (1H, m, Ar).

δ_C (75 MHz, $CDCl_3$) 30.0 (3), 52.6 (3), 126.5 (1), 128.8 (0), 129.7 (1), 130.1 (1), 132.0 (1), 142.6 (0), 167.4 (0), 203.0 (0).

LRMS (CI) *m/z* 179 (100%, $[M+H]^+$).

Spectroscopic data agrees with Underwood.[161]

Methyl 2-(2-methyl-1,3-dioxolan-2-yl)benzoate 489



Following the procedure described by Noyori.[163]

1,2-Bis(trimethylsilyloxy)ethane (28.1 ml, 115 mmol) was added to a stirred solution of ketone **488** (10.2 g, 57.3 mmol) in DCM (150 ml) under N_2. The reaction mixture was cooled to -78 °C, and TMSOTf (104 µl, 0.573 mmol) was added. The reaction mixture was allowed to warm to room temperature during 12 h, $NaHCO_3$ (10 ml) was added and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under

reduced pressure to give the crude product as a yellow oil. The crude product was purified by column chromatography (silica gel, 2-5% ethyl acetate in petroleum ether) to give the protected ketone **489** as a white solid (6.11 g, 48%), m.p. 60-64 °C, (lit.[161] m.p. 57-61 °C).

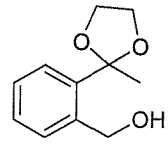
δ_H (300 MHz, $CDCl_3$) 1.81 (3H, s, CCH_3), 3.59-3.64 (2H, m, $OCH_AH_BH_AH_BCO$), 3.89 (3H, s, CH_3), 3.95-3.99 (2H, m, $OCH_AH_BH_AH_BCO$), 7.27-7.38 (2H, m, Ar), 7.44-7.54 (2H, m, Ar).

δ_C (75 MHz, $CDCl_3$) 27.3 (3), 52.3 (3), 64.2 (2), 108.7 (0), 126.6 (1), 127.4 (1), 127.8 (1), 129.9 (1), 131.9 (0), 141.2 (0), 171.2 (0).

LRMS (CI) *m/z* 223 (100%, $[M+H]^+$).

Spectroscopic data agrees with Underwood.[161]

[2-(2-Methyl-1,3-dioxolan-2-yl)phenyl]methanol 490



Following a method described by Hitchcock.[164]

Ester **489** (6.07 g, 27.3 mmol) in THF (20 ml) was added to a stirred suspension of $LiAlH_4$ (1.56 g, 41.0 mmol) in THF (150 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 2 h, cooled to 0 °C and 2M NaOH was added until excess $LiAlH_4$ was consumed. The reaction mixture was dried over $MgSO_4$ and concentrated *in vacuo* to give alcohol **490** as white solid (4.86 g, 93%), m.p. 39-41 °C.

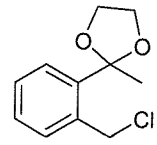
ν_{max} (liq. film) 3401 (br m), 2985 (m), 2886 (m), 1474 (m), 1441 (m), 1373 (s), 1189 (s), 1026 (s).

δ_H (300 MHz, DMSO-d_6) 3.39 (3H, s, CH_3), 3.62-3.67 (2H, m, $OCH_AH_BH_AH_BCO$), 3.97-4.02 (2H, m, $OCH_AH_BH_AH_BCO$), 4.74 (2H, d, J = 6 Hz, CH_2OH), 5.08 (1H, t, J = 6 Hz, OH), 7.25 (1H, dt, J = 2, 7 Hz, Ar), 7,34 (1H, dt, J = 2, 7 Hz, Ar), 7.46 (1H, dd, J = 2, 8 Hz, Ar), 7.62 (1H, dd, J = 2, 8 Hz, Ar).

δ_C (75 MHz, $CDCl_3$) 27.8 (3), 61.1 (2), 64.6 (2), 109.6 (0), 126.2 (1), 127.3 (1), 128.69 (1), 128.74 (1) 140.0 (0), 140.8 (0).

Spectroscopic data agrees with Underwood.[161]

2-[2-(Chloromethyl)phenyl]-2-methyl-1,3-dioxolane 491



Following a method described by Ohfune.[165]

Triphenylphosphine (9.51 g, 36.2 mmol) and *N*-Chlorosuccinimide (3.63 g, 27.2 mmol) were added to a stirred solution of alcohol **490** in DCM at 0 °C under N_2. The reaction mixture was stirred at room temperature for 3 h, concentrated *in vacuo* and purified by column chromatography (silica gel, 1-3 % ethyl acetate in petroleum ether) to give the chloride **491** as pale yellow solid (1.11 g, 29%), m.p. 30-32 °C.

ν_{max} (liq. film) 3061 (w), 2984 (m), 2890 (m), 1481 (m), 1435 (m), 1373 (m), 1192 (s), 1026 (s), 759 (s).

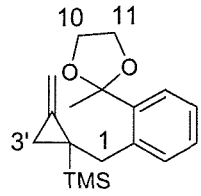
δ_H (300 MHz, $CDCl_3$) 1.74 (3H, s, CH_3), 3.72-3.84 (2H, m, $OCH_AH_BH_AH_BCO$), 4.01-4.12 (2H, m, $OCH_AH_BH_AH_BCO$), 4.96 (2H, s, CH_2Cl), 7.27-7.37 (2H, m, Ar), 7.48 (1H, m, Ar), 7.59 (1H, m, Ar).

δ_C (75 MHz, $CDCl_3$) 27.8 (3), 44.1 (2), 64.3 (2), 109.0 (0), 126.5 (1), 128.3 (1), 128.6 (1), 132.1 (1), 135.0 (0), 140.9 (0).

LRMS (GCCI) *m/z* 179 (100%, $[M-Cl]^+$), 213 (20%, $[M+H]^+$).

Spectroscopic data agrees with Underwood.[161]

Trimethyl-1-[2-(2-methyl-1,3-dioxolan-2-yl)benzyl]-2-methylenecyclopropylsilane 492



n-BuLi(2.1M in hexanes, 2.4 ml, 5.08 mmol) was added to a stirred solution of methylenecyclopropane (0.34 ml, 5.08 mmol) in THF (40 ml) at -78 °C under N_2. The

reaction mixture was allowed to warm to 10 °C during 1.5 h, cooled to -78 °C and TMSCl was added. The reaction mixture was allowed to warm to 0 °C during 1 h, cooled to -78 °C and *n*-BuLi (2.1M in hexanes, 2.4 ml, 5.08 mmol) was added. The reaction mixture was allowed to warm to 0 °C during 1 h, cooled to -78 °C and chloride **491** in THF (5 ml) was added. The reaction mixture was stirred at -78 °C for 20 min, quenched with aqueous saturated NH_4Cl and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 2% ethyl acetate in petroleum ether) to give the protected ketone **492** as a white solid (660 mg, 86%), m.p. 31-33 °C.

ν_{max} (liq. film) 2976 (m), 2951 (m), 2899 (m), 2868 (m), 2360 (w), 2330 (w), 1479 (w), 1366 (m), 1244 (s), 1184 (s), 1033 (s).

