THE UNIVERSITY OF WARWICK

Library Declaration and Deposit Agreement

1. **STUDENT DETAILS**

Please complete the following:

Full name: ……

University ID number: …….

2. **THESIS DEPOSIT**

2.1 I understand that under my registration at the University, I am required to deposit my thesis with the University in BOTH hard copy and in digital format. The digital version should normally be saved as a single pdf file.

2.2 The hard copy will be housed in the University Library. The digital version will be deposited in the University's Institutional Repository (WRAP). Unless otherwise indicated (see 2.3 below) this will be made openly accessible on the Internet and will be supplied to the British Library to be made available online via its Electronic Theses Online Service (EThOS) service. [At present, theses submitted for a Master's degree by Research (MA, MSc, LLM, MS or MMedSci) are not being deposited in WRAP and not being made available via EthOS. This may change in future.]

2.3 In exceptional circumstances, the Chair of the Board of Graduate Studies may grant permission for an embargo to be placed on public access to the hard copy thesis for a limited period. It is also possible to apply separately for an embargo on the digital version. (Further information is available in the Guide to Examinations for Higher Degrees by Research.)

2.4 If you are depositing a thesis for a Master's degree by Research, please complete section (a) below. For all other research degrees, please complete both sections (a) and (b) below:

(a) Hard Copy

I hereby deposit a hard copy of my thesis in the University Library to be made publicly available to readers (please delete as appropriate) EITHER immediately OR after an embargo period of ……..... months/years as agreed by the Chair of the Board of Graduate Studies.

I agree that my thesis may be photocopied. YES / NO (Please delete as appropriate)

(b) Digital Copy

I hereby deposit a digital copy of my thesis to be held in WRAP and made available via EThOS.

Please choose one of the following options:

EITHER My thesis can be made publicly available online.YES / NO (Please delete as appropriate)

OR My thesis can be made publicly available only after.....(Please give date)

YES / NO (Please delete as appropriate)

OR My full thesis cannot be made publicly available online but I am submitting a separately identified additional, abridged version that can be made available online.

YES / NO (Please delete as appropriate)

OR My thesis cannot be made publicly available online. YES / NO (Please delete as appropriate)

3. **GRANTING OF NON-EXCLUSIVE RIGHTS**

Whether I deposit my Work personally or through an assistant or other agent, I agree to the following:

Rights granted to the University of Warwick and the British Library and the user of the thesis through this agreement are non-exclusive. I retain all rights in the thesis in its present version or future versions. I agree that the institutional repository administrators and the British Library or their agents may, without changing content, digitise and migrate the thesis to any medium or format for the purpose of future preservation and accessibility.

4. **DECLARATIONS**

(a) I DECLARE THAT:

- I am the author and owner of the copyright in the thesis and/or I have the authority of the authors and owners of the copyright in the thesis to make this agreement. Reproduction of any part of this thesis for teaching or in academic or other forms of publication is subject to the normal limitations on the use of copyrighted materials and to the proper and full acknowledgement of its source.

- The digital version of the thesis I am supplying is the same version as the final, hardbound copy submitted in completion of my degree, once any minor corrections have been completed.

- I have exercised reasonable care to ensure that the thesis is original, and does not to the best of my knowledge break any UK law or other Intellectual Property Right, or contain any confidential material.

- I understand that, through the medium of the Internet, files will be available to automated agents, and may be searched and copied by, for example, text mining and plagiarism detection software.

(b) IF I HAVE AGREED (in Section 2 above) TO MAKE MY THESIS PUBLICLY AVAILABLE DIGITALLY, I ALSO DECLARE THAT:

- I grant the University of Warwick and the British Library a licence to make available on the Internet the thesis in digitised format through the Institutional Repository and through the British Library via the EThOS service.

- If my thesis does include any substantial subsidiary material owned by third-party copyright holders, I have sought and obtained permission to include it in any version of my thesis available in digital format and that this permission encompasses the rights that I have granted to the University of Warwick and to the British Library.

5. **LEGAL INFRINGEMENTS**

I understand that neither the University of Warwick nor the British Library have any obligation to take legal action on behalf of myself, or other rights holders, in the event of infringement of intellectual property rights, breach of contract or of any other right, in the thesis.

Please sign this agreement and return it to the Graduate School Office when you submit your thesis.

Student's signature: .....…… Date: .....

Lewis Acid-Promoted (3+2) Cycloadditions and Multi-Component Reactions of Methyleneaziridines

by

Karen Griffin

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry

Department of Chemistry, University of Warwick

December 2011

Table of Contents

Acknowledgements

First and foremost, I would like to express my sincere gratitude to my supervisor, Professor Mike Shipman, for affording me this wonderful opportunity, for his guidance and patience, and most of all for having faith in me. It's been tough, but I think we got there in the end. I am also grateful to the EPSRC for their financial assistance.

My thanks go to the technical staff (past and present) working in the Department of Chemistry at Warwick, specifically, Adam Clarke, Ivan Prokeš, Lijiang Song and the late John Bickerton, for providing excellent NMR and mass spec facilities.

A huge thankyou to my lovely friends, aka 'Team Shipman', namely Mark Davies, Pete Mumford, Claire Cariou, Estelle Gallienne, Emma Morris, Mike Brown, Matt Finerty, Gina Musio, Rosmara Mansueto, Thuy Hoang, Amélie Duraud, Greg Iacobini, Alex Hough, Penny Turner, Ben Beasley, Samiullah Samiullah, Fran Bayliffe, Nicola Powell, Sam Coe, Buster Collinson and Ellanna Griffin, for making me smile on a daily basis....I love you all!

To my dear father-in-law, Danny, who was taken far too soon. Our loss is heaven's gain!

To my dad....what can I say? Not a day goes by when I don't think of you. I wish you could have stuck around to share my life achievements....I know you would have been so proud. And mum, you are the kindest, most generous, humble person I know. Thankyou for loving me unconditionally and for moulding me into

the person I am today. To my brothers and sisters, Steve, Mick, Anna and Vicki, you mean the world to me and I love you all very much.

Daniel, thankyou for being a wonderful daddy and husband. You work so hard and I want you to know it doesn't go unnoticed. My achievement is equally yours because I could not have done anything without your unwavering love and support. Armadillo!

Finally, to my beautiful daughters, nothing comes close to the sense of pride that I feel when I look at you girls. Of everything I have achieved in my life, bringing my children into the world has been the most rewarding. Kate, Molly, Ellie and Lola….

I love you to the moon and back!

Declaration

I declare that the material described that is not original has been identified and appropriately referenced. I certify that no material within this thesis has been submitted for a prior degree or a degree at another university.

Signed:

Date:

Abstract

This thesis describes our attempts towards realising new chemistry involving methyleneaziridines, for the main part, focusing on novel cycloaddition reactions involving this unique, densely functionalised heterocycle.

Contrary to methyleneaziridines, the cycloaddition reactions of aziridines have been extensively studied. Thus, chapter one presents an introduction and literature review of cycloaddition reactions involving the aziridine nucleus, in order to contextualise the research described in chapter two.

Chapter two describes the discovery and development of a novel Lewis acid-promoted (3+2) cycloaddition reaction of methyleneaziridines onto alkyne and alkene acceptors. Both inter- and intramolecular variants of this methodology were examined. The latter substrates being readily made by functionalisation of the parent methyleneaziridines through an efficient lithiation/alkylation sequence. These cycloadditions most likely proceed in a stepwise manner through opening of the methyleneaziridine by the nucleophilic alkene (or alkyne) and subsequent ring closure of the nitrogen atom onto the resultant carbocation. This chemistry provides a powerful new approach to a variety of heterocyclic systems including highly functionalised pyrroles and pyrrolidines.

Chapter three begins with a brief introduction to multicomponent reactions, focusing on those which incorporate the methyleneaziridine nucleus. Our efforts towards realising new multicomponent reactions involving methyleneaziridines are detailed. Specifically, the attempted syntheses of 3,4-dihydro-1(*2H*)-isoquinolones, α-fluorinated and *N*-*t*-butylsulfinyl ketimines are described.

Chapter four details the experimental procedure and characterisation data for the novel compounds produced in this thesis.

Acronyms and Abbreviations

Ac	Acetyl
acac	Acetylacetonate
AIBN	Azobisisobutyronitrile
Alk	Alkyl
Anal.	Analysis
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	Broad
Bu	Butyl
Calcd.	Calculated
cat.	Catalytic
Cbz	Carbobenzyloxy
cf.	Confer
CI	Chemical ionisation
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
Cy	Cyclohexyl
δ	Chemical shift
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
1,3-DC	1,3-Dipolar cycloaddition
DCE	Dichloroethane

de	Diastereomeric excess
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
dr	Diastereomeric ratio
E	Electrophile
ee	Enantiomeric excess
EDG	Electron-donating group
EI	Electron impact
ES	Electrospray
esp	3,3’-(1,3-Phenylene)bis(2,2-dimethyl)propanoic acid
Et	Ethyl
Eq.	Molar equivalents
EWG	Electro-withdrawing group
FMO	Frontier molecular orbital
GCMS	Gas chromatography mass spectrometry
HMBC	Heteronuclear Multiple Bond Coherence
HMQC	Heteronuclear Multiple Quantum Coherence
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectroscopy
Hz	Hertz

i-	Iso
IR	Infrared
KHMDS	Potassium bis(trimethylsilyl)amide
L	Ligand
LA	Lewis acid
LDA	Lithium diisopropylamide
LHDMS	Lithium bis(trimethylsilyl)amide
Lit.	Literature value
LRMS	Low resolution mass spectroscopy
LUMO	Lowest occupied molecular orbital
m	Multiplet
M	Metal
m.p.	Melting Point
m-CPBA	*meta*-Chloroperoxybenzoic acid
MCR	Multi-component reaction
Me	Methyl
MeCN	Acetonitrile
MHz	Megahertz
MS	Mass spectroscopy
NBS	*N*-Bromosuccinimide
NFSI	*N*-Fluorobenzenesulfonimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
Ns	*para*-Nitrobenzenesulfonyl

Nu	Nucleophile
o-	*ortho*-
p-	*para*-
p	Pentet
PEG	Polyethylene glycol
Ph	Phenyl
Phth	Phthalimide
ppm	Parts per million
Pr	Propyl
q	Quartet
rcn.	Reaction
R_f	Retention factor
rt	Room temperature
s-	*sec*-
s	singlet
SM	Starting material
S_N2	Bimolecular nucleophilic substitution
t-	*tert*-
T	Temperature
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TCNE	Tetracyanoethylene
Tf	Triflate
TFA	Trifluoroacetic acid

TLC	Thin layer chromatography
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMM	Tetramethylene methane
TMS	Trimethylsilyl
Ts	Tosyl
w/v	Weight per unit volume

Chapter 1:

Cycloaddition Reactions of Aziridines

In chapter two, the discovery and development of a novel (3+2) cycloaddition process involving methyleneaziridines is discussed. However, literature precedent for this type of transformation is scant. In order to contextualise this work, this chapter outlines earlier related research into the cycloaddition reactions of aziridines which, on the contrary, have been extensively studied.

Chapter three details our efforts towards realising new multi-component reactions involving methyleneaziridines. Previous related research in this area is described therein.

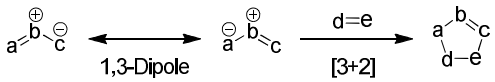
1.1. Introduction

Heterocyclic compounds as a group play a significant role in many life processes and dominate modern organic chemistry. Of more than 20 million chemical compounds currently registered, heterocycles are thought to constitute more than half. They are important, not only due to their abundance, but also due to their chemical and biological significance.[1] DNA, for example, is composed of heterocyclic bases - purines and pyrimidines. Many heterocyclic compounds, both natural products and synthetic derivatives, are pharmacologically active, while others have applications in the field of dyes, agrochemicals, polymers etc. Despite this, the field of heterocyclic chemistry is far from being fully explored,[2] justifying the continued efforts by the scientific community to develop optimal synthetic approaches to a variety of heterocyclic compounds.

Among the most powerful synthetic processes available for the construction of organic molecules are cycloaddition reactions, which involve simultaneous or asynchronous formation of two or more bonds, often with a high degree of stereo- and regio-selectivity.[3]

Cycloaddition reactions are typically classified according to the number of new σ-bonds or to the size of the ring formed. Pre-eminent among them is the Diels-Alder (4+2) cycloaddition reaction by virtue of its versatility and ability to construct six-membered rings with up to four stereogenic centres in a regio-, stereo- and enantio-controlled manner. Both inter- and intra-molecular variants of this process have been described.[4]

Five-membered carbocycles are commonly constructed using the (3+2) cycloaddition reaction, involving a 1,3-dipole and a dipolarophile (Scheme 1.1). 1,3-Dipolar cycloaddition (1,3-DC) reactions are isoelectronic with the Diels-Alder process in that they are both $[_{\pi}4_{s}+_{\pi}2_{s}]$ reactions and proceed through a 6π-electron 'aromatic' transition state.[5]



Scheme 1.1.

In the late 1950s, Rolf Huisgen conducted a general study into the mechanism of addition of diazoalkanes onto angularly strained double bonds. This pioneering work led to the classification of 1,3-dipoles and the generalisation of 1,3-dipolar cycloaddition reactions.[6] Ultimately this study resulted in the prediction and discovery of new classes of 1,3-dipoles, as well as numerous new reactions.

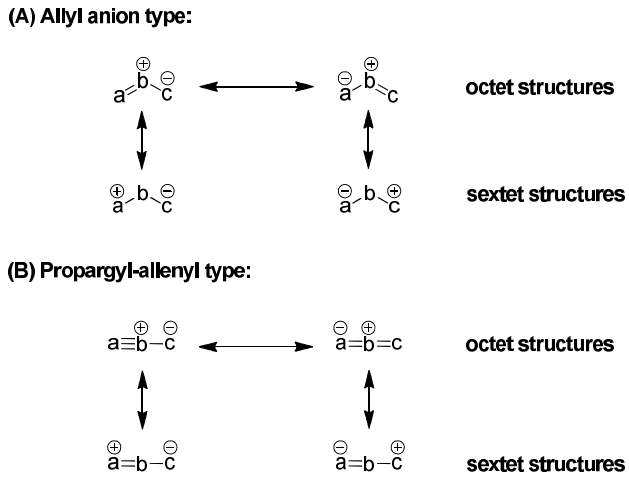
1.2. Classification of 1,3-dipoles

For 1,3-DC reactions, the 4π-electron component differs from the diene used in Diels-Alder reactions in that it contains only three atoms. The so-called 1,3-dipole is represented by zwitterionic octet resonance structures in which the positive charge is located on the central atom and the negative charge is distributed over the two terminal atoms (Scheme 1.2).[5] Common examples include atmospheric components such as ozone (O_3) and nitrous oxide (N_2O) as well as the highly popular azides (N_3R) employed in click chemistry.[8]

Like allyl anions, all 1,3-dipoles possess four electrons, occupying three parallel π-orbitals. However, while the terminal centres of allyl anions are only nucleophilic, the termini of 1,3-dipole systems are ambivalent, thus displaying both electrophilic and nucleophilic activity.[6a]

Restricting the permutations to carbon, nitrogen and oxygen, Huisgen developed a simple classification system for 1,3-dipoles resulting in eighteen possibilities, twelve of the allyl anion type and six of the propargyl-allenyl type.[9]

In dipoles of the allyl anion type, two resonance structures in which the three centres have an electron octet and two structures in which the terminal atoms *a* or *c* has an electron sextet, can be drawn.[10] The central atom can be nitrogen, oxygen or sulfur. Allyl anion type 1,3-dipoles are bent (Scheme 1.2, A).

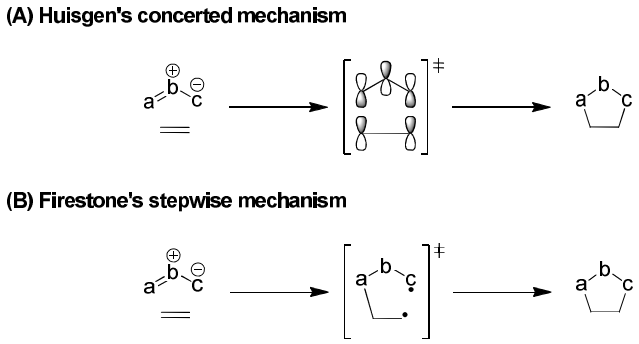


Scheme 1.2.

Dipoles of the propargyl-allenyl type are characterised by an additional π orbital located in the plane perpendicular to the allyl anion type molecular orbital. This additional π orbital makes 1,3-dipoles of this type linear in structure but is not directly involved in the resonance structures and reactivity of the dipole.[10] Atoms *a* and *c* can be carbon, nitrogen or oxygen, while the central atom *b* is restricted to nitrogen as no other element has an additional electron pair capable of donation to the electron deficient sextet centre *a*, while remaining in the triply bonded neutral state (Scheme 1.2, B).

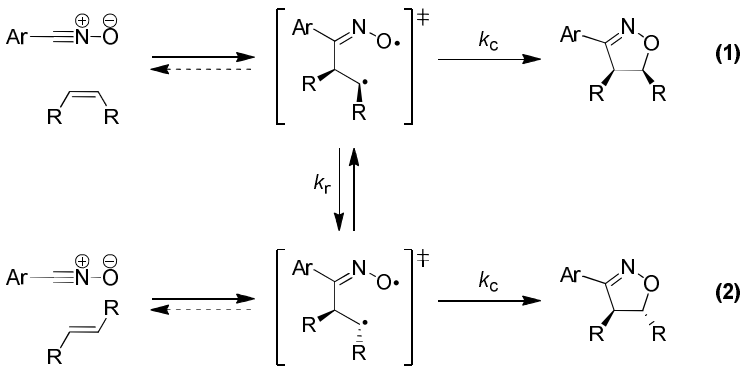
1.3. Mechanism of 1,3-dipolar cycloadditions

The mechanism of 1,3-DC reactions was the subject of vigorous debate.[11] On the basis of kinetic and stereochemical results, Huisgen developed a detailed rationale for a concerted (although sometimes asynchronous) mechanism (Scheme 1.3, A).[12]



Scheme 1.3.

On the basis of the same experimental results, Firestone presented a variety of challenges to the concerted mechanism, implicating diradical intermediates in a stepwise process (Scheme 1.3, B). In this two stage mechanism, he argued that one σ-bond is formed preferentially to afford an unstable diradical intermediate, and that if the rate constant for C-C bond rotation (k_r) in a diradical intermediate were significantly smaller than the rate constant for cyclisation (k_c), high levels of stereospecificity would still be observed (Scheme 1.4).[13]



Scheme 1.4. Hypothetical intermediates for stepwise 1,3-DC reactions of nitrile oxides onto *cis*- or *trans*-disubstituted olefins.[14]

The dispute was finally settled in favour of the concerted mechanism based on the stereospecificity observed in the 1,3-DC reaction of *p*-nitrobenzonitrile oxide with

trans-1,2-dideuterioethylene, which afforded the *trans*-isoxazoline exclusively (R = D , Scheme 1.4, eq. 2). If diradical intermediates were operative in this process, significant scrambling of stereochemistry would be observed in the cyclic product, since rotations about single bonds to deuterated primary radical centres in diradicals are rapid relative to the rate of cyclisation, *i.e.* $k_r > k_c$.[14]

Given the compelling, if not conclusive experimental evidence, it is now generally accepted that the majority of 1,3-DC reactions are concerted[9] and proceed *via* a thermally allowed suprafacial process governed by the Woodward-Hoffman rules.[15] Despite fiercely defending the notion of a concerted mechanism for many years however, Huisgen was keen to highlight that "orbital control allows concertedness, but does not forbid a two-step reaction course,"[16] and in 1986, went on to report the first example of a non-stereospecific stepwise 1,3-DC reaction, in which zwitterionic intermediates were proposed. The large difference in Frontier Molecular Orbital (FMO) energies of the reacting components was regarded as a prerequisite for this unusual two-step reaction pathway.[17]

Many aspects of 1,3-DC reactions can be accounted for by FMO theory,[18] which predicts that the reactivity of dipoles towards dipolarophiles is directed by the most favourable interaction between the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) of the two reactants.

Sustmann applied FMO theory to the reactivity of concerted 1,3-DC reactions for substituted dipolarophiles.[19] He classified these reactions into three types

according to the relative FMO energies of the 1,3-dipole and dipolarophile (Figure 1.1).

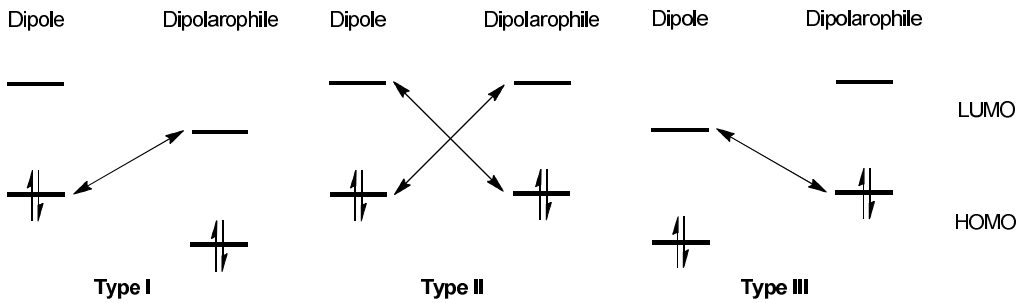


Figure 1.1.