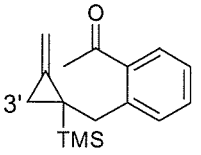
δ_H (300 MHz, $CDCl_3$) -0.05 (9H, s, CH_3), 0.69 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.15 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 1.69 (3H, s, CH_3), 2.95 (1H, d, J = 15 Hz, C(1)H_AH_B), 3.41 (1H, d, J = 15 Hz, C(1)H_AH_B), 3.69-3.81 (2H, m, C(10)H_AH_B, C(11)H_AH_B), 3.98-4.08 (2H, m, C(10)H_AH_B, C(11)H_AH_B), 5.35 (1H, m, =CH_AH_B), 5.37 (1H, m, =CH_AH_B), 7.12-7.19 (2H, m, Ar), 7.53 (1H, m, Ar), 7.56 (1H, m, Ar).

δ_C (75 MHz, $CDCl_3$) -2.65 (3), 12.1 (2), 13.8 (0), 27.3 (3), 35.1 (2), 64.1 (2), 101.4 (2), 109.4 (0), 125.68 (1), 125.72 (1), 127.1 (1), 130.7 (1), 137.0 (0), 138.9 (0), 140.6 (0).

LRMS (CI) *m/z* 303 (4%, $[M+H]^+$) 73 (100%, $[SiMe_3]^+$).

HRMS(EI) $C_{18}H_{26}O_2Si$ $[M]^+$ requires 302.1702, found 302.1692.

1-(2-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]methylphenyl)-1-ethanone 484



Following a method described by Underwood.[161]

Hydrochloric acid (10%, 0.5 ml) was added to a stirred solution of protected ketone **492** (570 mg, 1.89 mmol) in acetone/water (9:1, 50 ml) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* and the residue was taken up in diethyl ether. The organic phase was washed with aqueous

saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (2-5% ethyl acetate in petroleum ether) to give ketone **484** as colourless oil (386 mg, 79%).

ν_{max} (liq. film) 2954 (m), 1685 (s), 1571 (w), 1352 (m), 1245 (s), 838 (s).

δ_H (300 MHz, $CDCl_3$) -0.02 (9H, s, CH_3), 0.52 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 0.96 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B), 2.57 (3H, s, CH_3), 3.08 (1H, d, J = 14 Hz, C(1)H_AH_B), 3.48 (1H, d, J = 14 Hz, C(1)H_AH_B), 5.18 (1H, m, =CH_AH_B), 5.21 (1H, m, =CH_AH_B), 7.23-7.29 (2H, m, Ar), 7.36 (1H, m, Ar), 7.61 (1H, m, Ar).

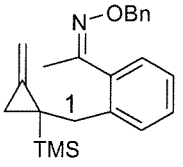
δ_C (75 MHz, $CDCl_3$) -3.2 (3), 10.1 (2), 14.4 (0), 34.3 (2), 36.0 (3), 102.0 (2), 126.0 (1), 128.7 (1), 130.5 (1), 132.6 (1), 137.5 (0), 138.4 (0), 138.6 (0), 201.9 (0).

LRMS (CI) *m/z* 73 (100%, $[SiMe_3]^+$), 243 (40%, $[M-CH_3]^+$), 259 (66%, $[M+H]^+$).

HRMS (EI) $C_{16}H_{22}Osi$ $[M]^+$ requires258.14399, found 258.14363.

Anal. Calcd for $C_{16}H_{22}OSi$: C, 74.36; H, 8.58. Found C, 74.40; H, 8.69.

1-(2-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]methylphenyl)-1-ethanone *O*1-benzyloxime 485



Following a method described by Booth.[152]

A solution of O-benzyl hydroxylamine hydrochloride (288 mg, 1.80 mmol) and ketone **484** (194 mg, 0.752 mmol) in pyridine (5 ml) was stirred at room temperature for 48 h. Pyridine was removed under reduced pressure and replaced with DCM (50 ml). The organic phase was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (0-2% ethyl acetate in petroleum ether) to give oxime **485** as a 1:3 mixture of isomers, as a colourless oil (331 mg, 81%).

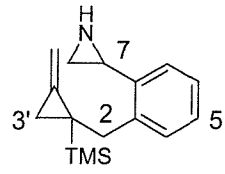
ν_{max} (liq. film) 2950 (m), 2355 (w), 1731 (w), 1453 (m), 1364 (m), 1248 (s), 1015 (s), 840 (s).

δ_H (300 MHz, $CDCl_3$) -0.31 (3H, s, CH_3), 0.68 (1H, m, C(3')H_AH_B), 1.04 (1H, m, C(3')H_AH_B), 2.15 (3H, s, CH_3, isomer a), 2.22 (3H, s, CH_3, isomer b), 2.67 (1H, d, J = 15 Hz, C(1)H_AH_B, isomer a), 2.76 (1H, d, J = 15 Hz, C(1)H_AH_B, isomer a), 2.93 (2H, s, C(1)H_2, isomer b), 5.22-5.32 (4H, m, =CH_2, CH_2Ph), 7.16-7.44 (9H, m, Ar).

δ_C (75 MHz, $CDCl_3$) -3.0 (3), 11.6 (2), 14.1 (0), 17.4 (2), 35.4 (3), 75.5 (0), 75.8 (2), 101.3 (2), 126.1 (1), 127.7 (1), 128.0 (1), 128.1 (1), 128.2 (1), 128.3 (1), 130.6 (1), 137.7 (0), 138.2 (0), 157 (0).

LRMS (CI) *m/z* 73 (100%, $[SiMe_3]^+$), 364 (14%, $[M+H]^+$).

2-(2-{[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]methyl}phenyl)azirane 493



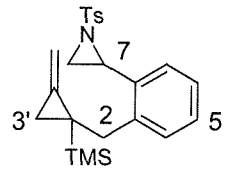
Benzyloxime **485** (120 mg, 0.330 mmol) in monoglyme (1 ml) was added to a stirred suspension of $LiAlH_4$ in monoglyme (2 ml) under N_2 at room temperature. The reaction mixture was heated to 100 °C for 8 h and stirred at room temperature overnight. Reaction mixture was diluted with diethyl ether and excess $LiAlH_4$ was quenched with drop wise addition of 2M NaOH. Reaction mixture was dried over $MgSO_4$, concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, 5-10% ethyl acetate in petroleum ether) to give aziridine **493** as a mixture of isomers in approximately 1:2 ratio, as colourless oil (28 mg, 33%).

δ_H (400 MHz, $CDCl_3$) 0.01 (9H, s, CH_3), 0.67 (1H, m, C(3')H_AH_B), 1.04 (1H, m, C(3')H_AH_B), 1.70 (1H, br s, CH_AH_B), 2.21 (1H, m, CH_AH_B), 3.03-3.14 (3H, m, CH_2, CH), 5.27 (2H, m, $=CH_2$), 7.13-7.15 (4H, m, Ar).

δ_C (75 MHz, $CDCl_3$) -3.2 (3), 10.3, 10.4 (2), 13.58, 13.61 (0), 28.40, 28.41 (2), 33.96, 34.0 (1), 35.7 (2), 101.5, 101.6 (2), 124.3, 124.4 (1), 126.07, 126.08 (1), 126.4 (1), 130.3, 130.4 (1), 137.3 (0), 138.60 (0), 138.62 (0).

LRMS (ES) *m/z* 258 (100%, $[M+H]^+$).

2-(2-{[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]methyl}phenyl)-1-[(4-methylphenyl)sulfonyl]azirane 494



Et_3N (0.10 ml) was added to a stirred solution of aziridine **493** (27 mg, 0.105 mmol) and tosyl chloride (24 mg, 0.126 mg) in DCM at -10 °C under N_2. The reaction mixture was stirred at room temperature overnight, quenched with water and diluted with DCM. The organic layer was washed with 1M $KHSO_4$ and aq. sat. $NaHCO_4$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 10% ethyl acetate in petroleum ether) to give tosylaziridine **494** as a mixture of isomers in approximately 1:2 ratio, as dense colourless oil (26 mg, 60%).

ν_{max} (liq. film) 2953 (w), 1597 (w), 1326 (s), 1248 (s), 1160 (s).

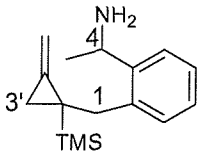
δ_H (300 MHz, $CDCl_3$) 0.01 (9H, s, CH_3, isomer a), 0.03 (9H, s, CH_3, isomer b), 0.49 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B, isomer b), 0.60 (1H, dt, J = 8, 2 Hz, C(3')H_AH_B, isomer a), 1.02 (1H, m, C(3')H_AH_B), 1.62 (1H, br s, CH_AH_B), 2.25 (1H, d, J = 4 Hz, CH_AH_B, isomer a), 2.28 (1H, d, J = 4 Hz, CH_AH_B, isomer b), 2.44 (3H, s, CH_3), 3.00 (2H, s, CH_2), 3.86 (1H, dd, J = 4, 7 Hz, CH, isomer b), 3.93 (1H, dd, J = 4, 7 Hz, CH, isomer a), 5.24 (1H, m, =CH_AH_B), 5.28 (1H, m, =CH_AH_B, isomer b), 5.31 (1H, m, =CH_AH_B, isomer a), 7.06-7.18 (4H, m, Ar), 7.34-7.36 (2H, m, Ar), 7.88-7.92 (2H, m, Ar).

δ_C (75 MHz, $CDCl_3$) -3.21, -3.18 (3), 10.2, 10.3 (2), 13.45, 13.48 (0), 21.6 (3), 33.8, 34.0 (2), 35.6, 35.9 (2), 39.1, 39.4 (1), 101.7, 102.0 (2), 125.1, 125.4 (1), 126.56, 126.60 (1), 127.20, 127.22 (1), 127.9, 128.0 (1), 129.7 (1), 130.5, 130.7 (1), 133.7 (0), 134.9, 135.0 (0), 136.80, 136.83 (0), 136.91, 136.94 (0), 144.61, 144.64 (0).

LRMS (ES) *m/z* 412 (60%, $[M+H]^+$), 450 (100%, $[M+K]^+$), 861 (80%, $[2M+K]^+$).

HRMS (ES) $C_{23}H_{29}NO_2SSi$ $[M+H]^+$ requires 412.1761, found 412.1770.

1-(2-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]methylphenyl)-1-ethanamine 486



Following a method described by Canary.[168]

Zn powder (10 g) was added to a stirred solution of oxime **485** (3.85 g, 10.6 mmol) in glacial acetic acid (10 ml) and EtOH (20 ml) in small portions at room temperature under N_2. The reaction mixture was stirred at room temperature for 48 h. Zn was removed by filtration, and the solvents were removed *in vacuo*. The residual oil was basified with aqueous saturated KOH, extracted with diethyl ether, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product as pink oil, 1.30 g. The crude product was purified by column chromatography (silica gel, 0-20% MeOH in DCM) to give amine **486** as a mixture of isomers in approximately 1:1:2:2 ratio, as yellow oil (496 mg, 18%).

ν_{max} (liq. film) 2955 (m), 1245 (s), 837 (s).

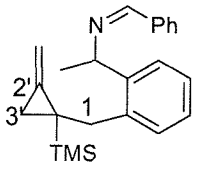
δ_H (300 MHz, $CDCl_3$) 0.02 (9H, s, CH_3, isomer a), 0.03 (9H, s, CH_3, isomer b), 0.57 (1H, dt, J = 2, 8 Hz, C(3')H_AH$_B$, isomer a), 0.95 (1H, dt, J = 2, 8 Hz, C(3')H_AH$_B$, isomer b), 1.01 (1H, dt, J = 2, 8 Hz, C(3')H$_A$$H_B$, isomer b), 1.12 (1H, td, J = 2, 7 Hz, C(3')H$_A$$H_B$, isomer a), 1.34 (3H, d, J = 6 Hz, C(5)H_3, isomer a), 1.36 (3H, d, J = 6 Hz, C(5)H_3, isomer b), 1.82 (2H, br s, NH_2), 2.96 (2H, m, C(1)H_2), 4.33 (1H, m, C(4)H), 5.25 (2H, m, =CH_2), 7.03-7.14 (2H, m, Ar), 7.22 (1H, m, Ar), 7.43 (1H, m, Ar).

δ_C (75 MHz, $CDCl_3$) -3.3, -3.2, -3.18, -3.1 (3); 9.5, 10.0, 10.2, 10.3 (2); 13.6, 13.7, 13.71, 13.8 (0); 24.78, 24.83 (2); 33.0, 33.2, 33.4, 33.5 (3); 41.9, 42.0 (1); 101.3, 101.5, 101.6 (2); 124.0, 124.1 (1); 125.6, 125.7 (1); 126.7, 126.8 (1); 130.7, 130.9, 131.1, 131,2 (1); 134.1, 134.5 (0); 136.9, 137.0, 137.3, 137.4 (0); 146.0, 146.4 (0).

MS (ES) *m/z* 260.3 (80%, $[M+H]^+$), 301.3 (35%, $[M+MeCN+H]^+$).

HRMS (ES) $C_{16}H_{25}NSi$ $[M+H]^+$ requires 260.1829, found 260.1832.

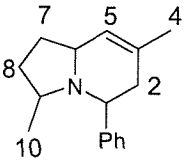
N1-[(*Z*)-1-Phenylmethylidene]-1-(2-[2-methylene-1-(1,1,1-trimethylsilyl) cyclopropyl]methylphenyl)-1-ethanamine 387



A solution of amine **486** (197 mg, 0.761 mmol) and benzaldehyde (77 µl, 0.761 mmol) in DCM (8 ml) was stirred over 4 Å molecular sieves under N_2 at room temperature for 2 h, filtered and concentrated *in vacuo* to give imine **387** as dense pale yellow oil (218 mg, 83%).

δ_H (300 MHz, $CDCl_3$) 0.03 (9H, s, CH_3, isomer a), 0.05 (9H, s, CH_3, isomer b), 0.55 (1H, dt, J = 8, 2 Hz, C(3')H_AH$_B$, isomer b), 0.64 (1H, dt, J = 8, 2 Hz, C(3')H_AH$_B$, isomer a), 0.98 (1H, dt, J = 8, 2 Hz, C(3')H$_A$$H_B$, isomer b), 1.06 (1H, dt, J = 8, 2 Hz, C(3')H$_A$$H_B$, isomer a), 1.54 (3H, d, J = 7 Hz, CH_3, isomer b), 1.55 (3H, d, J = 7 Hz, CH_3, isomer a), 2.88 (1H, d, J = 18 Hz, C(1)H_AH$_B$, isomer b), 2.99 (2H, s, C(1)H_2, isomer a), 3.08 (1H, d, J = 18 Hz, C(1)H$_A$$H_B$, isomer b), 4.83 (1H, m, CH), 5.24 (1H, m, =CH_AH$_B$), 5.28 (1H, m, =CH$_A$$H_B$), 7.09-7.26 (4H, m, Ar), 7.40-7.42 (3H, m, Ar), 7.76-7.79 (2H, m, Ar), 8.31 (1H, s, =CH, isomer b), 8.32 (1H, s, =CH, isomer a).