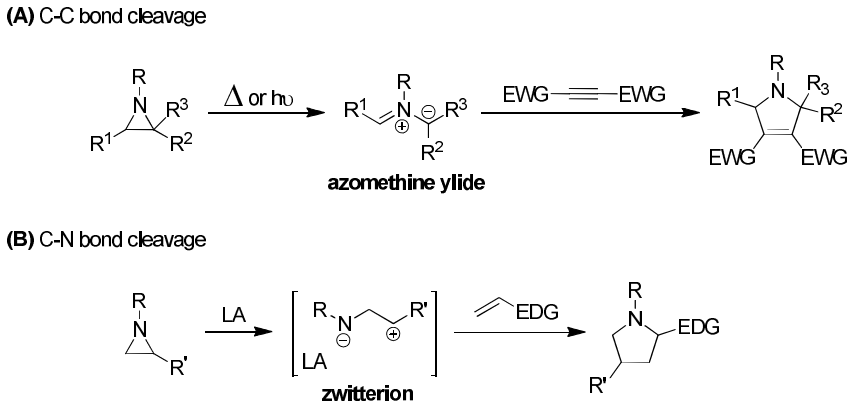
Type I reactions have the smallest energy separation between the $HOMO_{dipole}$ and the $LUMO_{dipolarophile}$. These reactions involve nucleophilic 1,3-dipoles such as diazomethane or other ylides,[20] and are accelerated by electron-donating substituents in the dipole and electron-withdrawing substituents in the dipolarophile.[5] In type III reactions, charge transfer occurs in the opposite direction and the $HOMO_{dipolarophile}$-$LUMO_{dipole}$ interaction is dominant. These reactions involve electrophilic 1,3-dipoles such as ozone and nitrous oxide. Electron-donating substituents in the dipolarophile enhance the rate of these reactions by increasing the energy of the $HOMO_{dipolarophile}$ and essentially diminishing the FMO energy gap. Most 1,3-DC reactions fall into a third class, *i.e*. type II reactions, in which the dipole and dipolarophile FMO energies are near equivalent. These reactions are referred to as ambiphilic.[20] The controlling interaction in these reactions depends on the nature of the dipolarophile and on the electronic nature of the dipole substituents and can be accelerated by both electron-donating and electron-withdrawing substituents in either component.[5]

Metals, such as Lewis acids, have been shown to accelerate the rate of 1,3-DC reactions. For example, in type III 1,3-DC reactions, coordination of a Lewis acid to the 1,3-dipole reduces the $LUMO_{dipole}$-$HOMO_{dipolarophile}$ energy gap, resulting in a faster reaction. Metal complexation is of fundamental importance to catalytic asymmetric variants of this reaction.

1.4. Aziridines: Synthetic precursors to azomethine ylides and zwitterions

Due to their versatile reactivity, aziridines are broadly used as synthetic precursors for many chemical transformations. Their chemistry is dominated by ring-opening reactions by virtue of their inherent ring strain.[21]

Bond cleavage of aziridines can occur *via* two pathways.[22] The first involves thermal or photolytic σ_{CC} bond cleavage to generate azomethine ylides as transient intermediates (Scheme 1.5, A). This manifold enjoys a prominent role in pyrrolidine synthesis due to the facility with which the derived 1,3-dipoles may be intercepted in 1,3-DC reactions.[23] The second approach involves σ_{CN} bond cleavage and involves the use of a Lewis acid to generate zwitterionic intermediates (Scheme 1.5, B). The actual reaction pathway is strongly influenced by the substitution pattern of the aziridine as well as the reaction conditions.[24]

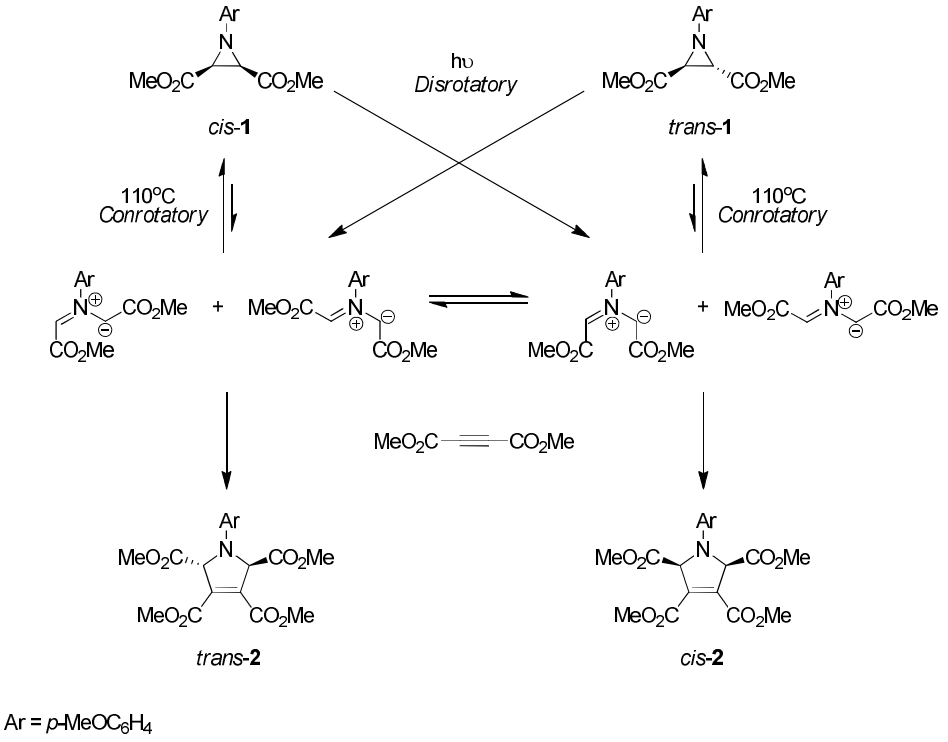


Scheme 1.5.

A number of methods are available for the generation of azomethine ylides including desilylation of α-silyl 'onium' salts,[25] 1,2-prototropic rearrangement of α-amino acid imines,[26] addition of carbenes or carbenoids onto imines,[27] and by thermal or photochemical ring opening of aziridines.

The first 1,3-DC reactions involving aziridines were reported by Heine and Peavy,[28] and by Padwa and Hamilton[29] in 1965, but it wasn't until a year later, through the pioneering work of Huisgen and co-workers that the thermolysis of aziridines was linked with the existence of reactive azomethine ylide intermediates.[30] Moreover, this study provided one of the first experimental verifications of the Woodward-Hoffman theory of stereochemistry in electrocyclic reactions.

The thermal equilibration of *cis*- and *trans*-**1** in carbon tetrachloride was followed by NMR spectroscopy at 100 and 120 °C. The mechanism for this stereoisomerisation was assumed to take place *via* azomethine ylide intermediates (Scheme 1.6).



Scheme 1.6.

Woodward-Hoffman theory predicts that thermolysis of *cis*-**1** should proceed with conrotatory ring-opening to give the *trans*-azomethine ylide.[31] However, interconversion of *trans*-azomethine ylides to their *cis*-counterparts is possible by virtue of rotation about the C-N bond. When a reactive dipolarophile was introduced into the system, the rate of ylide interconversion relative to the rate of cycloaddition was negligible, allowing the latter reaction pathway to predominate. The more reactive the dipolarophile, the higher the stereoselectivity of the overall process.[30a]

Dimethylacetylene dicarboxylate was found to be sufficiently reactive to completely suppress the equilibration process, *i.e.* dimethylacetylene dicarboxylate combined with *cis*-**1** to give exclusively the *trans*-pyrrolidine **2**, and with *trans*-**1** to give exclusively the *cis*-pyrrolidine **2**.[32]

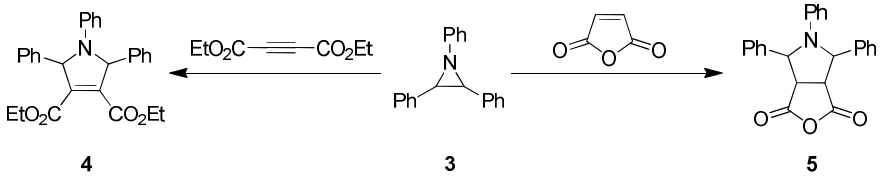
In a separate experiment, photolysis[33] of *trans*-**1** in dimethylacetylene dicarboxylate as solvent effected a stereospecific conversion to the *trans*-pyrrolidine **2**, corresponding to a disrotatory ring cleavage. This result is opposite to that obtained by thermolysis, reinforcing the predictions of Woodward and Hoffman.

1.5. Cycloaddition reactions of aziridines

1.5.1. (3+2) Cycloaddition reactions of aziridines

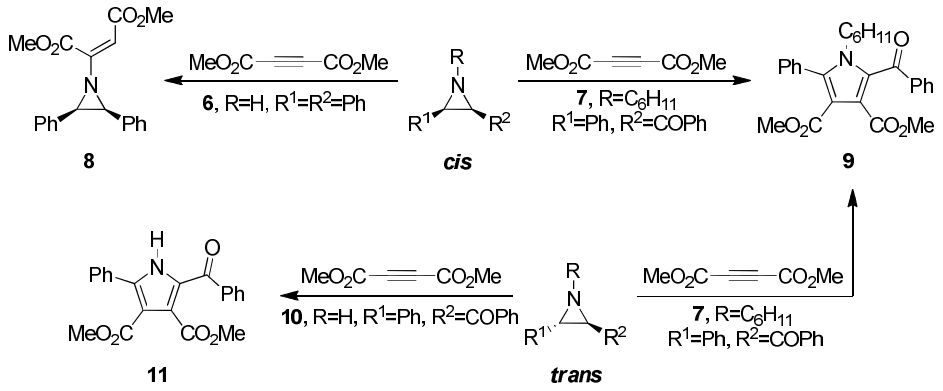
1.5.1.1. (3+2) Cycloaddition reactions involving C-C ring cleavage

The first documented (3+2) cycloadditions of azomethine ylides generated thermally from aziridines with olefins and acetylenes date back to the mid-1960s. Heine and Peavy disclosed "a new reaction involving carbon-carbon bond cleavage of the aziridine ring," by way of the reaction of 1,2,3-triphenylaziridine **3** with diethylacetylene dicarboxylate and maleic anhydride (Scheme 1.7). The products from these reactions were identified as pyrroline **4** and pyrrolidine **5** respectively.[28]



Scheme 1.7.

Later, Padwa and Hamilton noted a different mode of reactivity towards dimethylacetylene dicarboxylate depending on the nature of the aziridine (Scheme 1.8).[29]

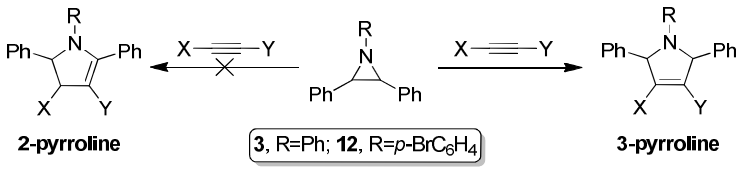


Scheme 1.8.

Under thermal conditions, the reaction of *cis*-2,3-diphenyl aziridine **6** with dimethylacetylene dicarboxylate resulted in *cis*-diester **8**, in which the aziridine ring remained intact. While the same reaction with *trans*-2-phenyl-3-benzoyl-aziridine **10** proved to be dramatically different, *i.e.* the reaction product in this case was identified as pyrrole **11**. The same reaction involving *cis*- and *trans*-1-cyclohexyl-2-phenyl-3-benzoylaziridine provided pyrrole **9**, following somewhat forcing oxidation conditions.[34]

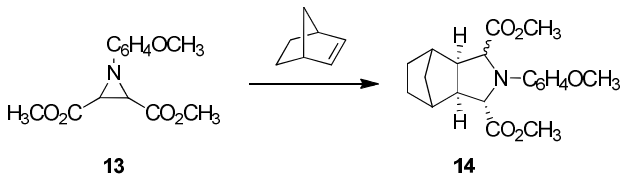
Heine and Peavy further contributed to this area through the reaction of aziridines with a number of acetylenes and olefins. In each instance σ_{CC} cleavage of the aziridine ring was observed. This was confirmed by examination of the ^{1}H NMR spectra of the cycloadducts derived from the reaction of 1,2,3-triphenylaziridine **3** or 1-*p*-bromophenyl-2,3-diphenylaziridine **12** with a number of acetylenes. In each case, a single resonance peak corresponding to the methine group of a 3-

pyrroline was detected. A 2-pyrroline would give rise to at least two peaks due to two non-equivalent hydrogens (Scheme 1.9).[35]



Scheme 1.9.

As part of his pioneering work in the field of 1,3-DC reactions, Huisgen focused his attention on the addition of diazoalkanes onto angularly strained, and thus energy-rich double bonds.[6] He later found that aziridines such as **13** could also undergo addition onto strained systems, such as norbornene, to form the corresponding cycloadducts **14** in high yields (Scheme 1.10).[30b] Thermally induced cycloadditions of aziridines onto other angularly strained π-systems, such as 1,2,3-triphenyl-cyclopropene[36] and dimethyl 1-cyclobutene-1,2-dicarboxylate,[37] have also been described.



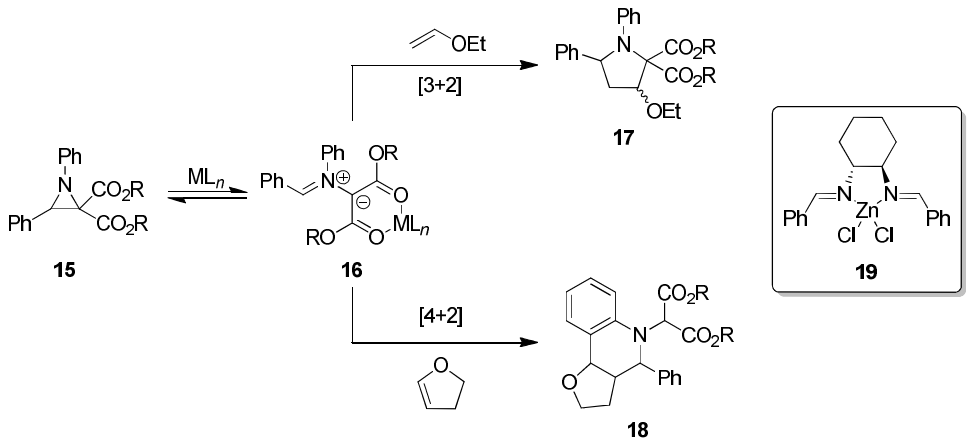
Scheme 1.10.

The activation barrier for electrocyclic σ_{CC} bond cleavage in a typical *N*-aryl-2,3-diester aziridine was calculated to be ca. 122 kJ mol^{-1}, which translates as rather forcing conditions in terms of conventional thermolysis.[38] With this in mind, the

search for mild, selective (3+2) cycloadditions of aziridines continues apace today.

Supercritical carbon dioxide ($scCO_2$) as a reaction medium has been shown to significantly enhance 1,3-DC reactions of aziridines, leading to cycloadducts in higher yields and shorter reaction times than those obtained in neat solvents,[39] while a number of efficient microwave-assisted cycloadditions of aziridines have also been described.[40]

Johnson and co-workers reported the first productive cycloadditions of azomethine ylides obtained from Lewis acid-promoted σ_{CC} bond cleavage of aziridines (Scheme 1.11).[41] They correctly predicted that metal coordinated ylides such as **16** would be extremely electron deficient, thus belonging to type III in Sustmann's classification of 1,3-dipolar cycloadditions, and that electron-rich dipolarophiles should accelerate the rate of cycloaddition.

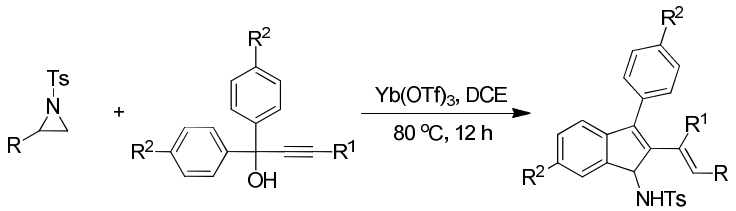


Scheme 1.11.

Among a number of representative Lewis acids tested, Zn(II) salts were found to be most suitable in promoting (3+2) cycloadditions of aziridines onto acyclic enol

ethers, as well as (4+2) cycloadditions onto cyclic electron-rich dipolarophiles. The latter manifold is thought to proceed *via* a Mannich-type addition to the ylide, followed by intramolecular Freidel-Crafts alkylation. Moreover, efforts to render the reaction catalytic in Lewis acid proved successful, *i.e.* (*N*,*N*'-dibenzylidenecyclohexane-1,2-diamine)-$ZnCl_2$ **19** provided good yields in both (3+2) and (4+2) cycloadditions at 20 mol% catalyst loading.

A recent communication described the synthesis of functionalised indenes *via* a novel Lewis acid-catalysed cascade reaction of *N*-tosylaziridines with propargylic alcohols (Scheme 1.12).[42]



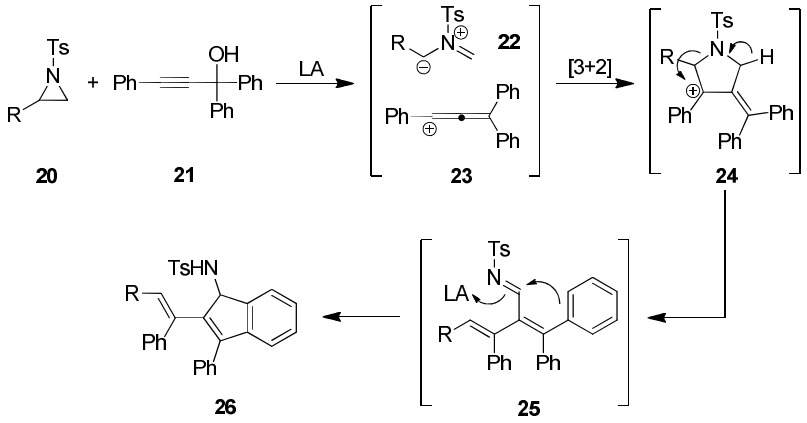
20 **21** **26**

Scheme 1.12.

Following an exhaustive screen of the reaction conditions, $Yb(OTf)_3$ (10 mol%) was identified as the most efficient catalyst for this transformation, while DCE was the most suitable solvent. This approach is attractive since many of the substrates are readily accessible and more importantly, since further elaboration of the products provides entry to a number of biologically active indene derivatives and related carbocycles, such a polycyclic indenes, indenimines and indenones.[43]

The proposed mechanism for this cascade reaction incorporates a key (3+2) cycloaddition step between reactive intermediates formed concurrently in the

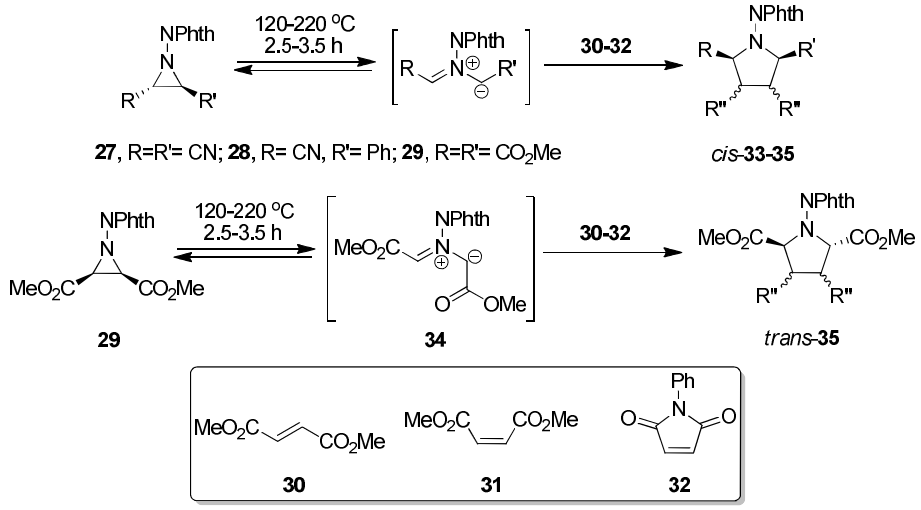
presence of a Lewis acid, *i.e.* azomethine ylide **22** and cation **23**, formed as a result of a Meyer-Schuster rearrangement[44] of propargyl alcohol **21** (Scheme 1.13).



Scheme 1.13.

Through research conducted by Kuznetsov and co-workers, 2,3-disubstituted phthalimidoaziridines emerged as useful precursors to various compounds in the difficult to access, *N*-aminodihydropyrrole and *N*-aminopyrrolidine series.[45] Aziridine substituents were carefully selected on the basis of published data.[46] Cyano groups are strongly electron withdrawing and facilitate aziridine ring cleavage, as do methoxycarbonyl substituents, albeit to a lesser extent, while phenyl substituents efficiently delocalise both positive and negative charges.

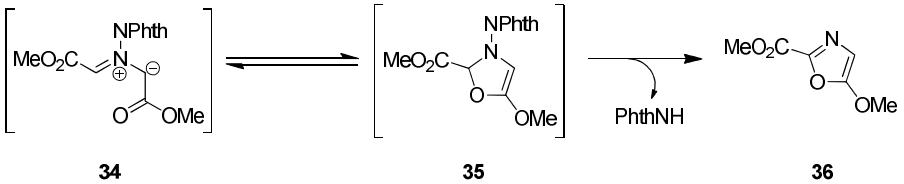
In general, thermolysis of *trans*- and *cis*-2,3-disubstituted phthalimidoaziridines **27-29** in the presence of dimethyl fumurate **30**, dimethyl maleate **31**, and *N*-phenylmaleimide **32** occurred stereospecifically and stereoselectively, to afford the corresponding *cis*- and *trans*-1-phthalimidopyrrolidine derivatives **33-35** respectively, *i.e.* products of 1,3-DC reactions involving azomethine ylides intermediates (Scheme 1.14).



Scheme 1.14.

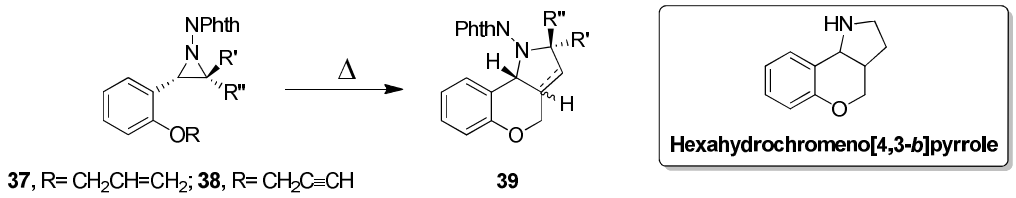
In accordance with the Woodward-Hoffman rules,[15] thermally-induced ring opening of *cis*- and *trans*-aziridines occurred in a conrotatory manner to afford *trans*- and *cis*-azomethine ylides respectively. Furthermore, retention of relative configuration of substituents in the dipolarophiles was observed, suggesting a concerted mechanism for the cycloaddition process.

A deviation from the general trend occurred upon reaction of *cis*-**29** with dimethyl fumurate **30**, *i.e.* as well as the expected cycloadduct *trans*-**35**, oxazole **36** was formed, presumably *via* competitive intramolecular 1,5-electrocyclisation of the transient azomethine ylide **34**[47,48] followed by aromatisation of oxazoline **35** by elimination of phthalimide (Scheme 1.15).[45b]



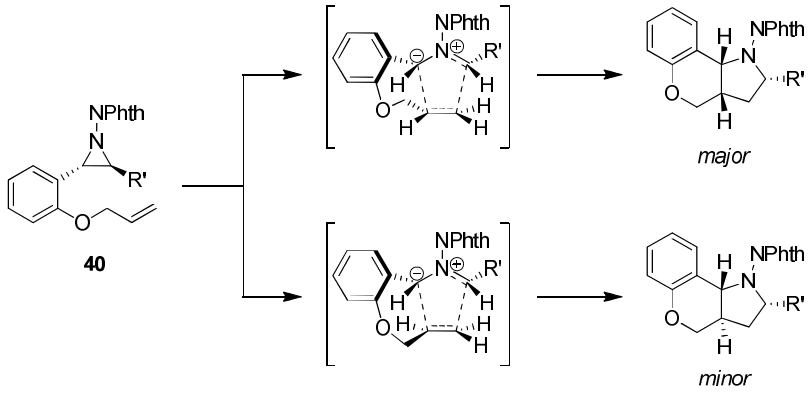
Scheme 1.15.

A number of *N*-phthalimidoaziridines bearing appropriately functionalised side-chains were later shown to participate in thermally-induced intramolecular cycloadditions reactions,[49] in some cases providing direct access to structural analogues of the hexahydrochromeno[4,3-b]pyrrole scaffold found in various natural products (Scheme 1.16).[50]



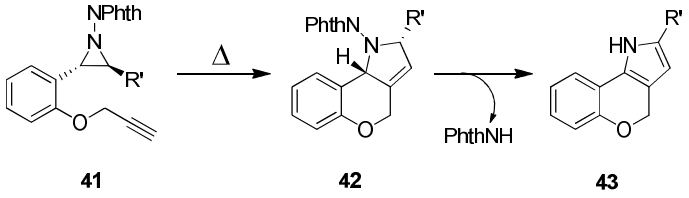
Scheme 1.16.

Thermolysis of 2,3-disubstituted systems, *i.e.* where R'=CO_2Me or CN and R''=H, generally resulted in stereospecific intramolecular cycloaddition to afford the expected *N*-phthalimidopyrrolidine derivatives (Scheme 1.16). In **40**, where R=$CH_2CH=CH_2$, two different plausible cycloaddition transition states gave rise to diastereoisomers in a ~2:1 ratio, with either *cis*- or *trans*-configuration at the five- and six-membered ring junctions (Scheme 1.17).



Scheme 1.17.

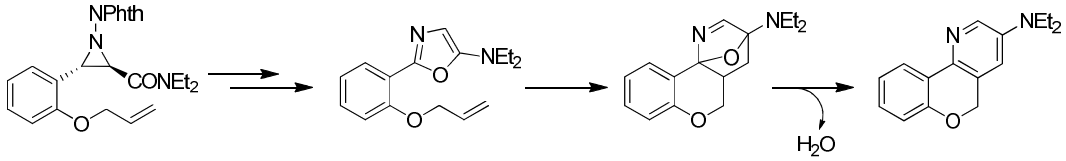
Thermolysis of aziridines bearing an alkynyl side chain gave mixtures of the corresponding pyrrolines **42** as well as pyrroles **43**, thought to be formed as a result of loss of phthalimide from the initially formed pyrrolines **42** (Scheme 1.18).



41 **42** **43**

Scheme 1.18.

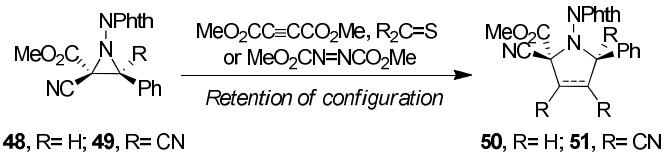
Interestingly in **44**, no trace of the expected cycloadduct was detected. Instead, the only isolated product was chromenopyridine **47**. A plausible mechanism for the formation of **47** might include competitive 1,5-electrocyclisation[47] and elimination of phthalimide to give oxazole **45**, followed by intramolecular Diels-Alder addition accompanied by loss of water (Scheme 1.19).



44 **45** **46** **47**

Scheme 1.19.

Contrary to previous findings, thermolysis of *tri*- and *tetra*-substituted *N*-phthalimidoaziridines **48**-**49** resulted in conservation of the spatial arrangement of the aziridine substituents in the final cycloadducts (Scheme 1.20).[51]



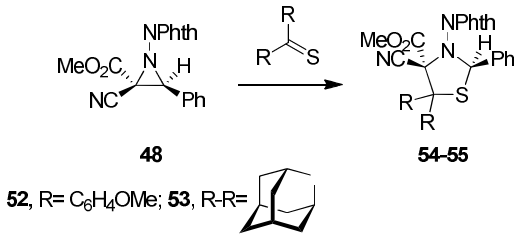
48, R= H; **49**, R= CN

50, R= H; **51**, R= CN

Scheme 1.20.

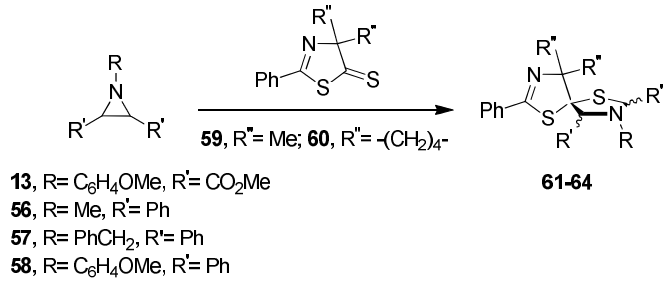
This phenomenon is explicable in a number of ways. Cycloaddition of the intermediate azomethine ylide may occur in a stepwise manner, in which case, the stereoselectivity of the entire transformation would be determined by the relative stability of the products. Alternatively, the process may be concerted but the equilibration process resulting in interconversion of the initially generated azomethine ylide is significantly faster than the rate of cycloaddition in the presence of a dipolarophile (Scheme 1.6). In the absence of a dipolarophile, a solution of pure *trans*-aziridine **49** at room temperature was observed to slowly isomerise to a mixture of *cis*- and *trans*-aziridines, providing experimental evidence in support of the latter mechanism.

Thioketones have been used for the efficient trapping of azomethine ylides generated from 1,2,3-trisubstituted aziridines,[51,52] and in their additions to 'unsymmetrical' 2,2,3-trisubstituted phthalimidoaziridines such as **48**, react regioselectively, *i.e.* with the S-atom connected to the least substituted aziridine C-atom (Scheme 1.21).[51]



Scheme 1.21.

The reactions of 1,3-thiazole-5(4*H*)-thiones **59** and **60** with *cis*- and *trans*-1,2,3-trisubstituted aziridines **13, 56-58** generally occur stereoselectively, in full agreement with orbital symmetry rules,[15] to provide the expected spirocyclic (3+2) adducts **61-64** in good yields (Scheme 1.22).[52a]

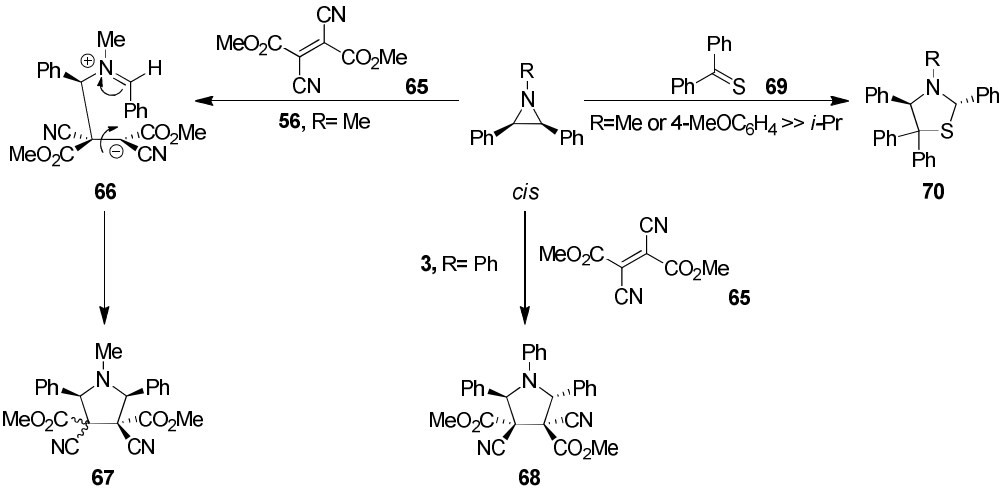


Scheme 1.22.

An exception to the general trend occurred upon reaction of *trans*-aziridine **13** with **59**, in which case the so-called 'false' *trans*-cycloadduct was formed in addition to the expected *cis*-cycloadduct. This observation is explicable in terms of competitive isomerisation of the initially formed azomethine ylide prior to cycloaddition.

The *N*-substituent of *cis*-2,3-diphenylaziridines was shown to influence both their reactivity as precursors to the corresponding azomethine ylides, as well as the reaction course with certain dipolarophiles (Scheme 1.23), *i.e*. a direct comparison

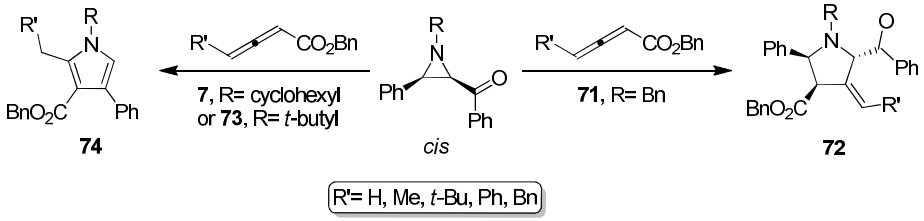
between R=Me or 4-$MeOC_6H_4$ and *i*-Pr showed that the first two substituents were significantly more reactive in the presence of a 'superdipolarophile' such as thiobenzophenone **69**.[52b] Moreover, the reaction of *cis*-1-methyl-2,3-diphenylaziridine **56** with the strongly electron deficient, dimethyl dicyanofumarate **65**, occurs stepwise *via* the corresponding zwitterionic intermediate **66**, while *cis*-1-phenyl-2,3-diphenylaziridine **3** with the same dipolarophile gave a single cycloadduct **68** with the configuration expected on the basis of a stereoselective, concerted reaction mechanism.[52c] Seemingly, steric as well as electronic effects are responsible for the stability of the resulting azomethine ylide and for its rate of formation.



Scheme 1.23.

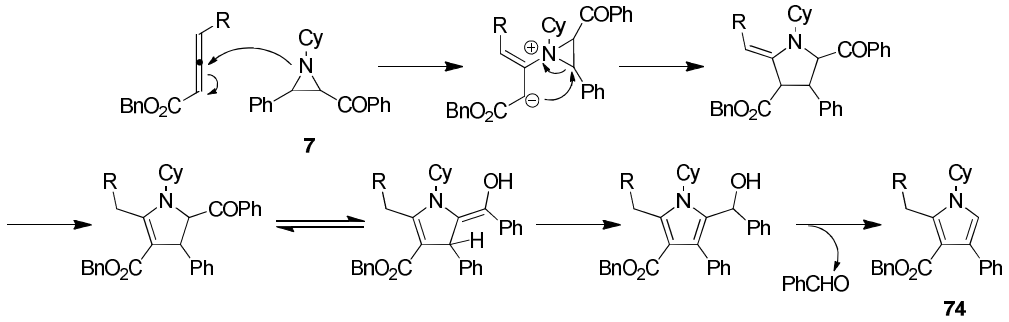
In a series of communications regarding the reactivity of allenoates towards aziridines, Pinho e Melo and co-workers also reported a significant difference in reactivity of buta-2,3-dienoates towards aziridines with varying *N*-substituent.[53] Allenoates typically react as the 2π-component in (3+2) cycloaddition reactions with azomethine ylides generated from aziridines, to afford the expected 4-

methylenepyrrolidines **72** in a site-, regio- and stereoselective manner. On the contrary, *N*-cyclohexyl- or *N*-*t*-butyl-2-benzoyl-3-phenylaziridines **7** and **73** result in a formal (3+2) cycloaddition *via* σ_{CN} bond cleavage of the aziridine ring to afford functionalised pyrroles **74** as the sole or major product (Scheme 1.24).



Scheme 1.24.

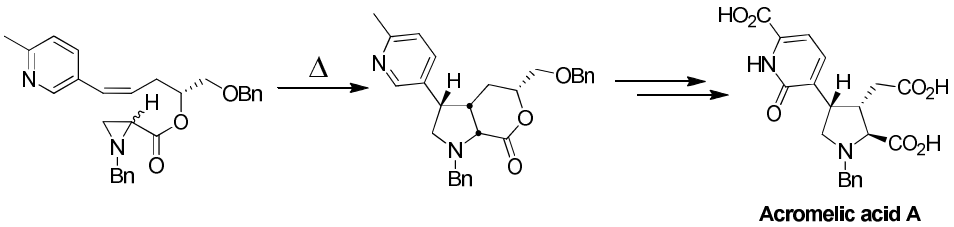
The absence of a signal with a chemical shift expected for a carbonyl carbon and the presence of a singlet at 6.61 ppm corresponding to a pyrrolic hydrogen in the ^{1}H and ^{13}C NMR spectra of compound **74** was evidence for loss of the benzoyl substituent in its formation. A plausible mechanism for this process is outlined below (Scheme 1.25).



Scheme 1.25.

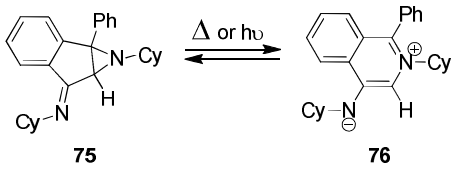
While intermolecular (3+2) cycloadditions of azomethine ylides generated from aziridines have been extensively studied, and several generalities have emerged

concerning the stereo- and regiochemical outcome of these reactions, the intramolecular variant of this reaction has received considerably less attention.[54] Nevertheless, this methodology has been successfully applied in the concise enantioselective synthesis of acromelic acid A (Scheme 1.26).[55]



Scheme 1.26.

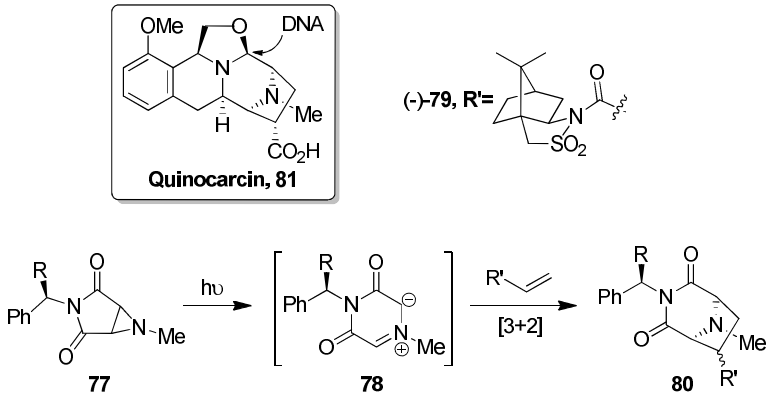
When the aziridine ring is incorporated into a bicyclic structure at the 2- and 3-position, conrotatory ring opening is not permitted due to steric constraints. On the contrary, thermal[56a] and photochemical[56b] valence tautomerisation of 1-cyclohexyl-6-(cyclohexylimino)-1a-phenyl-indano[1,2-*b*]aziridine **75** to the corresponding isoquinolinium imine **76** has been described, despite the geometrical restrictions imposed by the system (Scheme 1.27).



Scheme 1.27.

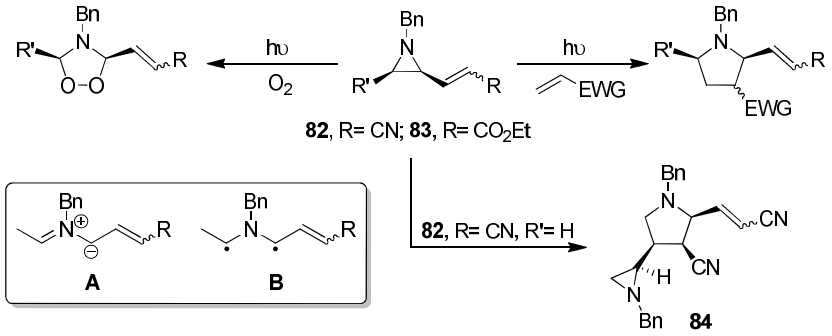
Photolysis of bicyclic aziridines and their subsequent reactions with mono-substituted electron deficient olefins and acetylenes provide adducts containing the naturally occurring 8-azabicyclo[3.2.1]octane (tropane alkaloid) skeleton.[57a] Using this methodology, Garner and co-workers developed an asymmetric

approach to the DNA-reactive alkaloid quinocarcin **81**, by way of an auxiliary-controlled dipolar cycloaddition between photochemically-generated azomethine ylides such as **78** and Oppolzer's chiral acryloyl sultam (-)-**79** (Scheme 1.28).[57b]



Scheme 1.28.

β-Aziridinylacrylonitriles **82** and acrylates **83** were shown to participate in photochemically induced (3+2) cycloadditions with a variety of mono-substituted dipolarophiles,[58] as well as molecular oxygen (Scheme 1.29).[58c] On the basis of the latter observation, it is possible that these reactions may involve intermediates which are biradical in character (*e.g.* B, Scheme 1.29). The reactions of β-aziridinylacrylonitriles such as **82** are limited to electron-deficient dipolarophiles, *i.e.* in the absence of a reactive dipolarophile or in the presence unactivated or electron-rich olefins, no cycloadducts were detected, only degradation products and dimer **84**.[58a,b]

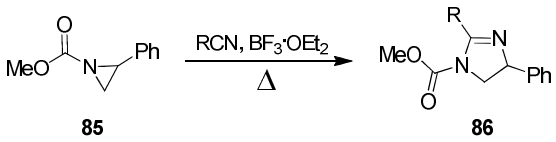


Scheme 1.29.

1.5.1.2. (3+2) Cycloaddition reactions involving C-N ring cleavage

Nucleophilic ring-opening reactions of aziridines dominate their chemistry as a consequence of their ring strain, and this property has been exploited for the construction of a number of important 1,2-difunctionalised scaffolds such as amino acids, amino sugars and β-lactams.[21] This reactivity has also been exploited through a formal (3+2) cycloaddition process involving σ_{CN} ring cleavage.[59] Formal (3+2) cycloadditions are not pericyclic reactions, rather stepwise processes between two fragments with complementary reactivity.

The seminal contribution to this reaction was made by Hiyama and co-workers who described the synthesis of imidazolines **86** by way of $BF_3{\cdot}OEt_2$-promoted cycloaddition of nitriles with *N*-alkoxycarbonylaziridines **85** (Scheme 1.30).[60]

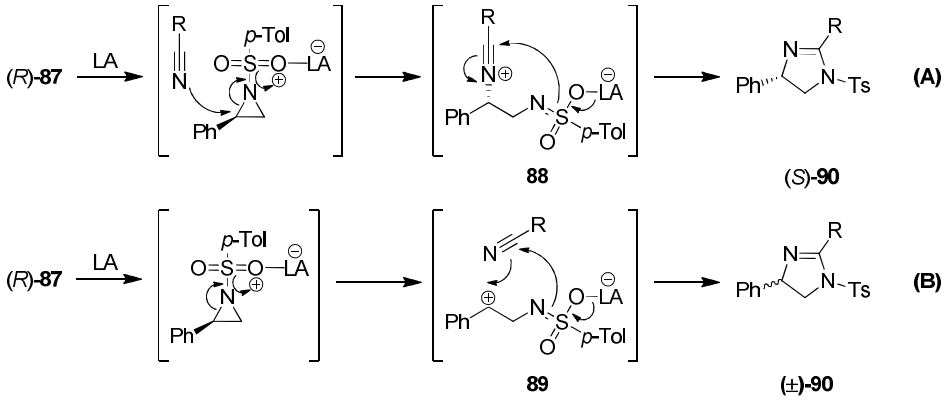


Scheme 1.30.