3,7-Dimethyl-5-phenyl-1,2,3,5,6,8a-hexahydroindolizidine 497



BF_3·Et_2O (31µl, 0.24 mmol) was added to a stirred solution of imine **380** (72 mg, 0.24 mmol) in DCM (3 ml) at –78 °C under Ar. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 20 h. The reaction mixture was quenched with water and extracted with DCM. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 0-2% methanol in DCM) to give the bicycle **497** as dense brown oil (24 mg, 44%).

ν_{max} (liq. film) 3054 (w), 2950 (w), 1453 (w), 1287 (s), 1244 (s), 1163 (s), 1034 (s), 760 (s).

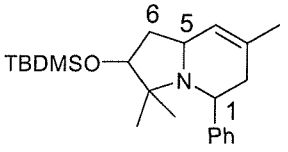
δ_H (300 MHz, $CDCl_3$) 1.11 (3H, d, J = 7 Hz, C(10)H_3), 1.73 (1H, m, C(8)H_AH$_B$), 1.82 (3H, s, C(4)H_3), 1.92 (1H, ddd, J = 7, 12, 15 Hz, C(7)H_AH$_B$), 2.21-2.28 (2H, m, C(8)H$_A$$H_B$, C(2)$H_AH_B$), 2.34 (1H, m, C(7)H$_A$$H_B$), 2.93 (1H, dd, J =12, 18 Hz, C(2)H$_A$$H_B$), 3.53 (1H, m, C(9)H), 3.98 (1H, dd, J = 4, 12 Hz, C(1)H), 4.43 (1H, m, C(6)H), 5.54 (1H, br s, C(5)H), 7.43-7.50 (3H, m, Ar), 7.55-7.58 (2H, m, Ar).

δ_C (75 MHz, $CDCl_3$) 19.0 (3), 22.6 (3), 30.7 (2), 31.6 (2), 35.8 (2), 62.9 (1), 63.2 (1), 64.8 (1), 117.1 (1), 128.4 (1), 129,7 (1), 130.0 (1), 133.8 (0), 134.0 (0).

LRMS (ES) *m/z* 228 (100%, $[M+H]^+$).

HRMS (ES) $C_{16}H_{22}N$ $[M+H]^+$ requires 228.1747, found 228.1741.

6-dimethyl-4-phenyl-3,4,6,10b-tetrahydropyrido[2,1-*a*]isoindole 501



$BF_3{\cdot}Et_2O$ (65 μl, 0.514 mmol) was added to a stirred solution of imine **449** (190 mg, 0.428 mmol) in DCM (4 ml) at -78 °C under N_2. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight. The reaction was quenched with water and extracted with DCM. The organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 0 - 10% MeOH in DCM) to give bicycle **501** as dense brown oil (23 mg, 14%).

ν_{max} (liq. film) 2956 (m), 2928 (m), 2856 (m), 1462 (s), 1360 (s), 1115 (s).

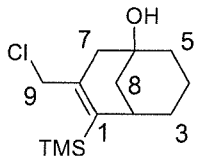
δ_H (300 MHz, $CDCl_3$) 0.05 (3H, s, Me), 0.07 (3H, s, Me), 0.09 (9H, s, Me), 1.00 (3H, s, Me), 1.15 (3H, s, Me), 1.45 (1H, ddd, J = 12, 11 Hz, J_3 = 9 Hz, C(6)H_AH$_B$), 1.73 (3H, s, Me), 2.19 (1H, dd, J = 16, 12 Hz, C(6)H$_A$$H_B$), 2.20 (1H, m, C(2)$H_AH_B$), 2.41 (1H, m, C(2)H$_A$$H_B$), 3.53 (1H, m, C(5)H), 3.87 (1H, dd, J =10, 7 Hz, C(7)H), 4.24 (1H, d, J = 7 Hz, C(1)H), 5.43 (1H, br s, C(4)H), 7.17 (1H, m, Ar), 7.25-7.35 (4H, m, Ar).

δ_C (75 MHz, $CDCl_3$) -4.6 (3), -4.0 (3), 18.3 (3), 19.2 (0), 24.7 (3), 26.2 (3), 27.1 (3), 32.5 (2), 38.5 (2), 50.4 (1), 51.8 (1), 62.8 (0), 79.1 (1), 126.3 (1), 126.9 (1), 127.5 (1), 128.4 (1), 129.5 (0), 145.5 (0).

LRMS (ES) *m/z* 372 (90%, $[M+H]^+$).

HRMS (ES) $C_{23}H_{37}NOSi$ $[M+H]^+$ requires 372.2717, found 372.2722.

3-Chloromethyl-4-trimethylsilanyl-bicyclo[3.3.1]non-3-en-1-ol 502



Following a method described by Peron.[17]

$TiCl_4$ (80 µl, 0.49 mmol) was added to a stirred solution of ketone **400** in DCM (20 ml) at -78 °C under N_2. The reaction mixture was stirred at -78 °C for 5 min, quenched with water and extracted with DCM and diethyl ether. The combined organic phases were dried over MgSO4 and concentrated *en vacuo* to give the bicycle **502** as pale yellow solid (108 mg, 86%). The product was purified for characterisation by column chromatography (silica gel, 10-30 % ethyl acetate in petroleum ether) to give alcohol **502** as an off-white solid, 84 mg, 67%, m.p. 74-76 °C.

ν_{max} (liq. film) 3366 (br m), 2913 (s), 2839 (m), 2357 (w), 1737 (s),1246 (s).

δ_H (400MHz, $CDCl_3$) 0.19 (9H, s, Me), 1.38-1.62 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2), 1.73 (2H, m, C(8)H_2), 2.38 (1H, d, J = 18 Hz, C(7)$H_A$$H_B$), 2.42 (1H, d, J = 18 Hz, C(7)$H_A$$H_B$), 2.83 (1H, m, C(2)H), 4.08 (1H, d, J = 4 Hz, C(9)$H_A$$H_B$), 4.19 (1H, d, J = 4 Hz, C(9)$H_A$$H_B$).

δ_C (100 MHz, $CDCl_3$) 0.32 (3), 19.2 (2), 28.8 (2), 37.7 (1), 40.4 (2), 41.7 (2), 44.5 (2), 47.9 (2), 68.9 (0), 141.0 (0), 143.8 (0).

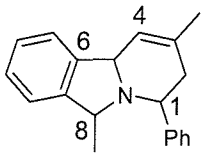
LRMS(EI) *m/z* 258 (6%, $[M]^+$), 73 (100%, $[SiMe_3]^+$).

HRMS $C_{13}H_{23}ClOSi$ $[M]^+$ requires 258.1207, found 258.1209.

Anal. Calcd for $C_{13}H_{23}ClOSi$: C, 60.32; H, 8.96. Found C, 60.56; H, 9.06.

Crystal structure see appendix.

6-Dimethyl-4-phenyl-3,4,6,10b-tetrahydropyrido[2,1-*a*]isoindole 504



$BF_3{\cdot}Et_2O$ (17 μl, 0.115 mmol) was added to a stirred solution of imine **386** (40 mg, 0.115 mmol) in DCM (2 ml) at -78 °C under N_2. The reaction mixture was allowed to warm to room temperature, and was stirred at room temperature overnight. $BF_3{\cdot}Et_2O$ (20 μl) was added and the reaction was stirred at room temperature for further 4 h, quenched with water and aq. sat. $NaHCO_3$, extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo* to give the bicycle **504** as dense brown oil (27 mg, 85%). The product was purified for characterisation by column chromatography (silica gel, 0-10% MeOH in DCM) to give the cyclised product **504** as dense brown oil (11 mg, 34%).

ν_{max} (liq. film) 2960 (w), 2922 (w), 2853 (w), 2361 (w), 1690 (s), 1259 (s).

δ_H (400MHz, $CDCl_3$) 1.36 (3H, d, J = 7 Hz, CH_3), 1.70 (3H, s, CH_3), 2.18 (1H, dd, J = 17, 5 Hz, C(2)H_AH_B), 2.58 (1H, dd, J = 17, 7 Hz, C(2)H_AH_B), 3.81 (1H, dd, J = 7, 5 Hz, C(1)H), 4.22 (1H, dd, J = 13, 7 Hz, C(8)H), 5.07 (1H, m, C(5)H), 5.73 (1H, m, C(4)H), 7.15-7.38 (5H, m, Ar).

δ_C (100 MHz, $CDCl_3$) 19.7 (3), 23.2 (3), 34.3 (2), 58.6 (1), 61.6 (1), 62.7 (1), 119.7 (0), 122.5 (1), 122.7 (1), 127.4 (1), 127.46 (1), 127.54 (1), 127.7 (1), 128.1 (1), 128.4 (0), 128.5 (0), 128.8 (1), 129.9 (1), 132.4 (1), 132.8 (0).

LRMS (ES) *m/z* 276 (100%, $[M+H]^+$).

HRMS (ES) $C_{20}H_{21}N$ $[M+H]^+$ requires 276.1747, found 276.1747.

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Appendix

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Table 1. Crystal data and structure refinement.

Identification code	**01SOT049**
Empirical formula	$C_{15}H_{17}NO_2$
Formula weight	243.30
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 12.5615(4) Å
	b = 13.0077(4) Å β = 96.942(2)°
	c = 15.4294(5) Å
Volume	2502.62(14) Å^3
Z	8
Density (calculated)	1.291 Mg / m^3
Absorption coefficient	0.086 mm^{-1}
F(000)	1040
Crystal	Colourless blade
Crystal size	0.30 × 0.10 × 0.07 mm^3
θ range for data collection	3.09 – 25.03°
Index ranges	$-14 \le h \le 14$, $-15 \le k \le 15$, $-18 \le l \le 18$
Reflections collected	16709
Independent reflections	4349 [R_{int} = 0.1421]
Completeness to θ = 25.03°	98.3 %
Max. and min. transmission	0.9940 and 0.9748
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4349 / 0 / 326
Goodness-of-fit on F^2	1.005
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0792, $wR2$ = 0.2178
R indices (all data)	$R1$ = 0.0979, $wR2$ = 0.2435
Extinction coefficient	0.008(3)
Largest diff. peak and hole	0.613 and –0.496 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C16	7968(2)	1264(2)	2876(1)	18(1)	1
C17	8820(2)	610(2)	3145(2)	20(1)	1
C18	9257(2)	670(2)	4017(2)	23(1)	1
C19	8861(2)	1349(2)	4596(2)	24(1)	1
C20	8014(2)	2005(2)	4319(2)	22(1)	1
C21	7582(2)	1945(2)	3445(1)	16(1)	1
C22	6676(2)	2524(2)	2978(1)	17(1)	1
C23	5869(2)	2624(2)	1425(2)	22(1)	1
C24	6638(2)	2999(2)	801(2)	25(1)	1
C25	7381(2)	2136(2)	603(2)	23(1)	1
C26	7309(2)	1337(2)	1989(1)	17(1)	1
C27	6908(2)	289(2)	1652(2)	21(1)	1
C28	5764(2)	4(2)	1329(2)	27(1)	1
C29	6295(2)	−448(2)	2170(2)	23(1)	1
N2	6485(1)	2087(2)	2158(1)	18(1)	1
O3	6178(1)	3246(1)	3243(1)	24(1)	1
O4	7987(1)	1772(1)	1399(1)	20(1)	1
C1	2004(2)	6224(2)	2079(1)	17(1)	1
C2	1139(2)	6862(2)	1806(2)	20(1)	1
C3	636(2)	6718(2)	958(2)	24(1)	1
C4	980(2)	5972(2)	412(2)	23(1)	1
C5	1854(2)	5346(2)	687(2)	21(1)	1
C6	2357(2)	5499(2)	1529(1)	18(1)	1
C7	3308(2)	4969(2)	1993(1)	17(1)	1
C8]	4207(2)	4990(2)	3518(2)	22(1)	1
C9	3486(2)	4627(2)	4177(2)	28(1)	1
C10	2728(2)	5483(2)	4370(2)	27(1)	1
C11	2713(2)	6214(2)	2944(1)	18(1)	1
C12	3101(2)	7284(2)	3219(2)	21(1)	1
C13	4246(2)	7603(2)	3494(2)	31(1)	1
C14	3664(2)	8001(2)	2650(2)	24(1)	1
C15	4021(2)	7681(2)	1795(2)	30(1)	1
C30	5901(2)	−159(2)	3018(2)	28(1)	1
N1	3539(2)	5470(2)	2778(1)	18(1)	1
O1	3801(1)	4233(1)	1744(1)	23(1)	1
O2	2081(1)	5800(1)	3579(1)	23(1)	1

Table 3. Bond lengths [Å] and angles [°].