Lewis acid catalysed (3+2) cycloadditions reactions of aziridines bearing a vicinal phenyl group as the donor substituent have since been extensively studied.

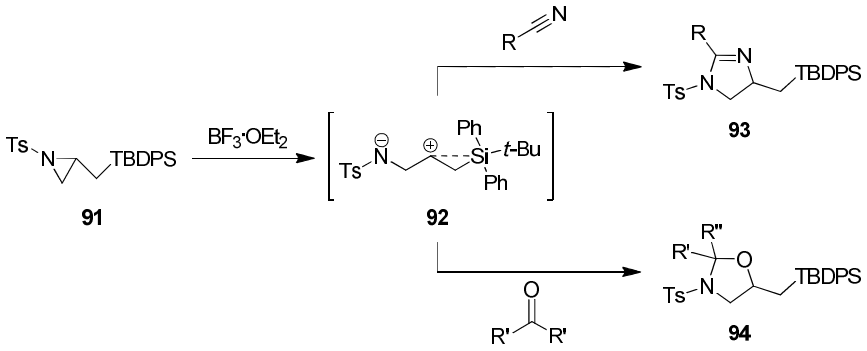
The reactions of aziridines with nitriles were later shown to be promoted by triethyloxoniumtetrafluoroborate (Et_3OBF_4) as well as a number of metal triflates.[61,63a] The mechanistic aspect of this transformation has been studied using chiral aziridines as substrates, although the conclusions reached by various research groups are somewhat contradictory.

Based on the observation that the cycloaddition of an optically pure aziridine (*R*)-**87**, provided nonracemic imidazoline (*S*)-**90**, a mechanism involving S_N2-type ring-opening of the aziridines to afford intermediates such as **88** was initially proposed (Scheme 1.31, A).[60,61] Concellón and co-workers have successfully applied this methodology for the synthesis of enantiopure tetrasubstituted imidazolines through a Ritter reaction of 2-(1-aminoalkyl)aziridines with a variety of nitriles.[62]



Scheme 1.31.

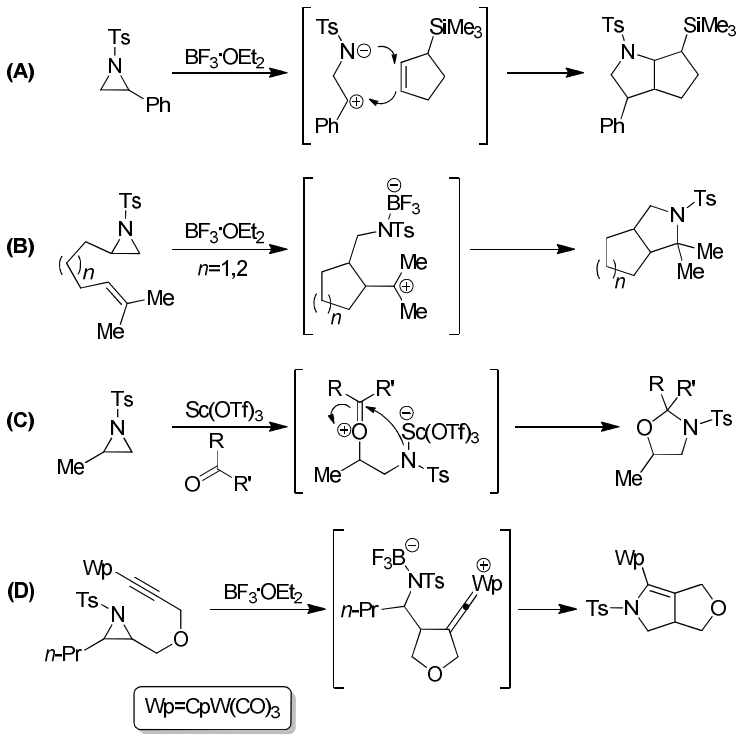
Singh and co-workers reported contrasting results upon reaction of the same aziridine (*R*)-**87** with nitriles and carbonyls in the presence of a variety of Lewis-acids.[63] Without exception, the isolated imidazoline or oxazolidine from each experiment was found to be racemic in nature, and thus an alternative S_N1-type mechanism was proposed (Scheme 1.31, B). Chelation of the Lewis acid to the sulfonyl oxygen generates a stabilised zwitterionic intermediate **89** bearing a discrete benzylic carbocation, which reacts with the dipolarophile in a Ritter-fashion to provide (±)-**90**. On the basis of this concept, Yadav and Sriramurthy cleverly exploited the β-silicon effect to generate 1,3-dipole **92** from the corresponding silylmethyl-substituted aziridine **91** (Scheme 1.32).[64] Addition of nitriles or carbonyls in the presence of stoichiometric $BF_3{\cdot}OEt_2$ provided the corresponding imidazolines **93** or oxazolidines **94** in good yields. Moreover, the silyl moiety can be considered as a masked hydroxymethyl substituent, providing the opportunity for further elaboration of the products from these reactions.



Scheme 1.32.

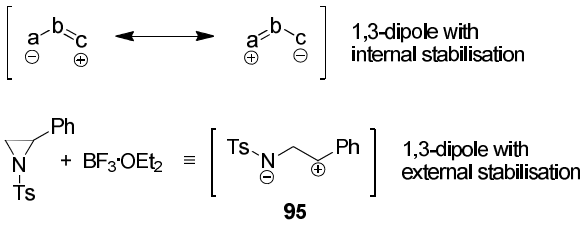
Similar non-concerted (3+2) cycloadditions have also been described employing π-nucleophiles such as allylsilanes (Scheme 1.33, A),[65] olefins (Scheme 1.33, B),[65f,66] aldehydes and ketones (Scheme 1.33, C),[67] and alkynyltungsten

complexes (Scheme 1.33, D).[68] In general, stoichiometric $BF_3{\cdot}OEt_2$ or catalytic $Sc(OTf)_3$ proved most effective for the promotion of these reactions.



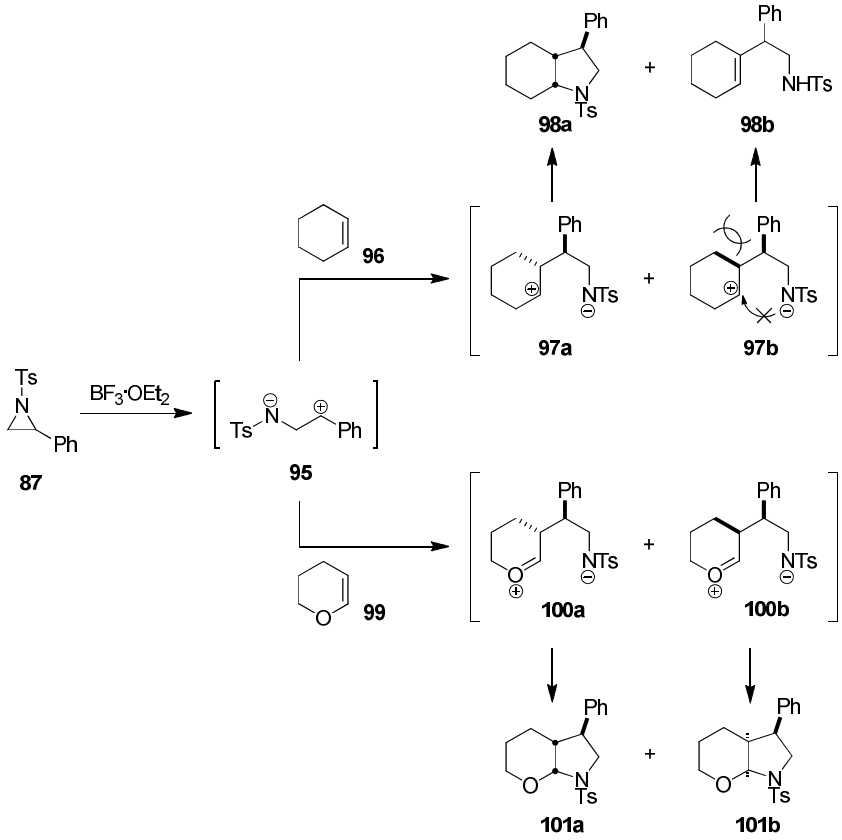
Scheme 1.33.

In contrast to azomethine ylides, which are internally stabilised by delocalisation, the two charges of zwitterionic 1,3-dipoles such as **95** are stabilised externally by the double contributions of the aromatic ring and the arylsulfonyl group (Scheme 1.34). More importantly, 1,3-dipoles of this type are electron deficient and should thus react with electron-rich dipolarophiles.



Scheme 1.34.

On the basis of this concept, Mann and co-workers investigated the reactions of 2-phenyl-*N*-tosylaziridine **87** with a variety of nonactivated olefins (Scheme 1.35).[69]

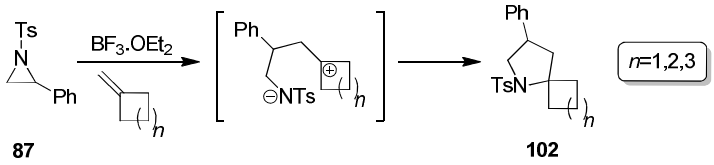


Scheme 1.35.

The reaction of **87** with cyclohexene **96** provided compounds **98a** and **98b** in a 1:1 ratio. The lack of stabilisation in the transient carbocation following initial ring-opening in addition to unfavourable *gauche* interactions in intermediate **97b**, are

thought to be responsible for the competing elimination pathway, giving olefin **98b**. Contrasting the reaction of cyclohexene, the reaction of **87** with dihydropyran **99** exclusively formed the fused pyrrolidine derivatives **101a** and **101b**. This observation is explicable in terms of the formation of more stabilised oxonium ion intermediates **100a** and **100b** to favour cyclisation.

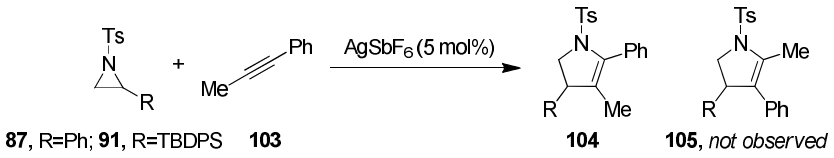
Since the nature of the products obtained in the reaction of **87** with olefins appeared to be dependent on the stability of the carbocation in the initially formed 1,5-zwitterionic intermediates, Mann and co-workers examined the same reaction with *gem*-disubstituted olefins, in which a more stable intermediate tertiary carbocation was expected. Indeed, cyclic olefins bearing an exocyclic double bond reacted cleanly with **87** to provide the corresponding spiropyrrolidines **102** as the sole products (Scheme 1.36).



Scheme 1.36.

Acetylenes have also been employed as highly efficient dipolarophiles in these cycloadditions in the presence of a catalytic quantity of various Lewis acids such as $FeCl_3$,[70] or $AgSbF_6$.[71] Brønsted acids, *e.g.* TsOH, have also proven to be compatible.[71] The reaction accommodates a wide range of substrates, including unsymmetrical alkyl- and arylacetylenes, which can be used in combination with 2-phenyl- **87** or 2-silylmethyl-*N*-tosylaziridine **91** to provide a wide range of 2-

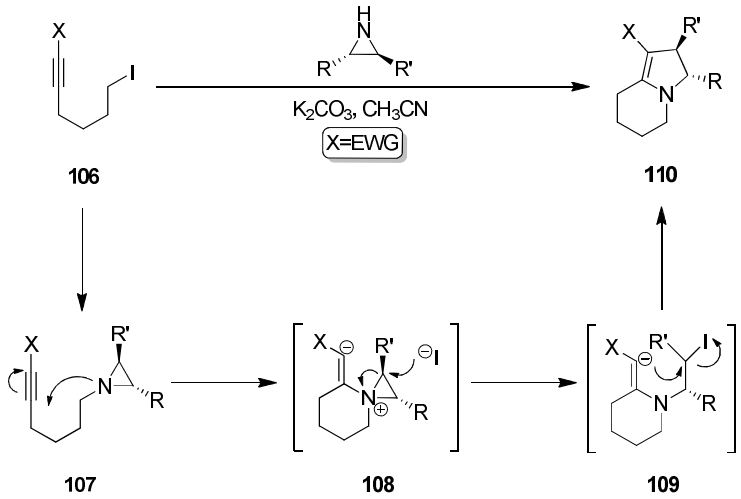
pyrrolidine derivatives **104** in a highly regioselective manner, under mild reaction conditions, and at low catalyst loadings (Scheme 1.37).



Scheme 1.37.

Basic functionalities including a methyl ether unit, a pivaloic ester group and a cyclopropyl ring were tolerated, while test experiments starting from an optically pure aziridine, as well as a competition experiment using isosteric but electronically differentiated phenylacetylenes, provided further evidence in support of the capture of a cationic intermediate in the product forming step.[71]

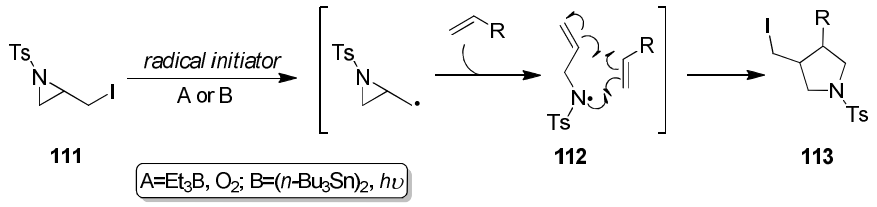
Ma and co-workers disclosed an efficient protocol for the assembly of polysubstituted indolizidines by way of a sequential S_N2/formal (3+2) cycloaddition process starting from nonactivated aziridines.[72] Mechanistic insight for this process was achieved through the reaction of a *trans*-α,β-disubstituted aziridine with iodide **106**, which provided indolizidine **110** as the sole product. Intriguingly, the relative configuration of the aziridine ring substituents had been conserved during this transformation. On the basis of this observation, iodide was assumed to play a role in the stereochemical outcome of this process and thus, the following reaction mechanism was proposed (Scheme 1.38).



Scheme 1.38.

Following addition of the aziridine to iodide **106** to give tertiary amine **107**, intramolecular Michael addition of the nitrogen lone pair onto the appended acetylene provides zwitterionic intermediate **108**. Contrary to a mechanism earlier proposed by Mattay involving direct ring-opening of the aziridine by the resultant carbanion in **108**,[73] iodide is thought to open the aziridine in an S_N2 fashion to afford intermediate **109**. A second S_N2 reaction between the carbanion in **109** and the resulting iodide moiety provides indolizine **110**.

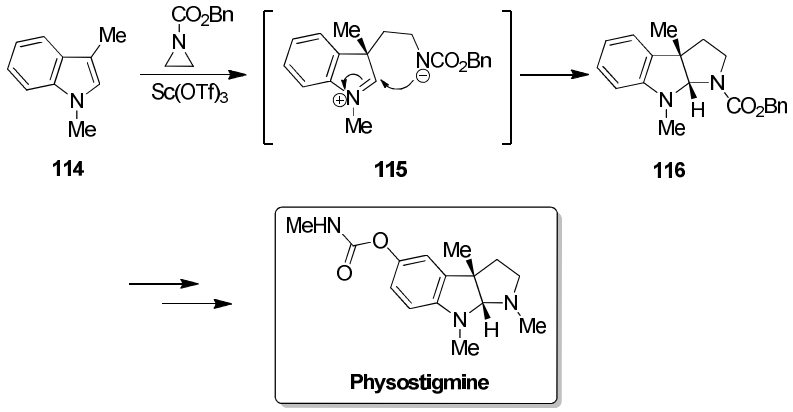
N-Tosyliodoaziridine derivatives have been employed as novel azahomoallyl radical precursors for (3+2) cycloadditions reactions with olefins (Scheme 1.39).[74]



Scheme 1.39.

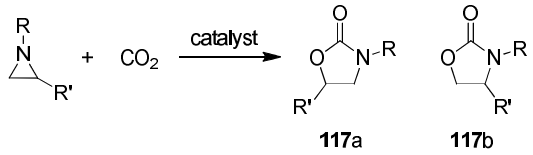
In the presence of a radical initiator, iodoaziridines such as **111** were shown to participate in (3+2) cycloadditions with a variety of electron-rich olefins such as enol ethers, to afford the corresponding functionalised pyrrolidine derivatives **113**. Since the reaction can be performed under neutral conditions, acid-sensitive silyl enol ethers can be employed. Addition to simple alkyl-substituted olefins is also possible due to the higher reactivity of the intermediate *N*-tosylamidyl radical **112** compared to a simple aminyl radical. All reactions proceeded regioselectively through attack of the *N*-tosylamidyl radical **112** onto the terminal carbon atom of the olefin.

Interestingly, the Lewis acid-catalysed reaction of 3-methylindole **114** with aziridines resulted in a formal (3+2) cycloaddition to afford tricyclic adducts such as **116** (Scheme 1.40). Most cyclisations of this type proceed through an elimination pathway in order to rearomatise the indole moiety. However, with a methyl group at the normal site of nucleophilic attack, aromatisation is not possible. Instead, the indolenium species **115** is intercepted intramolecularly by the amino side chain. The synthetic potential of this methodology has been demonstrated by its application to the total synthesis of physostigmine.[75]



Scheme 1.40.

The chemical fixation of carbon dioxide to aziridines *via* (3+2) cycloadditions, affording the corresponding oxazolidinones **117**, has been described (Scheme 1.41). A variety of homogeneous catalysts including (salen)chromium(III)/DMAP,[76a] phenol/DMAP,[76b] alkali metal halides,[76c-e] tetraalkylammonium halides,[76c,f] and iodine[76g] have been developed, as well as an electrochemical procedure as an alternative for this transformation.[76h] However, toxic organic solvents, catalysts and/or co-catalysts are usually required to achieve high catalytic efficiency.

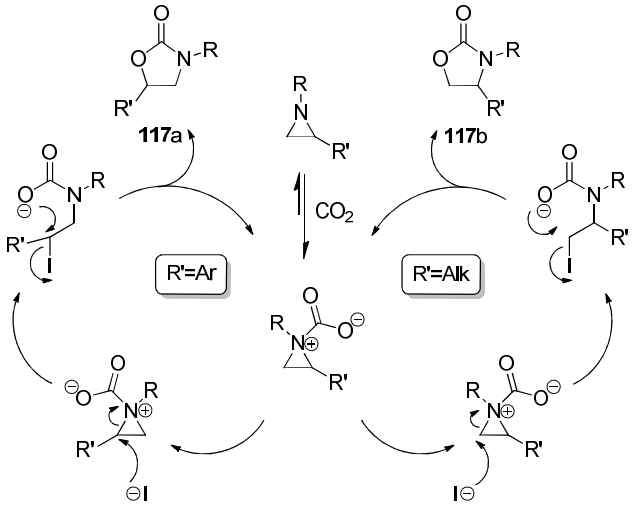


Scheme 1.41.

In light of the desire to develop environmentally benign methods for the synthesis of oxazolidinones, He and co-workers developed a quaternary ammonium salt functionalised PEG, *i.e.* PEG_{6000}-$(NBu_3Br)_2$ and zirconyl chloride as efficient, recyclable catalysts for the cycloaddition reactions of aziridines to CO_2 in the

absence of organic solvents or co-catalysts.[76f,77a] A self-catalytic process, controlled by subtly tuning CO_2 pressure, which requires neither organic solvent nor catalyst has also been described,[77b] while the naturally occurring α-amino acid, L-histidine, has been shown to successfully catalyse this process under mild conditions.[77c]

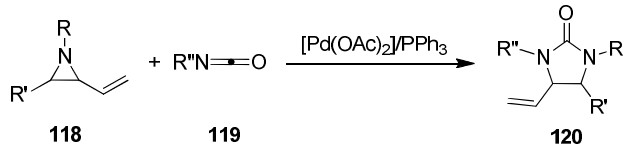
On the basis of experimental results, a putative catalytic cycle for the LiI-catalysed cycloaddition of aziridines with CO_2 has been proposed (Scheme 1.42).[76d,78] For *N*-alkylaziridines, the selective formation of 5-substituted-2-oxazolidinone **117a** or 4-substituted-2-oxazolidinone **117b** was shown to be dependent on the nature of the aziridine ring substituent(s), *i.e.* aziridines containing a monophenyl ring substituent showed a strong preference for ring cleavage at the more highly substituted carbon-nitrogen bond.



Scheme 1.42.

Heterocumulenes have been shown to participate in cycloaddition reactions with aziridines, providing access to a variety of important compound classes. For

example, the $[Pd(OAc)_2]/PPh_3$-catalysed ring-opening cyclisation of 2-vinylaziridines **118** with isocyanates **119** is highly effective for the synthesis of imidazolidinones **120** (Scheme 1.43).[79]

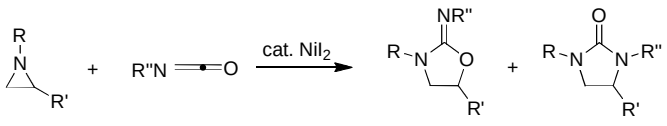


118 **119** **120**

Scheme 1.43.

Similar cycloaddition reactions of heterocumulenes such as carbo- and sulfur diimides, isothiocyanates and ketenimines, with aziridines involving catalysis by organoantimony(V) halides,[80a] organophosphines,[80b] palladium,[80c-i] and Lewis acids[80j-m] have also been described. Trost and co-workers have elegantly applied this methodology to the first total synthesis of (+)-Pseudodistomin D, incorporating a key palladium-catalysed dynamic kinetic asymmetric cycloaddition of an isocyanate to a vinyl aziridine.[81]

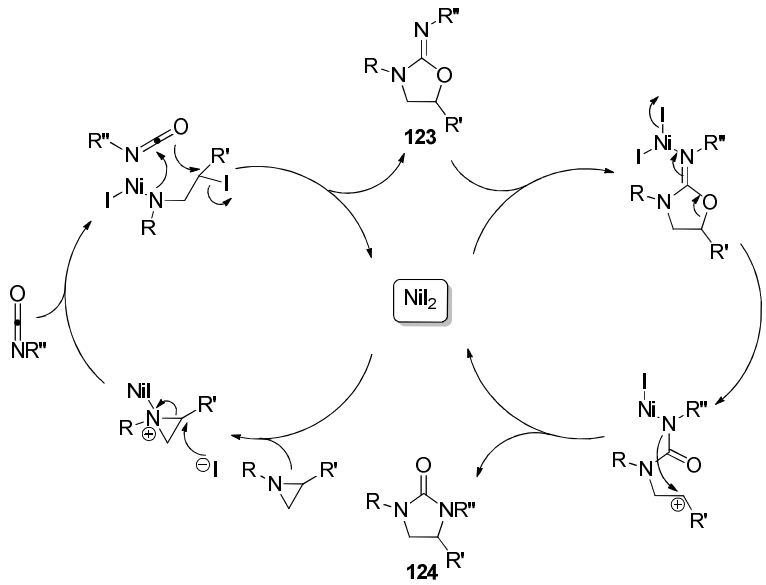
In the cycloaddition reactions of phenylisocyanate with aziridines, the corresponding imidazolidinones **124** were generally isolated as the major product. In contrast, nickel(II) iodide-catalysed reactions afforded the corresponding iminooxazolidine derivatives **123** (Scheme 1.44).[82]



121 **122** **123** **124**

Scheme 1.44.

Saito and co-workers noted that the ratio of **123** to **124** was dependent on the reaction time in some experiments, *i.e.* at shorter reaction times, **123** was isolated as the major product, while the yield of **123** decreased and that of **124** increased at extended reaction times. At reduced catalyst loadings, Trost *et al.* also encountered a mixture of *N*- and *O*-alkylated products from the reactions of vinyloxiranes with isocyanates.[83] It was hypothesised that **124** is formed as a result of isomerisation of **123** and that both products are formed in these reactions. However, with sufficient catalyst or time, the isomerisation is more efficient, masking the formation of **123** and ultimately providing only the thermodynamically favoured product **124**. A possible mechanism for the formation of **123** and **124** in the presence of NiI_2 is outlined below (Scheme 1.45).

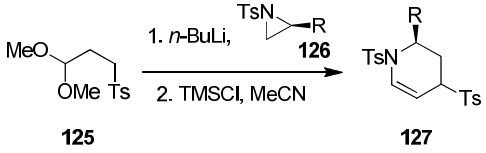


Scheme 1.45.

1.5.2. (3+3) Cycloaddition reactions of aziridines

In the context of six-membered ring formation, the Diels-Alder reaction holds a prominent position and formally comprises a (4+2) assembly strategy. In contrast, employment of a (3+3) cycloaddition approach has been much less widely studied. Despite this, a limited number of (3+3) cycloadditions involving aziridines have been described.

In 1998, Craig and co-workers described the synthesis of enantiomerically pure tetrahydropyridines **127** by way of a stepwise (3+3) cycloaddition process involving *N*-tosyl aziridines **126** (Scheme 1.46).[84] Specifically, lithiation of sulfonylacetal **125** generates a dipole equivalent that adds to aziridines to provide the corresponding cycloadducts **127**, following acid-catalysed ring closure.

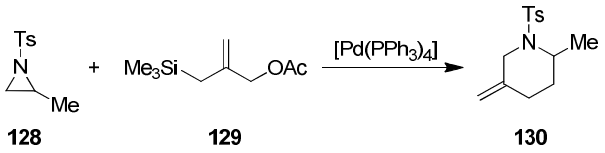


Scheme 1.46.

Recognising the propensity of aziridines to undergo nucleophilic ring-opening, Bambal and Kemmit investigated their cycloaddition reactions with the catalytic species [Pd(η^3-TMM)(PPh_3)$_2$], which is strongly nucleophilic in character.[85]

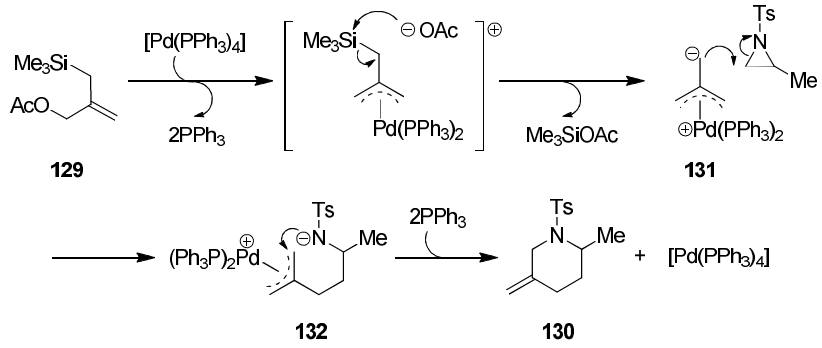
2-[(Trimethylsilyl)methyl]-2-propen-1-yl acetate **129** was selected as a source for the *in situ* generation of the desired Pd-TMM complex, since literature precedent already existed for its employment as an efficient partner for other cycloaddition processes.[86] In the presence of [Pd(PPh_3)$_4$], Pd-TMM complexes **131** are

generated from acetate **129** as transient reactive intermediates. Reactions of **131** with *N*-activated aziridines such as **128**, were shown to provide the corresponding 5-methylenepiperidines **130** in high yields (Scheme 1.47).



Scheme 1.47.

The mechanism was assumed to proceed *via* a zwitterionic intermediate as illustrated below (Scheme 1.48).



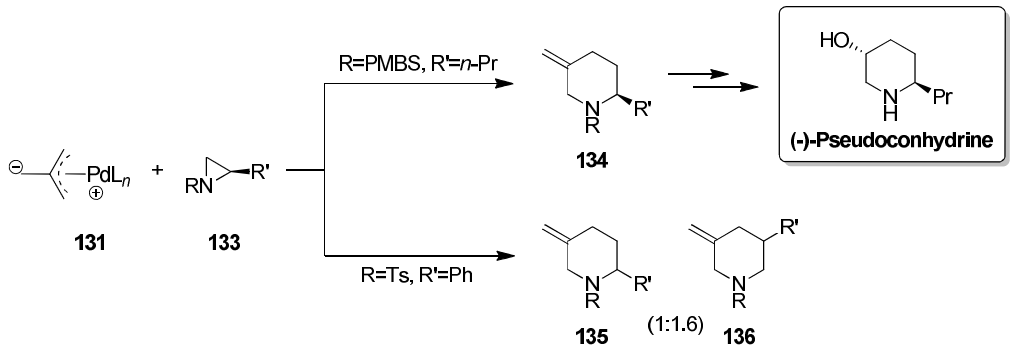
Scheme 1.48.

The cycloaddition reactions studied exhibited excellent regioselectivity; ring-opening occurred exclusively at the methylene carbon, as expected for *N*-activated aziridines bearing a simple alkyl ring substituent.

Attempting to explore the generality of this process, with a view to preparing enantiomerically pure piperidines, Harrity and co-workers were initially unable to reproduce the reaction using the conditions described by Kemmit *et al*.[87] Notably, Trost had earlier described the use of non-basic phosphite ligands to enhance the

reactivity of Pd-TMM complexes in analogous (3+2) and (4+3) cycloaddition processes[88] and thus, using $Pd(OAc)_2$ and $P(O\textit{i}\text{-}Pr)_3$ in a 1:6 ratio with *n*-BuLi as reductant, the desired piperidines were obtained in a high yield.

A range of chiral aziridines with varying *N*- and ring substituents, were examined and all but one underwent regioselective addition of the Pd-TMM complex at the least hindered site, furnishing enantiomerically pure piperidines in good to excellent yields. Useful functionalities, including silyl-protected alcohols and allyl groups, were well tolerated in this reaction. Notably, piperidine **134** was employed in the stereoselective synthesis of (-)-pseudoconhydrine (Scheme 1.49).[87a]

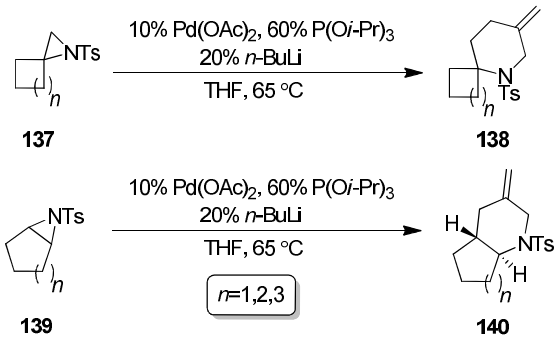


Scheme 1.49.

Unsurprisingly, *N*-tosyl-2-phenylaziridine provided regioisomeric products, **135** and **136**, by way of competitive aziridine cleavage at the benzylic position. The *N*-substituent proved crucial to the success of the reaction, with only *N*-tosyl (Ts) and *N*-*p*-methoxybenzenesulfonyl (PMBS) aziridines permitting smooth cycloadditions to take place. *N*-*p*-Nitrobenzylsulfonyl (Ns), *N*-Boc, *N*-Cbz and *N*-

diphenylphosphinoyl substituents gave either complex mixtures or returned starting materials.

Using the optimised ligand system, this methodology was successfully applied to the synthesis of spirocyclic and fused bicyclic piperidines **138** and **140** from the corresponding 2,2- and 2,3-disubstituted aziridines **137** and **139**, although the latter substrates were found to exhibit diminished reactivity, most likely as a result of increased steric hindrance at the site of nucleophilic attack (Scheme 1.50).



Scheme 1.50.

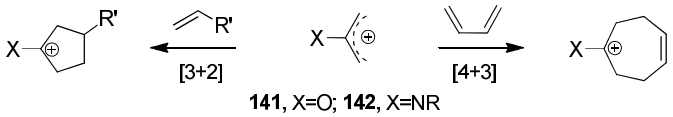
Attempts to extend this methodology to include 2,2,3-trisubstituted aziridines proved unsuccessful. Further elaboration of the products from these reactions was achieved by epoxidation, hydroboration, aziridination and hydrogenation of the exocyclic methylene group.[87b]

1.5.3. (4+3) Cycloaddition reactions of methyleneaziridines

Investigations into the chemistry of methyleneaziridines have revealed that they undergo a variety of interesting and potentially useful chemical transformations.[89] Notably, a number of simple cycloadditions onto the exocyclic double bond have been described, including (2+2) and (3+2) cycloaddition reactions with electron

deficient olefins[90] and organic azides[91] respectively, as well as photooxygenation of l-*tert*-butyl-2-adamantylideneaziridine to provide the corresponding 1,2-dioxetane.[92]

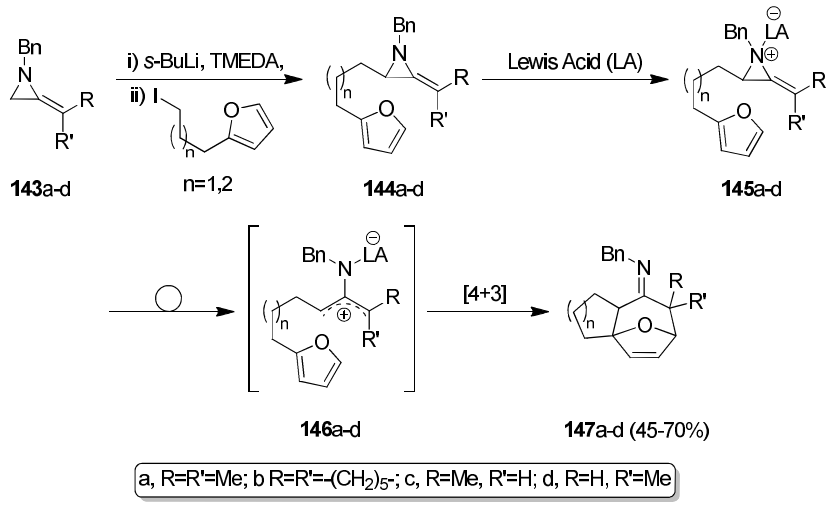
Interested in trying to incorporate all elements of the methyleneaziridine in the cycloaddition process, Shipman *et al*. realised that these heterocycles might serve as novel precursors to 2-aminoallyl cations **142**, intermediates that are known to participate in (4+3) cycloadditions with 1,3-dienes[93] and (3+2) cycloadditions with olefins (Scheme 1.51).[94]



Scheme 1.51.

2-Aminoallyl cations **142** closely resemble trimethylenemethane (TMM) and its synthetic equivalents, powerful synthons for the construction of five-membered rings,[95] as well as the related 2-oxyallyl cation species **141**.[96] Interestingly, these *N*-substituted cations offer certain advantages over their oxygen-based counterparts, specifically due to their ability to affect enantiocontrolled processes by incorporation of a chiral non-racemic *N*-substituent.[93g] Despite this, few papers describe the use of 2-aminoallyl cations, primarily since general and reliable methods for their generation are scarce. Both 2-chloroimine[93b,g] and α-chloroenamine[93a,c-f] activation though halide abstraction with stoichiometric silver(I) salts have been investigated, however the instability of the starting materials and generally low reaction efficiencies have prevented the widespread application of this methodology.

In an important advance, the Shipman group successfully applied the use of 2-aminoallyl cations, derived from the ring opening of methyleneaziridines for the construction of a range of polycyclic systems featuring seven-membered rings.[97] The general strategy entailed functionalisation of a range of methyleneaziridines by lithiation and subsequent alkylation at C-3 with a suitable 1,3-diene, providing entry to a number of 2-aminoallyl cation precursors such as **144**. Complexation of the nitrogen atom of **144** with a suitable Lewis acid [typically excess $BF_3{\cdot}OEt_2$ or catalytic $Sc(OTf)_3$] generates a highly strained and reactive aziridinium ion **145**, which undergoes fragmentation to Lewis acid complexed 2-aminoallyl cation **146**. Further intramolecular (4+3) cycloaddition with the appended 1,3-diene furnishes the corresponding cycloheptenone imine **147**, or ketone by incorporation of an acidic workup step (Scheme 1.52).

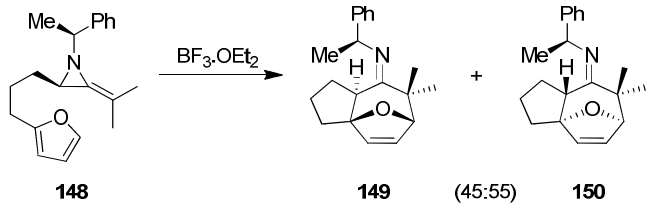


Scheme 1.52.

The reaction was shown to accommodate changes in the structure of the methyleneaziridine, however intramolecular cycloadditions involving

methyleneaziridines bearing two hydrogen atoms on the exocyclic double bond were shown to be unsuccessful.

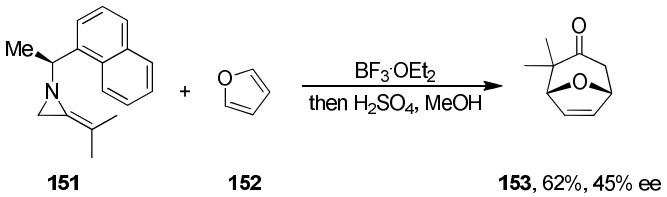
Importantly, the loss of stereochemical integrity in the conversion of **148** into **149** and **150** provided evidence for the formation of a planar 2-aminoallyl cation species (Scheme 1.53),



148 **149** (45:55) **150**

Scheme 1.53.

Preliminary investigations established that methyleneaziridines might also participate in the intermolecular variant of this novel (4+3) cycloaddition process. For example, treatment of (*S*)-1-(1-(naphthalene-1-yl)ethyl)-2-(propan-2-ylidene)aziridine **151** with excess furan **152**, in the presence of $BF_3{\cdot}OEt_2$(1.5 eq.) provided (1*R*,5*R*)-**153**, following acidic hydrolysis, in 62% yield and 45% ee (Scheme 1.54).[98]



151 **152** **153**, 62%, 45% ee

Scheme 1.54.

1.6. Conclusions

Comparison of the transformations involving aziridine-derived azomethine ylides with those involving zwitterionic intermediates derived from σ_{CN} ring cleavage, demonstrates that the formation of a given 1,3-dipole is strongly influenced by aziridine substitution patterns. Changing the electronic nature of the nitrogen substituent and/or the ring substituent(s) permits the induction of a distinct bond cleavage. In general, σ_{CN} ring cleavage is observed in the presence of electron-withdrawing *N*-substituents and ring substituents capable of stabilising the resulting intermediate carbocation. Ring substituents have also been shown to direct the regioselectivity of the ring-opening process by promoting cleavage of one of two C-N bonds. Conversely, simple *N*-alkyl aziridines bearing electron-withdrawing ring substituents favour σ_{CC} ring cleavage.

The cycloaddition reactions of aziridines have been extensively studied, and efforts continue apace today to develop ever more sophisticated applications for these highly versatile intermediates in the construction of novel heterocyclic scaffolds. Due to their close structural similarities to aziridines, and the fact that they have previously been shown to behave as precursors to zwitterionic intermediates in the presence of Lewis acids, we realised that methyleneaziridines might also participate in novel (3+2) cycloaddition processes. This work is detailed in chapter two.

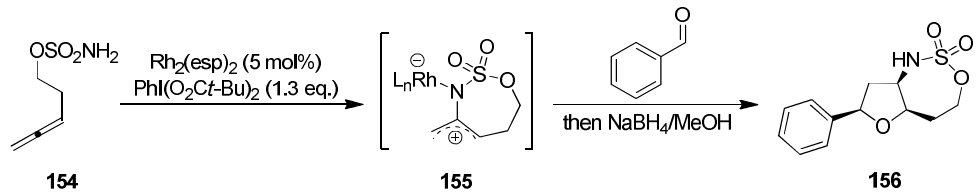
Chapter 2:

Lewis Acid-Promoted (3+2) Cycloaddition Reactions of Methyleneaziridines

2.1. (3+2) cycloaddition reactions involving methyleneaziridines

Having already established that the entire methyleneaziridine nucleus can participate in (4+3) cycloaddition reactions with internal and external 1,3-diene acceptors, presumably *via* an intermediate transient 2-aminoallyl cation species (Chapter 1, Section 1.52),[97] we hoped to determine whether they could also engage in cycloaddition processes with other dipolarophiles, such as olefins and/or acetylenes.

Stoll and Blakey recently described the *in situ* generation of 2-aminoallyl cations by way of interaction of a sulfamate ester-derived metallonitrene with allenes.[94] Importantly, the proposed 2-aminoallyl cation **155** could be intercepted by an external dipolarophile, providing evidence for its existence on the reaction pathway. Under optimised conditions, treatment of sulfamate ester **154** in the presence of benzaldehyde, followed by reductive work-up provided trisubstituted tetrahydrofuran **156** as a single regio- and diastereoisomer (Scheme 2.1). It was proposed that **156** is formed in a (3+2) cycloaddition reaction between the aldehyde and the intermediate 2-aminoallylcation.

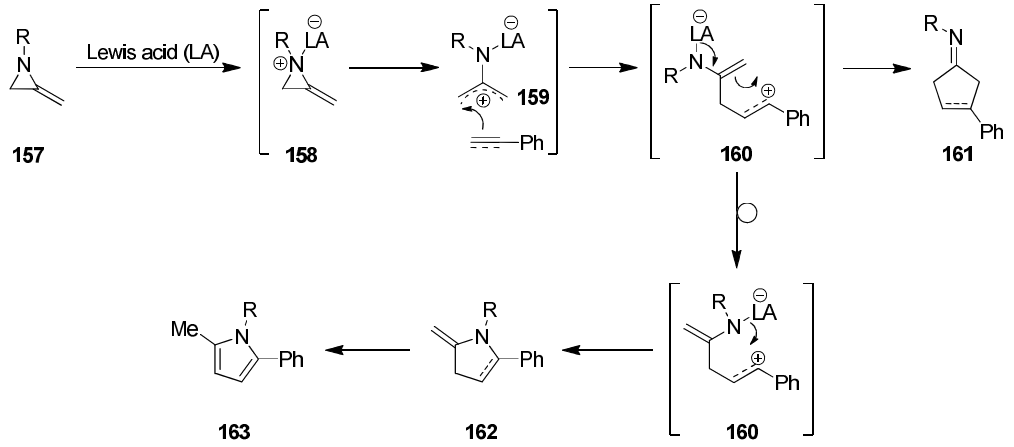


154 **155** **156**

Scheme 2.1.

Encouraged by these results and an earlier study in which (*S*)-1-(1-(naphthalene-1-yl)ethyl)-2-(propan-2-ylidene)aziridine **151** was shown to participate in a

$BF_3{\cdot}OEt_2$-promoted intermolecular (4+3) cycloaddition reaction with furan (Scheme 1.54), we first decided to investigate a potential intermolecular (3+2) cycloaddition process involving methyleneaziridines and an external dipolarophile. Our general strategy is depicted below (Scheme 2.2).

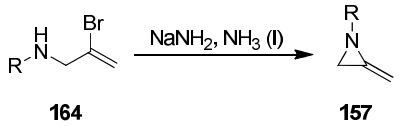


Scheme 2.2.