C16–C21	1.375(3)	C1–C6	1.378(3)
C16–C17	1.391(3)	C1–C2	1.391(3)
C16–C26	1.513(3)	C1–C11	1.512(3)
C17–C18	1.392(3)	C2–C3	1.396(3)
C18–C19	1.391(3)	C3–C4	1.387(3)
C19–C20	1.391(3)	C4–C5	1.392(3)
C20–C21	1.394(3)	C5–C6	1.390(3)
C21–C22	1.477(3)	C6–C7	1.486(3)
C22–O3	1.226(3)	C7–O1	1.227(3)
C22–N2	1.381(3)	C7–N1	1.375(3)
C23–N2	1.469(3)	C8]–N1	1.472(3)
C23–C24	1.524(3)	C8]–C9	1.516(3)
C24–C25	1.515(3)	C9–C10	1.518(4)
C25–O4	1.444(3)	C10–O2	1.442(3)
C26–O4	1.437(3)	C11–O2	1.438(3)
C26–N2	1.469(3)	C11–N1	1.464(3)
C26–C27	1.523(3)	C11–C12	1.518(3)
C27–C28	1.509(3)	C12–C13	1.508(3)
C27–C29	1.516(3)	C12–C14	1.515(3)
C28–C29	1.505(3)	C13–C14	1.506(3)
C29–C30	1.502(3)	C14–C15	1.503(3)
C21–C16–C17	121.4(2)	C28–C27–C29	59.68(15)
C21–C16–C26	109.9(2)	C28–C27–C26	126.6(2)
C17–C16–C26	128.6(2)	C29–C27–C26	123.6(2)
C16–C17–C18	116.9(2)	C29–C28–C27	60.39(16)
C19–C18–C17	121.8(2)	C30–C29–C28	119.7(2)
C18–C19–C20	120.8(2)	C30–C29–C27	122.9(2)
C19–C20–C21	117.2(2)	C28–C29–C27	59.93(15)
C16–C21–C20	121.8(2)	C22–N2–C23	121.83(19)
C16–C21–C22	109.09(19)	C22–N2–C26	112.80(17)
C20–C21–C22	129.0(2)	C23–N2–C26	119.80(18)
O3–C22–N2	125.5(2)	C26–O4–C25	112.16(16)
O3–C22–C21	128.5(2)	C6–C1–C2	121.3(2)
N2–C22–C21	105.97(18)	C6–C1–C11	109.8(2)
N2–C23–C24	108.84(19)	C2–C1–C11	128.9(2)
C25–C24–C23	110.1(2)	C1–C2–C3	116.9(2)
O4–C25–C24	110.21(19)	C4–C3–C2	121.6(2)
O4–C26–N2	109.53(18)	C3–C4–C5	121.1(2)
O4–C26–C16	107.26(17)	C6–C5–C4	117.0(2)
N2–C26–C16	101.60(17)	C1–C6–C5	122.0(2)
O4–C26–C27	109.45(18)	C1–C6–C7	108.74(19)
N2–C26–C27	116.34(18)	C5–C6–C7	129.2(2)
C16–C26–C27	112.11(19)	O1–C7–N1	125.9(2)

O1–C7–C6	128.1(2)	C13–C12–C14	59.76(16)
N1–C7–C6	106.02(19)	C13–C12–C11	126.5(2)
N1–C8]–C9	108.72(19)	C14–C12–C11	124.0(2)
C8]–C9–C10	110.1(2)	C14–C13–C12	60.33(16)
O2–C10–C9	110.2(2)	C15–C14–C13	120.0(2)
O2–C11–N1	109.41(18)	C15–C14–C12	123.3(2)
O2–C11–C1	106.87(17)	C13–C14–C12	59.90(16)
N1–C11–C1	101.89(17)	C7–N1–C11	112.88(18)
O2–C11–C12	109.74(18)	C7–N1–C8]	121.41(19)
N1–C11–C12	116.35(19)	C11–N1–C8]	119.67(18)
C1–C11–C12	112.0(2)	C11–O2–C10	112.55(18)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C16	9(1)	29(1)	13(1)	2(1)	−3(1)	−2(1)
C17	9(1)	31(1)	18(1)	3(1)	−5(1)	0(1)
C18	12(1)	35(2)	18(1)	6(1)	−7(1)	2(1)
C19	16(1)	40(2)	13(1)	3(1)	−8(1)	−3(1)
C20	17(1)	34(1)	16(1)	−2(1)	−2(1)	−2(1)
C21	10(1)	25(1)	14(1)	3(1)	−3(1)	−3(1)
C22	9(1)	26(1)	16(1)	1(1)	−2(1)	−1(1)
C23	14(1)	31(1)	16(1)	3(1)	−8(1)	4(1)
C24	24(1)	33(1)	17(1)	7(1)	−4(1)	3(1)
C25	20(1)	35(2)	12(1)	7(1)	−3(1)	−2(1)
C26	9(1)	28(1)	12(1)	1(1)	−5(1)	1(1)
C27	14(1)	32(1)	15(1)	−3(1)	−3(1)	−1(1)
C28	22(1)	37(2)	19(1)	−2(1)	−7(1)	−7(1)
C29	18(1)	30(1)	20(1)	1(1)	−4(1)	−2(1)
N2	9(1)	31(1)	11(1)	0(1)	−6(1)	4(1)
O3	16(1)	32(1)	23(1)	−4(1)	−2(1)	4(1)
O4	11(1)	35(1)	14(1)	5(1)	−2(1)	0(1)
C1	8(1)	28(1)	14(1)	2(1)	−3(1)	−4(1)
C2	9(1)	31(1)	18(1)	0(1)	−2(1)	1(1)
C3	11(1)	38(2)	21(1)	7(1)	−4(1)	1(1)
C4	16(1)	40(2)	12(1)	3(1)	−8(1)	0(1)
C5	18(1)	31(1)	14(1)	−3(1)	−3(1)	−1(1)
C6	10(1)	28(1)	14(1)	1(1)	−5(1)	−3(1)
C7	10(1)	27(1)	14(1)	0(1)	−3(1)	−1(1)
C8]	16(1)	31(1)	16(1)	2(1)	−10(1)	2(1)
C9	28(2)	38(2)	16(1)	6(1)	−4(1)	4(1)
C10	31(2)	38(2)	12(1)	6(1)	−3(1)	3(1)
C11	11(1)	31(1)	11(1)	1(1)	−2(1)	0(1)
C12	16(1)	30(1)	15(1)	−5(1)	−4(1)	−1(1)
C13	24(1)	39(2)	25(1)	−2(1)	−15(1)	−7(1)
C14	21(1)	27(1)	21(1)	−1(1)	−7(1)	−2(1)
C15	21(1)	38(2)	29(2)	1(1)	2(1)	−5(1)
C30	23(1)	38(2)	22(1)	3(1)	0(1)	−6(1)
N1	11(1)	30(1)	11(1)	0(1)	−6(1)	3(1)
O1	16(1)	33(1)	19(1)	−3(1)	−4(1)	4(1)
O2	17(1)	38(1)	14(1)	4(1)	0(1)	0(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H17	9091	143	2752	24	1
H18	9841	235	4221	27	1
H19	9173	1364	5188	28	1
H20	7740	2474	4709	27	1
H23A	5483	3216	1644	26	1
H23B	5333	2152	1115	26	1
H24A	6226	3243	252	30	1
H24B	7065	3583	1068	30	1
H25A	6956	1564	315	27	1
H25B	7879	2386	198	27	1
H27	7436	−72	1323	25	1
H28A	5204	532	1366	32	1
H28B	5639	−456	815	32	1
H29	6510	−1185	2129	28	1
H2	902	7372	2180	24	1
H3	44	7142	749	28	1
H4	612	5887	−158	28	1
H5	2096	4837	314	26	1
H8]1	4735	5493	3793	26	1
H8]2	4604	4399	3310	26	1
H9A	3929	4418	4723	33	1
H9B	3067	4023	3942	33	1
H10A	2258	5240	4798	33	1
H10B	3146	6077	4629	33	1
H12	2584	7654	3553	25	1
H13A	4384	8092	3987	37	1
H13B	4814	7083	3459	37	1
H14	3434	8735	2671	29	1
H15A	3560	8006	1314	44	1
H15B	3972	6932	1736	44	1
H15C	4766	7898	1776	44	1
H30A	6330	−516	3499	42	1
H30B	5147	−359	3003	42	1
H30C	5969	585	3104	42	1

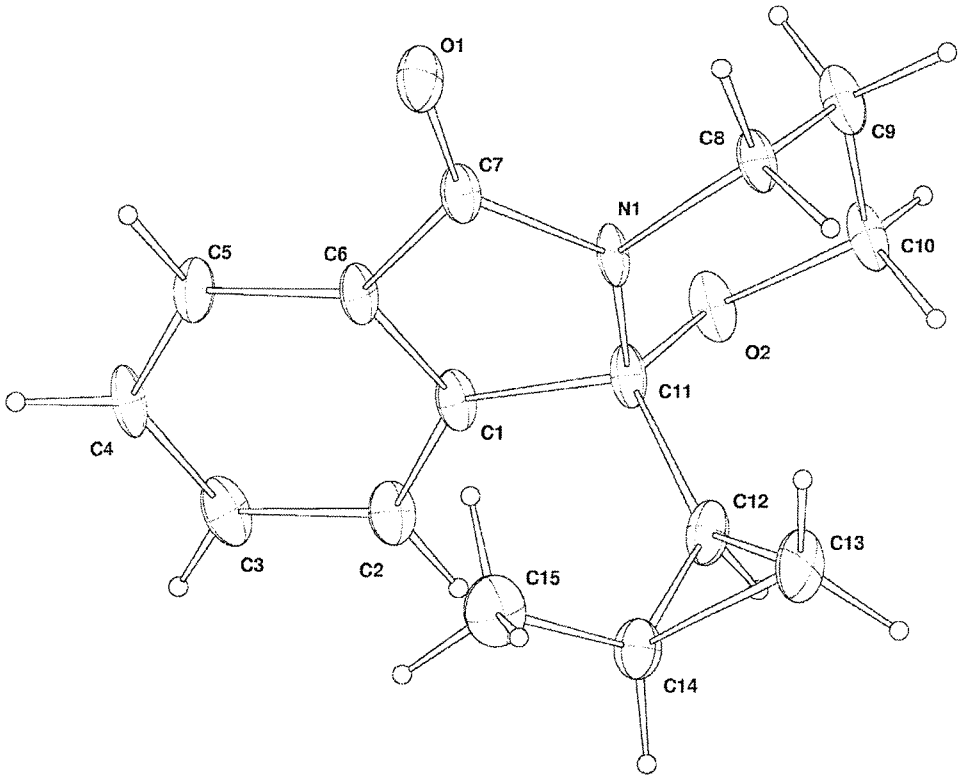
O1
C7
C8
C9
N1
C5
C6
C10
O2
C11
C1
C4
C12
C13
C3
C2
C15
C14

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Table 1. Crystal data and structure refinement.

Identification code	**03AND021**	
Empirical formula	$C_{13}H_{23}ClOSi$	
Formula weight	258.85	
Temperature	120(2) K	
Wavelength	0.71069 Å	
Crystal system	Triclinic	
Space group	*P*-1	
Unit cell dimensions	a = 8.288(5) Å	α = 73.237(5)°
	b = 11.391(5) Å	β = 80.730(5)°
	c = 16.409(5) Å	γ = 79.876(5)°
Volume	1450.2(12) Å^3	
Z	4 (2 Molecules)	
Density (calculated)	1.186 Mg / m^3	
Absorption coefficient	0.327 mm^{-1}	
F(000)	560	
Crystal	?; ?	
Crystal size	0.10 × 0.10 × 0.10 mm^3	
θ range for data collection	2.93 – 25.02°	
Index ranges	$-9 \le h \le 9$, $-13 \le k \le 13$, $-19 \le l \le 19$	
Reflections collected	18476	
Independent reflections	5050 [R_{int} = 0.0806]	
Completeness to θ = 25.02°	98.5 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9681 and 0.9681	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5050 / 0 / 298	
Goodness-of-fit on F^2	1.024	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0524, *wR2* = 0.1163	
R indices (all data)	*R1* = 0.0977, *wR2* = 0.1328	
Extinction coefficient	0.0081(17)	
Largest diff. peak and hole	0.416 and –0.387 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Si1	5971(1)	1836(1)	8328(1)	28(1)	1
Cl1	8083(1)	3837(1)	5861(1)	36(1)	1
O1	3834(3)	1020(2)	5129(1)	32(1)	1
C1	8004(4)	2215(3)	6409(2)	28(1)	1
C2	6259(3)	1932(3)	6540(2)	23(1)	1
C3	5303(3)	1787(3)	7285(2)	24(1)	1
C4	3523(4)	1564(3)	7317(2)	28(1)	1
C5	3408(4)	869(3)	6664(2)	29(1)	1
C6	3942(4)	1634(3)	5773(2)	25(1)	1
C7	5743(3)	1816(3)	5722(2)	25(1)	1
C8	2370(4)	2797(3)	7136(2)	35(1)	1
C9	2746(4)	3591(3)	6229(2)	32(1)	1
C10	2799(4)	2860(3)	5575(2)	29(1)	1
C11	6911(4)	3238(3)	8247(2)	38(1)	1
C12	7500(5)	439(3)	8703(2)	46(1)	1
C13	4141(4)	1767(4)	9163(2)	46(1)	1
C14	3914(3)	−2570(3)	7005(2)	29(1)	1
C15	2062(4)	−2324(3)	7075(2)	24(1)	1
C16	1079(4)	−2446(3)	7820(2)	27(1)	1
C17	−782(4)	−2280(3)	7796(2)	29(1)	1
C18	−1275(4)	−1364(3)	6957(2)	30(1)	1
C19	−400(4)	−1852(3)	6210(2)	26(1)	1
C20	1445(3)	−1941(3)	6204(2)	26(1)	1
C21	−1347(4)	−3534(3)	7896(2)	35(1)	1
C22	−609(4)	−4050(3)	7138(2)	32(1)	1
C23	−927(4)	−3103(3)	6284(2)	29(1)	1
C24	2967(6)	−1662(4)	8997(2)	69(1)	1
C25	3196(5)	−4415(3)	9120(2)	52(1)	1
C26	64(4)	−3027(4)	9766(2)	51(1)	1
Si2	1851(1)	−2900(1)	8910(1)	33(1)	1
Cl2	4663(1)	−4032(1)	6766(1)	38(1)	1
O2	−826(3)	−1023(2)	5404(1)	32(1)	1

Table 3. Bond lengths [Å] and angles [°].