Complexation of the nitrogen atom of **157** to a suitable Lewis acid may generate aziridinium ion **158**, which might be expected to undergo fragmentation, driven by the relief of ring strain, to give Lewis acid complexed 2-aminoallyl cation **159**. Intermolecular addition of an external dipolarophile such as phenylacetylene, might be expected to generate a zwitterionic intermediate such as **160**. We anticipated that ring closure onto the benzylic carbocation might occur through carbon to form ketimine **161**, or through nitrogen to form pyrrole **163**, following isomerisation of pyrroline **162**. We felt that if this chemistry could be implemented, then this could provide a concise route to a range of useful (3+2) cycloadducts from readily accessible starting materials.

2.1.1. Synthesis of methyleneaziridines

Methyleneaziridines **157** were first unknowingly prepared 60 years ago by Pollard and Parcell upon treatment of *N*-(2-bromoallyl)alkylamines **164** with sodium amide in liquid ammonia,[99] and while other preparative methods have been described,[91b,100] the original approach still remains the most reliable and general (Scheme 2.3).

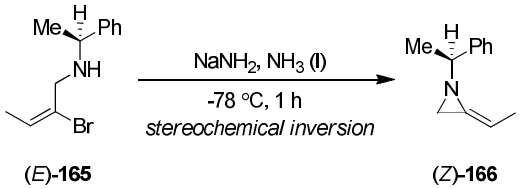


164 **157**

Scheme 2.3.

Despite the harsh conditions employed, $NaNH_2$-induced ring closure accommodates considerable structural variation with respect to the nitrogen substituent: acetals and alcohols,[101] benzyl and silyl ethers,[102] double bonds and aryl selenides,[103] and chiral, non-racemic derivatives[104,105] all survive unscathed. Substitution at the exocyclic double bond, including *gem*-dimethyl[98,106,107] and cyclohexyl derivatives,[98] is also well tolerated.

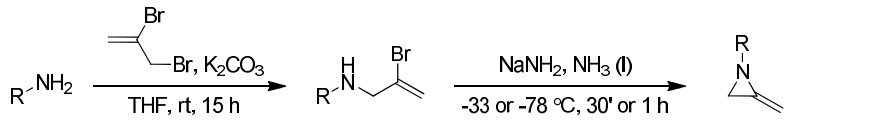
Using deuterium labelling studies,[108] Shipman and co-workers gained insight into the likely mechanism for this transformation and were able to discount the elimination-addition mechanism originally proposed by Bottini and Olsen.[109] It is now generally accepted that this transformation is a rare example of an S_N2-like reaction, proceeding with net stereochemical inversion at the vinylic carbon atom. For example, cyclisation of (*E*)-**165** provides (*Z*)-**166** in 93% yield (Scheme 2.4).



(*E*)-**165** (*Z*)-**166**

Scheme 2.4.

In preparation for the proposed (3+2) cycloaddition studies, methyleneaziridines **169**,[104] **172,**[110] **175**,[107] **177**,[111] **182**,[108] and **187**[108] were synthesised in two to four steps from the corresponding amines in accordance with standard procedures.[89] Alkylation of amines **167** and **170** with 2,3-dibromopropene in THF in the presence of K_2CO_3 provided the corresponding 2-bromoallylamines **168** and **171**. Subsequent ring closure with sodium amide, generated *in situ* from sodium and ammonia using $Fe(NO_3)_3.9H_2O$ as catalyst, afforded methyleneaziridines **169** and **172** in good yields (Scheme 2.5).



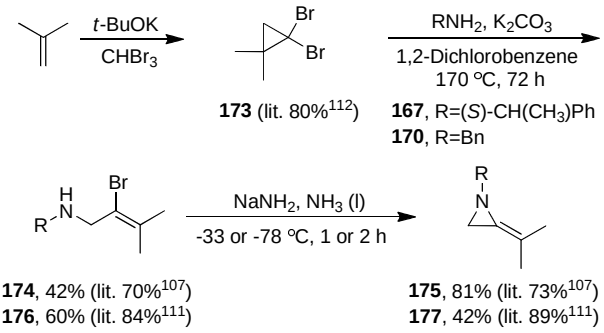
167, R=(*S*)-CH(CH$_3$)Ph
170, R=Bn

168, 100% (**lit.** 76%[104])
171, 62% (**lit.** 68%[104])

169, 57% (**lit.** 76%[104])
172, 59% (**lit.** 78%[110])

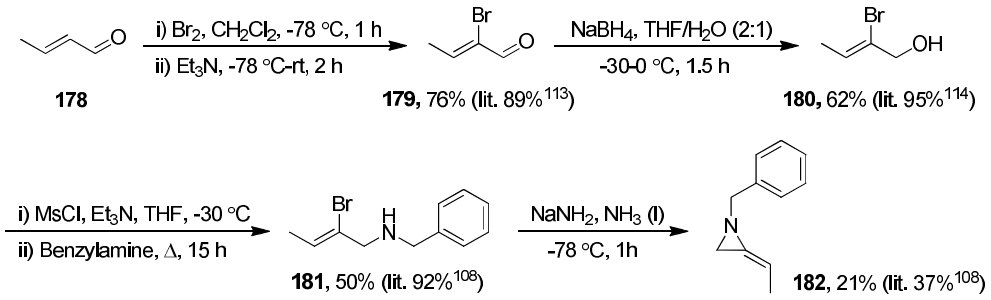
Scheme 2.5.

The carbene addition reaction to isobutylene gave 1,1-dibromo-2,2-dimethylcyclopropane **173**[112] in good yield. Subsequent ring opening of **173** with amines **167** and **170** in refluxing 1,2-dichlorobenzene in the presence of K_2CO_3 provided the corresponding 2-bromoallylamines **174**[107] and **176**.[111] Ring closure of **174**[107] and **176**[111] with sodium amide, generated *in situ* from sodium and ammonia then afforded isopropylideneaziridines **175**[107] and **177**[107] (Scheme 2.6).



Scheme 2.6.

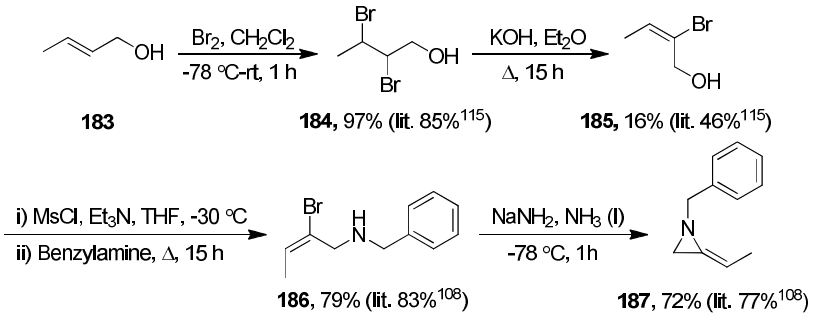
(*E*)-1-Benzyl-2-ethylideneaziridine **182**[108] was prepared in four steps from commercially available crotonaldehyde **178** (Scheme 2.7). Bromination of **178**, followed by base treatment (Et_3N) afforded (*Z*)-2-bromobut-2-enal **179**.[113] Reduction of **179** to the corresponding alcohol **180** was accomplished using $NaBH_4$ in THF/H_2O at 0 °C for 1 h.[114] Treatment of (*Z*)-2-bromobut-2-en-1-ol **180** with methanesulfonyl chloride and further alkylation with benzylamine provided (*Z*)-*N*-benzyl-2-bromobut-2-en-1-amine **181**,[108] which was converted to (*E*)-1-benzyl-2-ethylideneaziridine **182**[108] by ring closure with sodium amide.



Scheme 2.7.

(*Z*)-1-Benzyl-2-ethylideneaziridine **187** was prepared in four steps from commercially available crotyl alcohol **183** (Scheme 2.8). Bromination of **183** afforded 2,3-dibromobutan-1-ol **184**,[115] which was further treated with KOH in

refluxing Et_2O for 15 h to afford (*E*)-2-bromobut-2-en-1-ol **185**.[115] Treatment of **185** with methanesulfonyl chloride and further alkylation with benzylamine provided (*E*)-*N*-benzyl-2-bromobut-2-en-1-amine **186**,[108] which was converted to (*Z*)-1-benzyl-2-ethylideneaziridine **187**[108] ring closure in the presence of excess sodium amide in liquid ammonia.



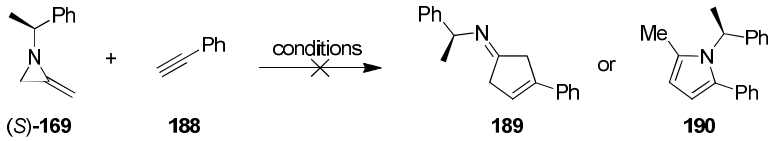
Scheme 2.8.

2.1.2. Attempted Lewis acid promoted intermolecular (3+2) cycloaddition reaction involving methyleneaziridines

Methyleneaziridine (*S*)-**169** was selected for our initial investigations, primarily since multigram quantities were readily accessible over the fewest chemical steps. In the (4+3) cycloaddition reactions involving methyleneaziridines, reactions were carried out in CH_2Cl_2, so this was our initial solvent of choice for the proposed (3+2) cycloaddition reaction. In an experiment closely resembling that described by Wender and Strand, involving the Lewis/Brønsted acid-catalysed cycloaddition reactions of aziridines onto nonactivated alkynes (Scheme 1.37),[71] $AgSbF_6$ (0.05 eq, 0.05 M in DCE) was added to a stirred solution of (*S*)-**169** and phenylacetylene **188** (3.0 eq.) in CH_2Cl_2 at -30 °C. The reaction was allowed to

gradually warm to room temperature, and monitored by TLC. However, after 24 h no new products were detected (Table 2.1, Entry 1).

Undeterred by this, we conducted a series of experiments in which the Lewis acid, catalyst loading and temperature were varied. Each reaction was monitored by TLC and the outcome determined by examination of the crude ^{1}H NMR spectra. The results are summarised below (Table 2.1).



(*S*)-**169** **188** **189** **190**

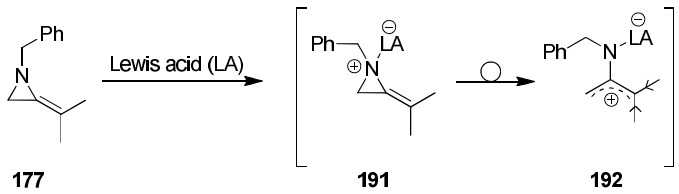
Entry	Catalyst (mol%)	T	Outcome
1[a]	$AgSbF_6$ (5)	-30 °C-rt	No reaction
2[a]	$Sc(OTf)_3$ (5)	-30 °C-rt	No reaction
3[a]	$Zn(OTf)_3$ (5)	-30 °C-rt	No reaction
4[a]	AgOTf (5)	-30 °C-rt	No reaction
5[a]	TfOH (5)	-30 °C-rt	Decomposition
6[a]	$BF_3{\cdot}OEt_2$ (150)	-30 °C-rt	Decomposition
7[b]	$AgSbF_6$ (5)	-30-85 °C	No reaction
8[b]	$Sc(OTf)_3$ (5)	-30-85 °C	No reaction
9[b]	$Zn(OTf)_3$ (5)	-30-85 °C	No reaction
10[b]	AgOTf (5)	-30-85 °C	No reaction
11[a]	$AgSbF_6$ (100)	-30 °C-rt	Decomposition
12[a]	$Sc(OTf)_3$ (100)	-30 °C-rt	Decomposition
13[a]	$Zn(OTf)_3$ (100)	-30 °C-rt	Decomposition
14[a]	AgOTf (100)	-30 °C-rt	Decomposition

[a] Reaction performed in CH_2Cl_2;[b] Reaction performed in DCE.

Table 2.1.

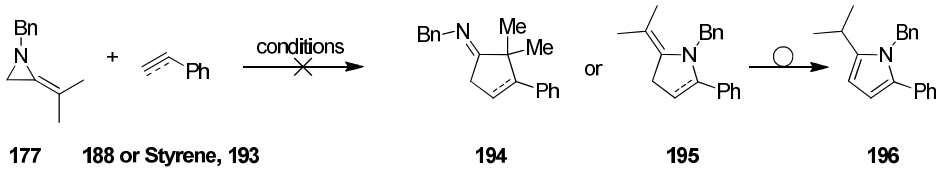
At 5 mol% catalyst loading, $Sc(OTf)_3$, $Zn(OTf)_3$ and AgOTf returned only starting materials (Table 2.1, Entries 2-4), while TfOH resulted in decomposition (Table 2.1, Entry 5). Given that excess $BF_3{\cdot}OEt_2$ successfully promoted the corresponding (4+3) cycloaddition reactions of methyleneaziridines,[97] we hoped it might also promote this process. Unfortunately however, treatment of (*S*)-**169** with $BF_3{\cdot}OEt_2$ (1.5 eq.) resulted in decomposition (Table 2.1, Entry 6). Switching the solvent to DCE and heating the reaction at reflux temperature, again returned starting materials (Table 2.1, Entries 7-10), while using stoichiometric Lewis acid gave only decomposition (Table 2.1, Entries 11-14).

Concerned that the absence of a cation stabilising group in (*S*)-**169** might impair the formation of a 2-aminoallyl cation, we decided to investigate whether isopropylideneaziridine **177** might be a more suitable substrate for this process, since the mildly inductive nature of the two methyl groups might be expected to have a stabilising effect on the presumed 2-aminoallyl cation **192** (Scheme 2.9).



Scheme 2.9.

Hence, **177** was treated with $AgSbF_6$ (5 mol%) in the presence of phenylacetylene **188** or styrene **193**, but in both cases no new products were detected, only starting materials were returned (Table 2.2, Entries 1-2). Excess $BF_3{\cdot}OEt_2$ again resulted in decomposition (Table 2.2, Entries 3-4).



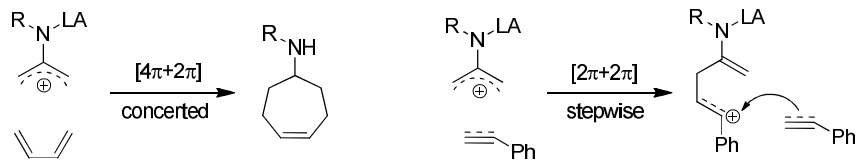
177 188 or Styrene, 193 194 195 196

Entry	Catalyst (mol%)	Dipolarophile (eq)	Outcome
1	$AgSbF_6$ (5)	**188** (3)	No reaction
2	$AgSbF_6$ (5)	**193** (3)	No reaction
3	$BF_3{\cdot}OEt_2$ (150)	**188** (3)	Decomposition
4	$BF_3{\cdot}OEt_2$ (150)	**193** (3)	Decomposition

All reactions were performed in CH_2Cl_2, -30 °C-rt

Table 2.2.

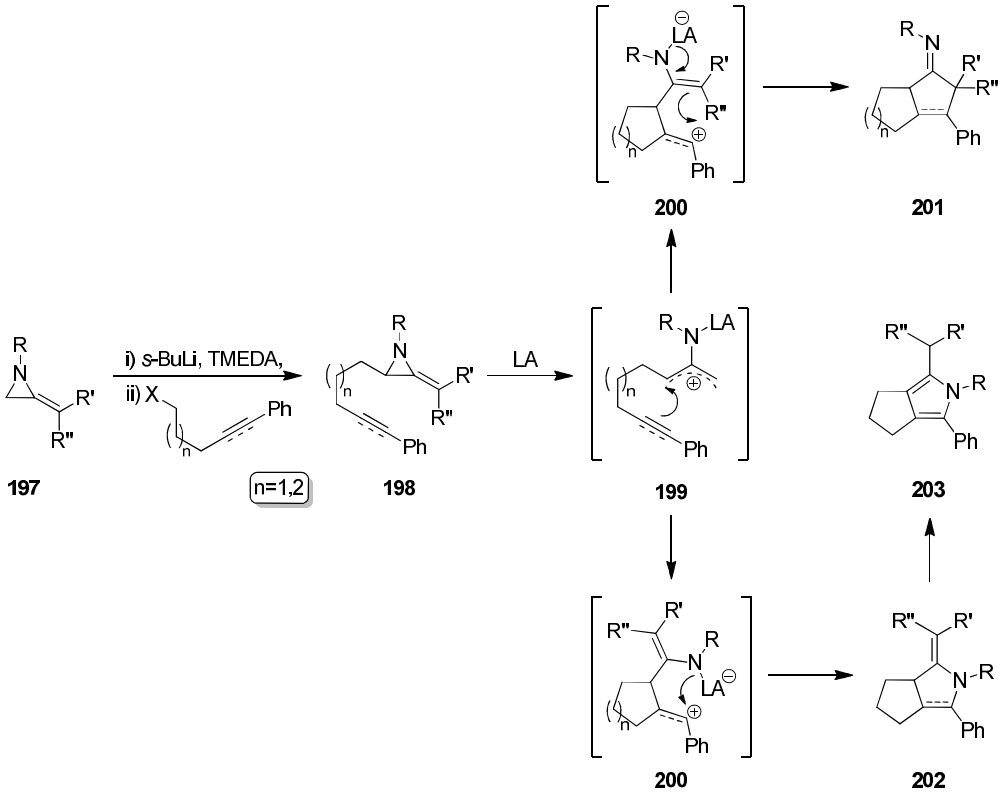
Unfortunately, our attempts at realising an intermolecular (3+2) cycloaddition reaction involving methyleneaziridines met with failure. It is possible that since the proposed cycloaddition reaction is a 4π-electron, and therefore non-concerted process, there is a greater chance for competitive polymerisation to occur compared with the corresponding intermolecular (4+3) manifold, which most likely proceeds *via* a stable 6π-electron 'aromatic' transition state (Scheme 2.10).



Scheme 2.10.

2.2. Lewis acid promoted intramolecular (3+2) cycloaddition reactions involving methyleneaziridines

Undeterred by our initial findings, we next turned our attention to the intramolecular variant of this reaction. Since methyleneaziridines can be readily functionalised at C-3,[105,116] we felt we could easily assemble a range of 2-aminoallyl cation precursors bearing suitable alkene or alkyne acceptor groups. Our general strategy for the proposed intramolecular (3+2) cycloaddition is outlined below (Scheme 2.11).

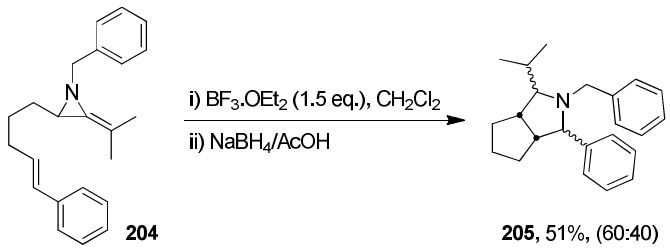


Scheme 2.11.

Lithiation and alkylation of **197** with an appropriately substituted alkene or alkyne is expected to provide entry to cycloaddition precursor **198**. Complexation of the

nitrogen atom of **198** to a suitable Lewis acid might then generate Lewis acid complexed 2-aminoallyl cation **199**, following fragmentation of the initially formed aziridinium ion. Further intramolecular addition of the appended alkene or alkyne might be expected to generate a zwitterionic intermediate such as **200**. Alternatively, it is possible that ring opening might occur by direct nucleophilic attack of the appended alkene or alkyne onto the highly strained aziridinium ion. Again, we anticipated that ring closure onto the benzylic carbocation might occur through carbon to form (3+2) cycloadduct **201**, or through nitrogen to form bicyclic pyrrole **203**, following isomerisation of **202**.

From the outset, we were optimistic that the proposed new intramolecular (3+2) cycloaddition reaction would be successful. In earlier unpublished work conducted by a previous member of the Shipman group, Dr Cyril Montagne, the main product upon treatment of 1-benzyl-2-((*E*)-5-phenylpent-4-enyl)-3-(propan-2-ylidene)aziridine **204** with $BF_3{\cdot}OEt_2$ (1.5 eq.) followed by $NaBH_4$, was tentatively assigned as a 60:40 diastereomeric mixture of the corresponding fused bicyclic pyrrolidine **205** (Scheme 2.12).[117]

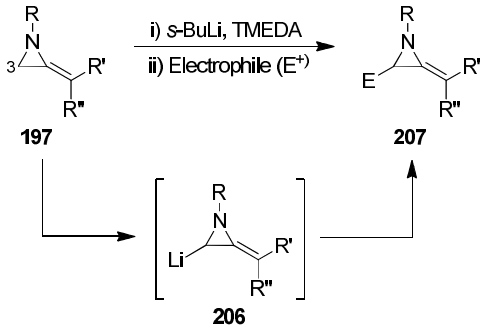


204 **205**, 51%, (60:40)

Scheme 2.12.

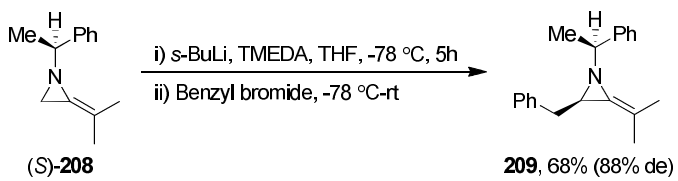
To assemble substrates for the proposed intramolecular (3+2) cycloaddition studies, an efficient route to C-3 substituted methyleneaziridines was required.