Si1–C11	1.860(3)	C14–C15	1.502(4)
Si1–C13	1.869(3)	C14–Cl2	1.802(3)
Si1–C12	1.870(4)	C15–C16	1.340(4)
Si1–C3	1.899(3)	C15–C20	1.514(4)
Cl1–C1	1.814(3)	C16–C17	1.527(4)
O1–C6	1.447(3)	C16–Si2	1.896(3)
C1–C2	1.505(4)	C17–C18	1.534(4)
C2–C3	1.330(4)	C17–C21	1.536(4)
C2–C7	1.520(4)	C18–C19	1.518(4)
C3–C4	1.530(4)	C19–O2	1.442(3)
C4–C5	1.528(4)	C19–C20	1.514(4)
C4–C8	1.534(4)	C19–C23	1.529(4)
C5–C6	1.511(4)	C21–C22	1.522(4)
C6–C10	1.525(4)	C22–C23	1.532(4)
C6–C7	1.528(4)	C24–Si2	1.866(4)
C8–C9	1.517(4)	C25–Si2	1.856(4)
C9–C10	1.528(4)	C26–Si2	1.865(4)
C11–Si1–C13	108.19(17)	C8–C9–C10	111.0(3)
C11–Si1–C12	108.52(17)	C6–C10–C9	112.7(2)
C13–Si1–C12	107.67(18)	C15–C14–Cl2	110.8(2)
C11–Si1–C3	114.17(14)	C16–C15–C14	124.0(3)
C13–Si1–C3	109.17(15)	C16–C15–C20	124.2(3)
C12–Si1–C3	108.92(15)	C14–C15–C20	111.8(3)
C2–C1–Cl1	110.3(2)	C15–C16–C17	118.1(3)
C3–C2–C1	123.8(3)	C15–C16–Si2	124.3(2)
C3–C2–C7	124.5(3)	C17–C16–Si2	117.5(2)
C1–C2–C7	111.7(2)	C16–C17–C18	111.1(2)
C2–C3–C4	118.3(3)	C16–C17–C21	110.0(2)
C2–C3–Si1	125.0(2)	C18–C17–C21	109.8(3)
C4–C3–Si1	116.7(2)	C19–C18–C17	109.0(3)
C5–C4–C3	110.4(2)	O2–C19–C20	107.4(2)
C5–C4–C8	109.7(3)	O2–C19–C18	111.1(2)
C3–C4–C8	110.5(2)	C20–C19–C18	109.0(2)
C6–C5–C4	109.4(2)	O2–C19–C23	107.8(2)
O1–C6–C5	111.5(2)	C20–C19–C23	112.1(2)
O1–C6–C10	107.0(2)	C18–C19–C23	109.4(2)
C5–C6–C10	109.4(3)	C15–C20–C19	115.8(2)
O1–C6–C7	107.8(2)	C22–C21–C17	111.0(3)
C5–C6–C7	108.8(2)	C21–C22–C23	111.6(3)
C10–C6–C7	112.3(2)	C19–C23–C22	112.6(2)
C2–C7–C6	115.4(2)	C25–Si2–C26	107.47(18)
C9–C8–C4	112.1(3)	C25–Si2–C24	110.5(2)

C26–Si2–C24	107.1(2)	C26–Si2–C16	109.75(15)
C25–Si2–C16	112.39(16)	C24–Si2–C16	109.51(16)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si1	36(1)	29(1)	20(1)	−5(1)	−5(1)	−6(1)
Cl1	35(1)	31(1)	40(1)	−7(1)	−2(1)	−9(1)
O1	34(1)	35(1)	34(1)	−19(1)	−10(1)	1(1)
C1	27(2)	29(2)	28(2)	−7(1)	−4(1)	−5(1)
C2	24(2)	22(2)	25(2)	−7(1)	−5(1)	−1(1)
C3	28(2)	21(2)	22(2)	−5(1)	−6(1)	−2(1)
C4	29(2)	31(2)	23(2)	−5(1)	−1(1)	−10(1)
C5	30(2)	29(2)	31(2)	−11(2)	−2(1)	−8(1)
C6	30(2)	29(2)	21(2)	−13(1)	−5(1)	−5(1)
C7	24(2)	30(2)	23(2)	−10(1)	−3(1)	0(1)
C8	27(2)	46(2)	37(2)	−21(2)	−3(2)	−1(2)
C9	32(2)	30(2)	37(2)	−16(2)	−11(2)	4(1)
C10	28(2)	28(2)	32(2)	−11(2)	−9(1)	1(1)
C11	50(2)	37(2)	29(2)	−7(2)	−7(2)	−11(2)
C12	66(3)	37(2)	31(2)	−6(2)	−13(2)	5(2)
C13	47(2)	70(3)	26(2)	−18(2)	3(2)	−19(2)
C14	26(2)	29(2)	31(2)	−6(2)	−6(1)	−5(1)
C15	28(2)	20(2)	26(2)	−4(1)	−8(1)	−6(1)
C16	32(2)	24(2)	24(2)	−7(1)	−6(1)	−2(1)
C17	27(2)	31(2)	26(2)	−7(1)	−3(1)	0(1)
C18	28(2)	25(2)	34(2)	−5(2)	−7(1)	3(1)
C19	28(2)	24(2)	20(2)	1(1)	−6(1)	−2(1)
C20	26(2)	28(2)	22(2)	−3(1)	−1(1)	−8(1)
C21	30(2)	37(2)	33(2)	−1(2)	−5(2)	−5(1)
C22	37(2)	24(2)	36(2)	−5(2)	−7(2)	−9(1)
C23	30(2)	31(2)	27(2)	−4(2)	−7(1)	−9(1)
C24	115(4)	71(3)	35(2)	−9(2)	−22(2)	−47(3)
C25	54(2)	50(3)	38(2)	3(2)	−10(2)	5(2)
C26	53(2)	67(3)	30(2)	−11(2)	−9(2)	1(2)
Si2	42(1)	35(1)	23(1)	−3(1)	−11(1)	−6(1)
Cl2	32(1)	33(1)	48(1)	−10(1)	−4(1)	0(1)
O2	33(1)	34(1)	25(1)	3(1)	−14(1)	−5(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	4776	678	4983	48	1
H1A	8717	1695	6065	33	1
H1B	8426	2018	6971	33	1
H4	3165	1050	7903	33	1
H5A	4126	62	6790	35	1
H5B	2258	710	6700	35	1
H7A	6456	1107	5558	30	1
H7B	5949	2572	5259	30	1
H8A	1213	2630	7224	42	1
H8B	2484	3257	7547	42	1
H9A	3822	3889	6170	38	1
H9B	1888	4323	6114	38	1
H10A	1670	2695	5564	35	1
H10B	3175	3368	4998	35	1
H11A	6226	3976	7941	57	1
H11B	8020	3179	7934	57	1
H11C	6981	3300	8823	57	1
H12A	8455	432	8265	69	1
H12B	6985	−310	8803	69	1
H12C	7862	462	9237	69	1
H13A	4467	1840	9693	69	1
H13B	3722	976	9274	69	1
H13C	3276	2449	8960	69	1
H14A	4283	−2579	7552	34	1
H14B	4381	−1898	6547	34	1
H17	−1347	−1947	8285	34	1
H18A	−2485	−1267	6954	36	1
H18B	−961	−544	6905	36	1
H20A	2001	−2542	5882	31	1
H20B	1785	−1124	5888	31	1
H21A	−1002	−4126	8432	42	1
H21B	−2566	−3431	7939	42	1
H22A	−1096	−4803	7184	39	1
H22B	595	−4288	7155	39	1
H23A	−317	−3434	5809	34	1
H23B	−2119	−2983	6223	34	1
H24A	3284	−1863	9577	104	1
H24B	2245	−868	8880	104	1
H24C	3959	−1605	8580	104	1
H25A	4232	−4341	8737	78	1
H25B	2633	−5038	9017	78	1
H25C	3432	−4667	9717	78	1

H26A	−596	−3633	9717	77	1
H26B	−621	−2219	9703	77	1
H26C	469	−3296	10329	77	1
H2	−1733	−1154	5305	48	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O1–H1···O1^{i}	0.84	2.11	2.836(4)	144.3
O2–H2···O1^{ii}	0.84	1.95	2.771(3)	164.8

Symmetry transformations used to generate equivalent atoms:
(i) −x+1,−y,−z+1 (ii) −x,−y,−z+1