Methyleneaziridinyl anions **206** can be produced by selective lithiation of the parent methyleneaziridine **197** at C-3 using *s*-BuLi/TMEDA. Subsequent alkylation with a wide variety electrophiles furnishes the corresponding C-3 mono-functionalised[118] derivatives **207** in modest to good yields (Scheme 2.13).[105,116]



Scheme 2.13.

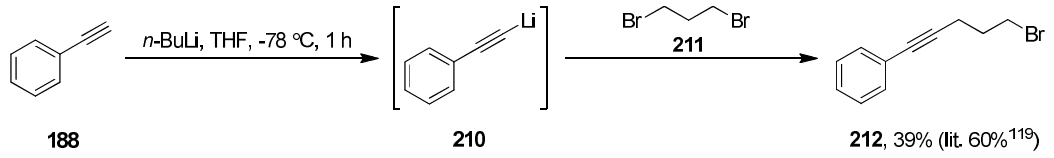
Importantly, in methyleneaziridines incorporating a chiral non-racemic element within the *N*-substituent, high levels of diastereocontrol (up to 90% de) can be achieved.[105,116c] For example, lithiation of 1-((*S*)-1-phenylethyl)-2-(propan-2-ylidene)aziridine (*S*)-**208** and subsequent alkylation with benzyl bromide provides the corresponding C-3 substituted methyleneaziridine **209** with 88% de (Scheme 2.14). The stereochemistry of **209** was tentatively assigned by analogy with literature precedent.[111]



Scheme 2.14.

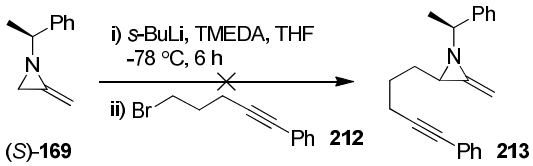
2.2.1. Intramolecular (3+2) cycloadditions onto alkyne acceptors

We first examined the synthesis and cyclisation of methyleneaziridine **213**, which bears a three-carbon linking chain between the reaction partners. With a supply of (*S*)-**169** in hand, we set about synthesising alkynyl bromide **212**.[119] Treatment of phenylacetylene **188** with an equimolar quantity of *n*-BuLi in THF at -78 °C for one hour, followed by addition of the resulting lithium phenylacetylide **210** to a stirred solution of 1,3-dibromopropane **211** provided **212** in 39% yield (Scheme 2.15).



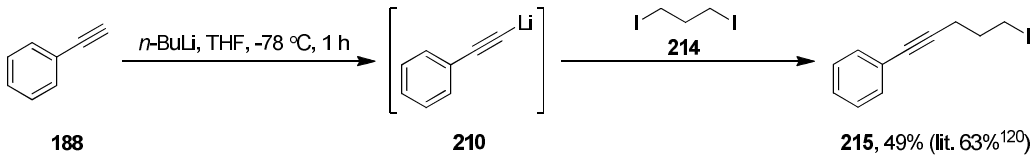
Scheme 2.15.

Unfortunately however, attempts to alkylate (*S*)-**169** with 1-(5-bromopent-1-ynyl)benzene **212** met with failure. Treatment of (*S*)-**169** with *s*-BuLi/TMEDA and then **212** returned only unreacted starting materials instead of the expected cycloaddition precursor **213** (Scheme 2.16).



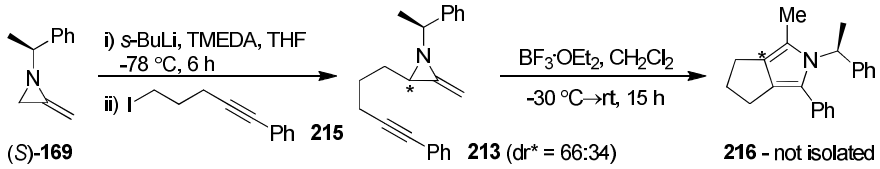
Scheme 2.16.

In a similar manner to bromide **212**, alkynyl iodide **215**[120] was prepared in 49% yield by the reaction of phenylacetylene **188** with *n*-BuLi in THF at -78 °C for one hour, followed by 1,3-diiodopropane **214** (Scheme 2.17).



Scheme 2.17.

Pleasingly, lithiation of (*S*)-**169** and subsequent alkylation with 1-(5-iodopent-1-ynyl)benzene **215** provided the corresponding C-3 functionalised product **213**, which was used in the next step without further purification (Scheme 2.18). For methyleneaziridines bearing two hydrogens on the exocyclic double bond, a substoichiometric quantity of the electrophile (0.95 eq.) must be used. This is necessary because these systems are known to be unstable to silica-gel chromatography. Purification of **213** was achieved by removal of any unreacted methyleneaziridine by bulb-to-bulb distillation.



* Determined by integration of the crude ^{1}H NMR spectrum.

Scheme 2.18.

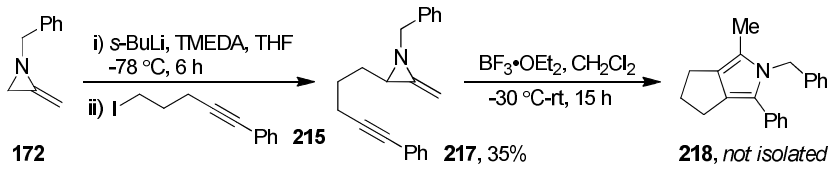
With methyleneaziridine **213** in hand, we set about examining its use in the proposed (3+2) cycloaddition reaction. For our preliminary experiments, we selected conditions known to successfully promote the aforementioned

intramolecular (4+3) cycloaddition reactions, namely $BF_3{\cdot}OEt_2$ (150 mol%) in CH_2Cl_2 at -30 °C with slow warming to room temperature over 15 hours.

Gratifyingly, treatment of **213** under these reaction conditions resulted in conversion to the corresponding pyrrole **216**, which was assigned by examination of its crude ^{1}H NMR spectra. By comparison of the ^{1}H NMR spectra of cycloaddition precursor **213** and pyrrole **216**, a downfield shift of the benzylic signal from 3.00 to 5.55 ppm was revealed. An isolated methyl singlet at 1.86 ppm, in addition to two triplets at 2.62 and 3.74 ppm, which correlated with a pentet at 2.33 ppm, was consistent with a product derived from ring closure through nitrogen. Additionally, an MH^+ ion (*m/z* = 302) was detected by analysis of the crude product by ESMS.

Since the new asymmetric centre produced at C-3 during the lithiation/alkylation sequence is effectively destroyed upon cyclisation of **213** to pyrrole **216**, we next decided to examine the same reaction using a methyleneaziridine bearing an achiral *N*-substituent.

Thus, lithiation of **172** and subsequent alkylation with a substoichiometric quantity of 1-(5-iodopent-1-ynyl)benzene **215**, followed by removal of any unreacted methyleneaziridine by bulb-to-bulb distillation, provided cycloaddition precursor **217** in 35% yield (Scheme 2.19).



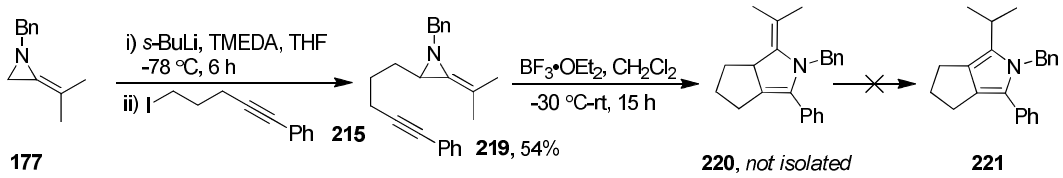
Scheme 2.19.

Again, treatment of **217** with $BF_3{\cdot}OEt_2$ (150 mol%) in CH_2Cl_2 at -30 °C to room temperature for 15 hours resulted in conversion to the corresponding pyrrole **218**, which was assigned by examination of its crude ^{1}H NMR spectra. By comparison of the ^{1}H NMR spectra of cycloaddition precursor **217** and pyrrole **218**, a downfield shift of the benzylic signal from 3.73 to 5.07 ppm was revealed. An isolated methyl singlet at 2.03 ppm, in addition to a triplet and multiplet at 2.58 and 2.72 ppm, which both correlated with a pentet at 2.32 ppm, and an MH^+ ion (*m/z* = 288) in the mass spectrum, were all evidence of a product derived from ring closure through nitrogen.

It is noteworthy that no products derived from ring closure through carbon were detected in either case. Unfortunately however, **216** and **218** appeared to be unstable since numerous attempts to obtain clean samples for full characterisation met with failure. In particularly, exposure to silica gel (even when neutralised with Et_3N) resulted in significant degradation. Although we were unable to isolate the products from these reactions, we had reason to believe we had unearthed the first example of methyleneaziridines participating in a (3+2) cycloaddition reaction of this type and were very encouraged by these results.

From a practical standpoint, the synthesis of isopropylideneaziridine **219** was desirable since methyleneaziridines of this type are chromatographically stable

and thus easier to manipulate (Scheme 2.20). Moreover, we predicted that the exocyclic *gem*-dimethyl substituents might serve to stabilise the presumed 2-aminoallyl cation intermediate, leading to a pyrrole better protected against degradation. The benzyl group was selected to eliminate the generation of diastereomers, as observed in the lithiation/alkylation sequence of methyleneaziridines bearing a chiral non-racemic *N*-substituent.



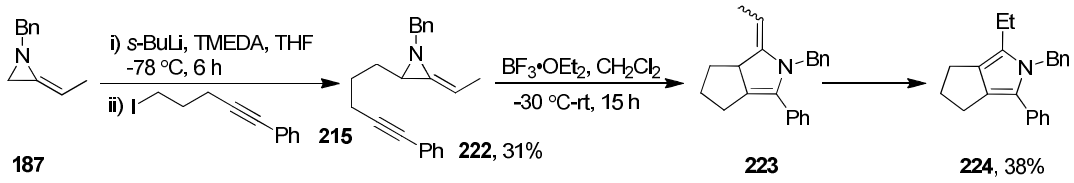
Scheme 2.20.

Lithiation of **177** and subsequent alkylation with excess 1-(5-iodopent-1-ynyl)benzene **215** (120 mol%) provided C-3 substituted isopropylideneaziridine **219** in 54% yield. Treatment of **219** with $BF_3{\cdot}OEt_2$ provided a product assigned as enamine **220** (see Appendix), and not pyrrole **221** which might be expected following isomerisation of double bond. We had expected that conversion of tetrasubstituted olefin **220** to tetrasubstituted 'heteroaromatic' olefin **221** might be an energetically favourable process,* and would therefore occur spontaneously. Unfortunately, **220** was found to be chromatographically unstable, and attempts towards purification on silica gel and basic or neutral alumina, resulted in extensive degradation. Attempts to reduce **220** with $NaBH_4$/AcOH or by hydrogenation (H_2, Pd/C) also met with failure, presumably due to steric congestion. Attempted isomerisation of **220** to pyrrole **221** using glacial acetic

*Aromatic resonance energy of benzene = 150 kJ mol^{-1} *cf.* pyrrole = 90 kJ mol^{-1}

acid at reflux was more successful. ^{1}H NMR analysis indicated partial conversion to **221**, although the reaction was messy and conversion low (ca. 33%).

To circumvent these problems, we decided to study the synthesis and cyclisation of ethylideneaziridine **222** (Scheme 2.21). We anticipated that isomerisation of the initially formed trisubstituted exocyclic olefin **223** to the corresponding tetrasubstituted 'heteroaromatic' olefin **224** would be easier. Thus, ethylideneaziridine **222** was synthesised in 31% yield following column chromatography, by lithiation and subsequent alkylation of **187** with 1-(5-iodopent-1-ynyl)benzene **215** (120 mol%).

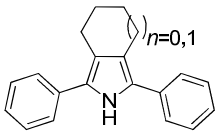


Scheme 2.21.

We were delighted to find that our earlier prediction was correct, as **222** was shown to react smoothly in the presence of $BF_3{\cdot}OEt_2$ (150 mol%) to afford pyrrole **224** in 38% yield following column chromatography. Notably, intermediate **223** was not detected upon examination of the crude ^{1}H NMR spectrum. Evidence for the formation of pyrrole **224** was obtained by comparison of its ^{1}H NMR spectrum with that of cycloaddition precursor **222**. A downfield shift of the benzylic signal from 3.75 to 5.10 ppm was revealed, in addition to a triplet and quartet at 1.18 and 2.44 ppm respectively, corresponding to an isolated ethyl group. Two multiplets at 2.76-2.72 ppm (4H) and 2.37-2.33 ppm (2H), in addition

to an MH^+ ion (*m/z* = 302) in the mass spectrum, were all consistent with pyrrole **224**.

Interestingly, a number of closely related tetrahydro-*2H*-isoindoles **225** were shown to be potent and selective inhibitors of the COX-2 isoenzyme, of potential use in the treatment of pain, fever and inflammatory conditions including osteoarthritis (Figure 2.1).[121]



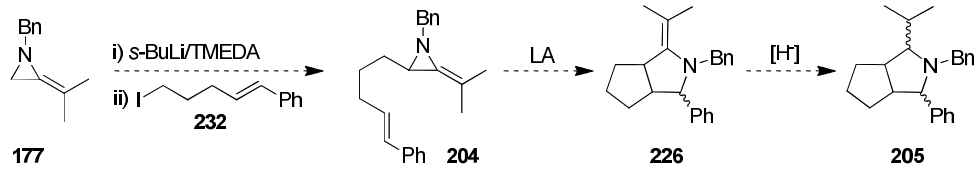
225

Figure 2.1.

No attempt was made to vary the length of the carbon tether or the substituent attached to the alkyne terminus, although a study of this type may be warranted in the future.

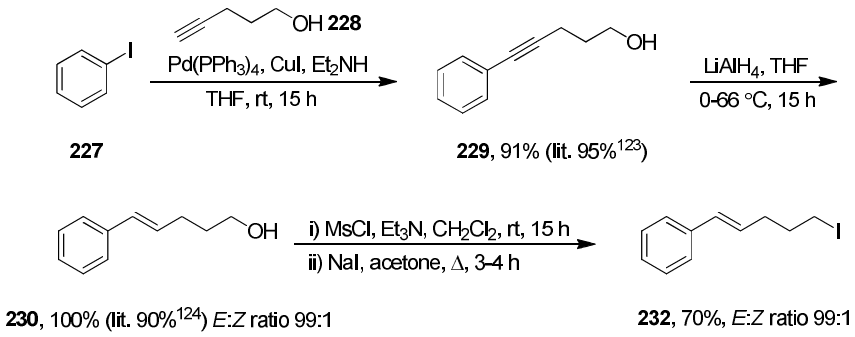
2.2.2. Intramolecular (3+2) cycloadditions onto alkene acceptors

Next, we examined the intramolecular (3+2) cycloaddition reactions of methyleneaziridines bearing alkene acceptors. As a starting point, we decided to repeat the experiment first conducted Dr Cyril Montagne (Scheme 2.12). Based on our earlier observations, we anticipated that treatment of **204**, in the presence of excess $BF_3{\cdot}OEt_2$ would provide an intermediate enamine **226** that might be readily reduced to provide the corresponding pyrrolidine **205** (Scheme 2.22).



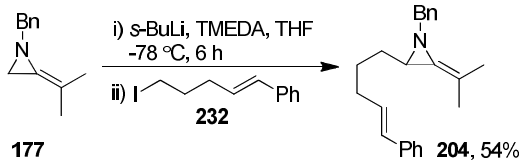
Scheme 2.22.

Iodide **232** was prepared in four steps, commencing with Sonogashira coupling[122] of commercially available iodobenzene **227** with 4-pentynol **228** (Scheme 2.23).



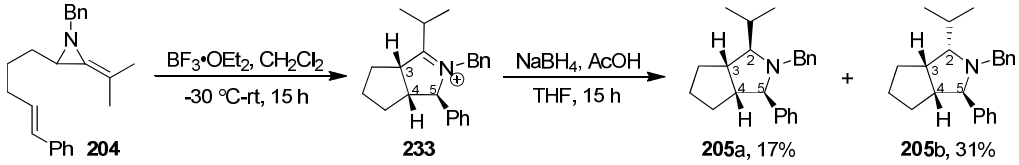
Scheme 2.23.

Reduction of alcohol **229**[123] with $LiAlH_4$ in THF at 0-66 °C for 15 h furnished the corresponding (*E*)-alkenyl alcohol **230**[124] in good yield. Treatment of **230** with methanesulfonyl chloride in the presence of Et_3N in CH_2Cl_2 at room temperature for 15 hours afforded mesylate **231**, which was further converted to iodide **232** in 70% over two steps by way of a Finkelstein reaction with sodium iodide in refluxing acetone. Cycloaddition precursor **204** was assembled in a single operation by lithiation and alkylation of **177** with a slight excess 1-((*E*)-5-iodopent-1-enyl)benzene **232** (120 mol%). The methyleneaziridine **204** produced in this reaction was isolated as a single geometrical isomer as interpreted by ^1H NMR spectroscopy (Scheme 2.24).



Scheme 2.24.

Upon reaction with excess $BF_3{\cdot}OEt_2$, **204** was converted to iminium ion **233** as a single diastereomer (Scheme 2.25), instead of the expected enamine tautomer **226** (*cf.* Scheme 2.22). The structure of **233** was assigned based on the observation that its crude ^{1}H NMR spectrum contained two doublets at 1.43 and 1.55 ppm, which coupled with a pentet at 3.58 ppm, consistent with an isolated isopropyl group: for an enamine such as **226**, the exocyclic isopropylidene group would be expected to give rise to two methyl singlets. Coupling of a multiplet at 3.14 ppm, corresponding to H-4 with a multiplet at 4.20 ppm (H-3) and a doublet at 4.86 ppm (H-5) was also observed, in addition to coupling of H-3 and H-4 with the cyclopentyl ring hydrogens.



Scheme 2.25.

Reduction of iminium ion **233** was achieved using $NaBH_4$/AcOH in THF at room temperature for 15 hours, and provided diastereomers **205a** and **205b** in a crude ratio of 41:59 respectively. Gratifyingly, **205a** and **205b** were fully separable by silica gel chromatography and were isolated in a combined yield of 48%. The gross structure of **205a** and **205b** was deduced using COSY correlation NMR

spectroscopy. In **205a**, coupling of the isopropyl hydrogen at 1.93 ppm with H-2 at 2.23 ppm was observed. H-2 was shown to couple with H-3 at 2.29 ppm. H-3 coupled with H-4 at 2.15 ppm and H-4 coupled with H-5 at 3.05 ppm. Coupling between H-3 and H-4 with the cyclopentyl ring hydrogens was also observed. In **205b**, coupling of the isopropyl hydrogen at 1.84 ppm with H-2 at 3.14 ppm was observed. H-2 was shown to couple with H-3 at 2.43 ppm. H-3 coupled with H-4 at 2.54 ppm and H-4 coupled with H-5 at 3.92 ppm. Coupling between H-3 and H-4 with the cyclopentyl ring hydrogens was also observed. The presence of an MH^+ ion (m/z = 320) in the mass spectrum of **205a** and **205b** was further evidence of the structures drawn above (Scheme 2.25). Additionally, the gross structure of a closely related analogue **268b** was later unambiguously confirmed by X-ray crystallography (Figure 2.4).

The relative stereochemistry of **205a** and **205b** was deduced using NOESY correlation experiments, which revealed a *cis*-relationship between the isopropyl group and H-3, H-4 and the phenyl group at C-5 in the minor diastereomer **205a** and a *trans*-relationship in the major diastereomer **205b** (Figure 2.2).

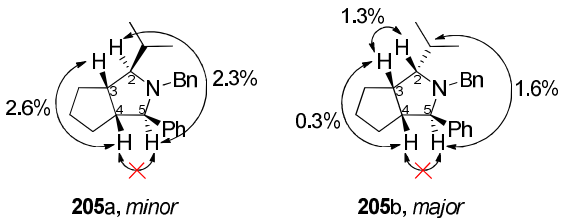
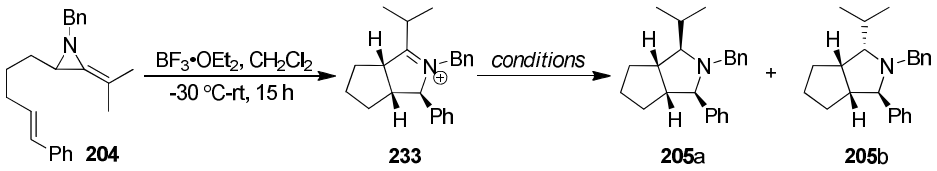


Figure 2.2.

Significantly, irradiation of the signal corresponding to the isopropyl methyl groups in **205a**, resulted in a 2.6% enhancement of the signals corresponding to

H-3 and H-4. In **205b**, irradiation of the signal corresponding to H-2, resulted in 3.2% enhancement of the signal corresponding to the ortho hydrogens of the phenyl substituent at C-5. Evidently, hydride delivery from the convex (*Re*) face of the iminium ion **233** is favoured, as approach from the concave (*Si*) face is more sterically encumbered.

Hoping to improve the diastereoselectivity in the reduction of iminium ion **233**, we examined three alternative sets of reaction conditions, detailed in Table 2.3. Each reaction was conducted separately on a 100 mg scale starting from the same batch of cycloaddition precursor **204**, and assessed by examination of the crude ^{1}H NMR spectra following reduction.



Entry	Conditions	dr[a] a:b	Yield (%)	
1	$NaBH_4$/AcOH, THF, rt, 15 h	41:59	17	31
2	Et_3SiH/TFA, CH_2Cl_2, -30 °C-rt, 15 h.[125]	Not detected	0	0
3	$NaBH_3CN$/AcOH, MeOH, rt, 15 h.[126]	64:36	16	3
4	L-Selectride®, THF, -78 °C-rt, 15 h.	0:100	0	0

[a] By integration of crude ^{1}H NMR spectrum

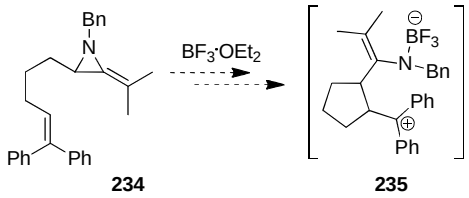
Table 2.3.

For comparison, our original results are included (Table 2.3, Entry 1). Treatment of **233** with triethylsilane and trifluoroacetic met with failure, *i.e.* neither **205a** nor **205b** was observed upon examination of the crude ^{1}H NMR spectrum (Table 2.3, Entry 2). Reduction of **233** with $NaBH_3CN$/AcOH in MeOH resulted in a reversal

of the original diastereoselectivity. However, these conditions also resulted in a more complex mixture and **205a** and **205b** were isolated in a significantly reduced 19% combined yield (Table 2.3, Entry 3). We were initially encouraged to find that treatment of **233** with L-Selectride® in THF, gave only **205b**. However, it was apparent that a rather complex mixture had resulted and so the product was not isolated (Table 2.3, Entry 4). Based on these results, our original conditions ($NaBH_4$/AcOH, THF, rt, 15 h) gave best conversion and highest yield and were thus employed thereafter.

To further improve the reaction, and gain a deeper understanding of the factors that govern the process, we next chose to make seemingly small structural changes to the cycloaddition precursor to examine their impact on this new (3+2) cycloaddition reaction.

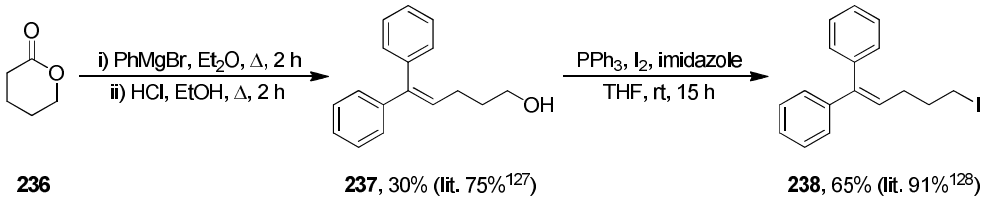
We imagined that the introduction of an additional phenyl group on the alkene terminus might serve to further stabilise the presumed benzylic carbocation intermediate **235** leading to improvements in the reaction efficiency (Scheme 2.26).



Scheme 2.26.

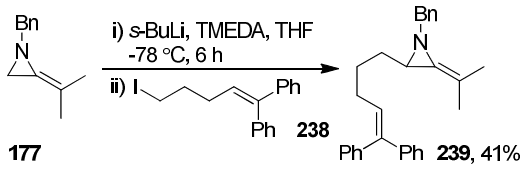
To test this idea, we set about constructing cycloaddition precursor **234**, commencing with the synthesis of 5-iodo-1,1-diphenylpent-1ene **238** in two steps

from commercial δ-valerolactone (Scheme 2.27). Ring opening of **236** with freshly prepared phenylmagnesium bromide in refluxing Et_2O for 2 hours, followed by treatment of the resulting diol with HCl in refluxing EtOH for 2 hours provided 5,5-diphenylpent-4-en-1-ol **237** in 30% yield.[127] Iodination of **237** in the presence of PPh_3, I_2 and imidazole afforded 5-iodo-1,1-diphenylpent-1ene **238** in a moderate yield.[128]



Scheme 2.27.

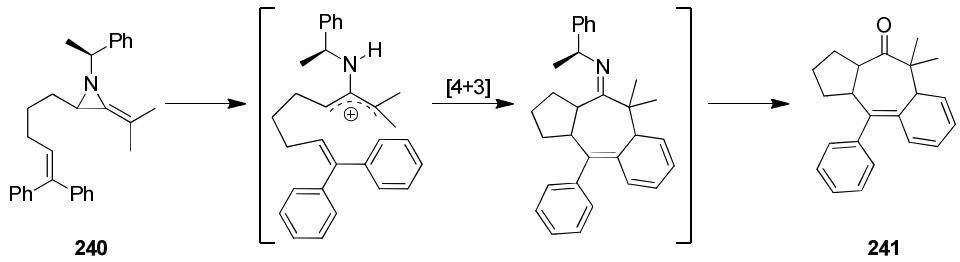
Lithiation and subsequent alkylation of isopropylideneaziridine **177** with 5-iodo-1,1-diphenylpent-1ene **238** afforded the desired cycloaddition precursor **239** in 41% yield following column chromatography (Scheme 2.28).



Scheme 2.28.

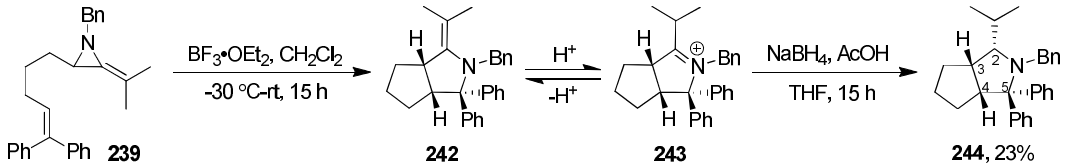
It is noteworthy that while isopropylideneaziridines are chromatographically stable, neutralisation of the stationary phase (SiO_2) with 1% Et_3N is necessary to prevent degradation. Interestingly, we had earlier attempted to purify a diastereomeric mixture of **240** by silica gel chromatography without first treating the column with Et_3N. We were initially confused to find signals in the ^1H NMR

spectrum of the 'purified' material that were not detected in the original crude spectrum. We later concluded that protonation of **240** under the slightly acidic column conditions had led to the formation of a product seemingly derived from a (4+3) cycloaddition reaction of the methyleneaziridine nucleus onto the *gem*-diphenyl alkene acceptor followed by hydrolysis of the initially formed ketimine (Scheme 2.29). We successfully acquired spectroscopic evidence in the form of ^{1}H, COSY and ^{13}C NMR and mass spectra, which were all in good agreement with the structure of **241** (see Appendix).



Scheme 2.29.

Having isolated a clean sample of *N*-benzyl **239**, we found that its treatment with excess $BF_3{\cdot}OEt_2$ provided enamine **242** which, upon reduction with $NaBH_4$/AcOH, provided pyrrolidine **244** as a single diastereomer (Scheme 2.30).



Scheme 2.30.

The gross structure of **244** was deduced using COSY correlation NMR spectroscopy. Coupling of the isopropyl hydrogen at 1.54 ppm with H-2 at 3.28

ppm was observed. H-2 was shown to couple with H-3 at 2.73 ppm. H-3 coupled with H-4 at 3.20 ppm. Coupling between H-3 and H-4 with the cyclopentyl ring hydrogens was also observed. The presence of an MH^+ ion (*m*/*z* = 396) in the mass spectrum was also consistent with pyrrolidine **244**. Upon closer inspection of the ^1H NMR spectrum of **244**, an impurity (~6%), possibly corresponding to a second diastereomer was detected.

Analysis of the NOESY correlation data for **244**, revealed a *cis*-relationship between H-2, H-3 and H-4 (Figure 2.3). Irradiation of the signal corresponding to H-3 resulted in enhancement of the signals corresponding to H-2 and H-4. Crucially, no NOE interaction was observed across the pyrrolidine ring between H-4 and the isopropyl methyl groups.

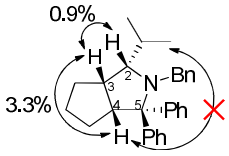
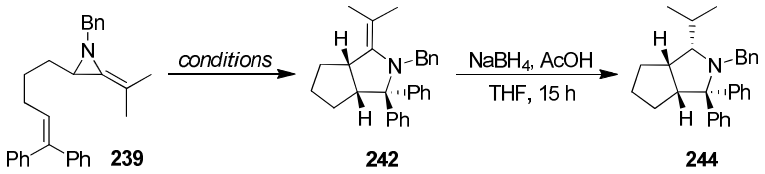


Figure 2.3.

On the basis of this observation, we suggest that hydride delivery occurs exclusively from the convex (*Re*) face of enamine **242** because (in comparison to iminium ion **233**) the concave (*Si*) face is even more sterically encumbered by incorporation of an additional phenyl substituent at C-5.

Disappointingly, pyrrolidine **244** was only isolated in 23% yield using $BF_3.OEt_2$ in CH_2Cl_2. A possible explanation for this could be steric clashing of the *gem*-diphenyl alkene substituents and the bulky Lewis acid complexed amino substituent in the enamine forming step. To improve the efficiency of this

reaction, we decided to screen a number of alternative Lewis/Brønsted acids and solvents as detailed in Table 2.4.



Entry	Lewis/Brønsted acid	Eq.	Solvent	Aromatic:1H[a]	Yield (%)
1	$BF_3{\cdot}OEt_2$	1.5	CH_2Cl_2	32:1	23
2	$Sc(OTf)_3$	1.5	CH_2Cl_2	22:1	27
3	$SnCl_4$	1.5	CH_2Cl_2	36:1	0
4	$AgSbF_6$	1.5	CH_2Cl_2	51:1	0
5	Diphenylphosphate	1.5	CH_2Cl_2	Decomposition	0
6	TsOH	1.5	CH_2Cl_2	Decomposition	0
7[b]	$Sc(OTf)_3$	0.1	CH_2Cl_2	Incomplete	0
8[c]	$Sc(OTf)_3$	0.2	DCE	35:1	1
9	$BF_3{\cdot}OEt_2$	1.5	DCE	45:1	0
10	$BF_3{\cdot}OEt_2$	1.5	Benzene	30:1	0
11	$BF_3{\cdot}OEt_2$	1.5	CH_3CN	26:1	0
12	$BF_3{\cdot}OEt_2$	1.5	Et_2O	27:1	0

[a] By integration of crude ^{1}H NMR spectrum;[b] -30 °C, 1h; then rt, 24 h; then reflux, 24 h;
[c] -30 °C, 1h; then reflux, 48 h.

Table 2.4.

Each reaction was conducted separately on a 100 mg scale starting from the same batch of cycloaddition precursor **239**, monitored by TLC and the efficiency of each cyclisation assessed by integration of the entire aromatic region, relative to one hydrogen of the desired enamine **242** at 4.21 ppm. An efficient cyclisation should result in a 15:1 ratio respectively. Unless otherwise stated, the

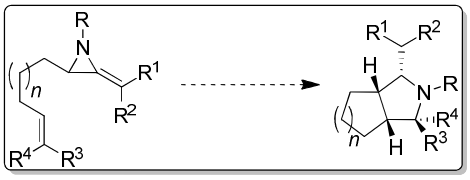
Lewis/Brønsted acid was added at -30 °C, held at that temperature for 1 hour then allowed to slowly warm to room temperature and stirred overnight.

For comparison, our original results are included (Table 2.4, Entry 1). Of the Lewis acids examined (Table 2.4, Entries 1-4), $Sc(OTf)_3$ gave the cleanest conversion to enamine **242**, and thus after reduction with $NaBH_4$/AcOH, pyrrolidine **244** was isolated in a slightly improved 27% yield. Using the Brønsted acids, diphenylphosphate and TsOH, none of the expected product was detected, with only decomposition observed (Table 2.4, Entries, 5-6).

Since $Sc(OTf)_3$ had been shown to successfully promote this reaction when used in excess, we hoped it might also work catalytically. However when **239** was treated with $Sc(OTf)_3$ at 10 mol% catalyst loading in CH_2Cl_2 at -30 °C to room temperature, the reaction was incomplete after 24 hours. Even after a further 24 hours in refluxing CH_2Cl_2, the crude reaction mixture consisted of starting material **239** and enamine **242** in a ratio of 53:47 respectively (Table 2.4, Entry 7). At 20 mol% catalyst loading in refluxing DCE, complete conversion of **239** to **242** was observed after 48 hours. Unfortunately however, after reduction of **242**, the expected pyrrolidine **244** was isolated in just 1% yield (Table 2.4, Entry 8). Furthermore, the alternative solvents investigated failed to give significantly cleaner conversion and so were disregarded for future use (Table 2.4, Entries 9-12). Although excess $Sc(OTf)_3$ had given the cleanest conversion, the improvement in overall yield for the reaction was deemed insufficient to warrant its widespread use in this chemistry. From a cost perspective, it was not economically viable to use $Sc(OTf)_3$ as a stoichiometric reagent ($Sc(OTf)_3$ =

£13,000/mol *cf*. $BF_3{\cdot}OEt_2$ = £13/mol). Thus, our original conditions ($BF_3{\cdot}OEt_2$, CH_2Cl_2) were employed thereafter.

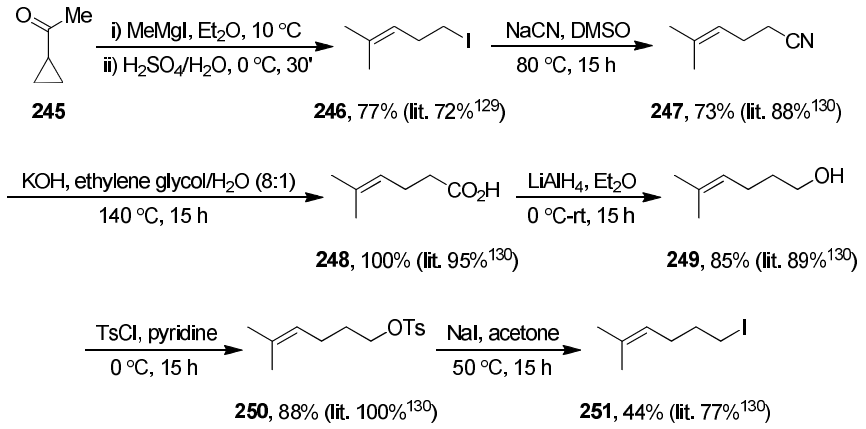
Further substrates were constructed to ascertain if this new chemistry might provide a concise route to a range of structurally diverse bicyclic pyrrolidines (Scheme 2.31).



Scheme 2.31.

Thus, a range of *N*-benzyl cycloaddition precursors **265**, **267**, **269** and **275-278,** varying in aziridine substitution pattern, alkene substitution/geometry and length of the carbon tether, were assembled employing the aforementioned lithiation/alkylation strategy. With methyleneaziridines **172**, **175**, **177** and **182** in hand, a range of suitable electrophiles were synthesised from commercially available starting materials in preparation for the construction of a variety of intramolecular (3+2) cycloaddition substrates detailed below (Table 2.5).

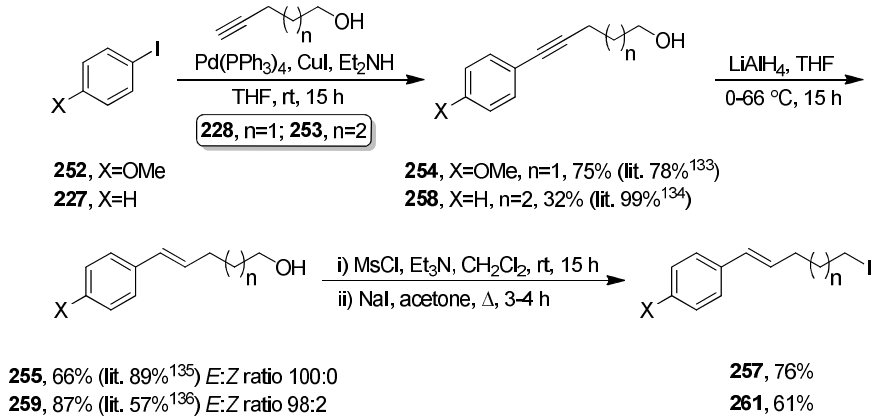
6-Iodo-2-methylhex-2-ene **251** was prepared in six steps from cyclopropyl methyl ketone **245** (Scheme 2.32). Ring opening of **245** with methylmagnesium iodide in Et_2O, followed by treatment with aqueous H_2SO_4, afforded homoallylic iodide **246** in good yield.[129] The reaction of **246** with sodium cyanide in DMSO at 80 °C for 15 hours gave 5-methylhex-4-enenitrile **247** [130] which, following hydrolysis with KOH in ethylene glycol and water at 140 °C for 15 hours, provided 5-methylhex-4-enoic acid **248**[130] in quantitative yield.



Scheme 2.32.

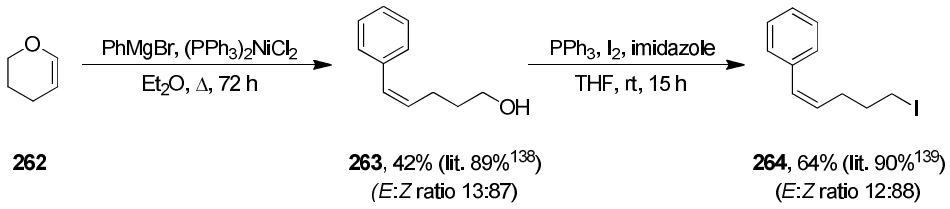
Reduction of **248**[130] with $LiAlH_4$ in Et_2O at 0 °C to room temperature for 15 hours gave the corresponding alcohol **249**[130] in good yield. Treatment of 5-methylhex-4-en-1-ol **249** with *p*-toluenesulfonyl chloride in pyridine at 0 °C overnight afforded tosylate **250**,[130] which was further converted to the corresponding iodide **251**[130] through its reaction with sodium iodide in refluxing acetone for 15 hours, in 39% yield over two steps.

Iodides **257**[131] and **261**[132] were prepared according to the same sequence used for the synthesis of **232** (Scheme 2.23), commencing with Sonogashira coupling of commercially available 4-iodoanisole **252** and iodobenzene **227** with 4-pentynol **228** and 5-hexyn-1-ol **253** respectively (Scheme 2.33). Reduction of **254**[133] and **258**[134] with $LiAlH_4$ in THF at 0-66 °C for 15 h furnished the corresponding (*E*)-alkenyl alcohols **255**[135] and **259**[136] in moderate to good yields. Treatment of **255** and **259** with methanesulfonyl chloride in the presence of Et_3N in CH_2Cl_2 at room temperature for 15 hours afforded the corresponding mesylates **256**[136] and **260**,[137] which were further converted to iodides **257**[131] and **261**,[132] in 61-76% by way of a Finkelstein reaction with sodium iodide in refluxing acetone.



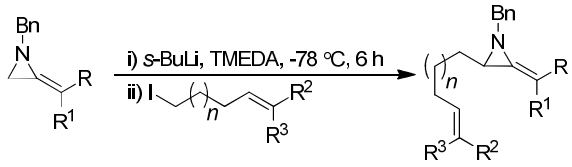
Scheme 2.33.

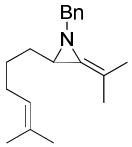
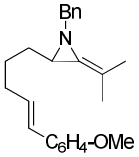
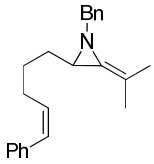
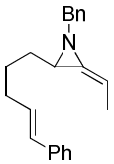
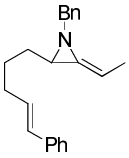
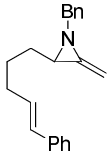
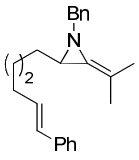
(*Z*)-Alkenyl iodide **264** was prepared in two steps from commercially available 3,4-dihydro-2*H*-pyran **262** (Scheme 2.34). Ring opening of **262** with phenylmagnesium bromide in the presence of bis(triphenylphosphine)nickel(II) dichloride in refluxing Et_2O for 72 hours gave (*Z*)- and (*E*)-5-phenylpent-4-en-1-ol **263** as an inseparable mixture of geometrical isomers.[138] Iodination of **263** in the presence of PPh_3, I_2 and imidazole afforded (5-iodopent-1-en-1-yl)benzene, also as an inseparable 12:88 mixture of geometrical isomers (*Z*)- and (*E*)-**264**.[139]



Scheme 2.34.

Having synthesised a number of suitable electrophiles, we set about constructing the cycloaddition precursors detailed below (Table 2.5).



Entry	Aziridine	R	R^1	R^2	R^3	*n*	Product	Yield (%)
1	**177**	Me	Me	Me	Me	1		23
2	**177**	Me	Me	C_6H_4-OMe	H	1		57
3	**177**	Me	Me	H	Ph	1		57
4	**182**	H	Me	Ph	H	1		39
5	**187**	Me	H	Ph	H	1		18
6[a]	**172**	H	H	Ph	H	1		59
7	**177**	Me	Me	Ph	H	2		37

[a] Purification achieved by removal of unreacted starting material by bulb-to-bulb distillation.

Table 2.5.

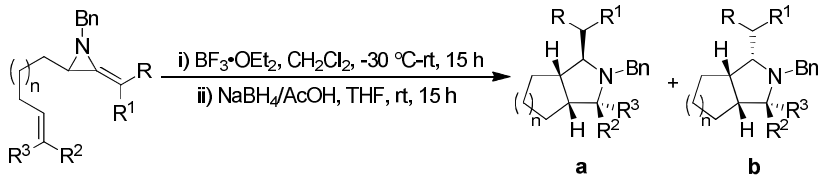
Using our well established lithiation/alkylation sequence, methyleneaziridine **172**, isopropylideneaziridine **177** and (*E*)- and (*Z*)-ethylideneaziridines **182** and **187** were reacted with iodides **232**, **251**, **257**, **261** and **264** to afford the corresponding C-3 functionalised products **265**, **267**, **269** and **275-278** in 18-59 % yield. All cycloaddition precursors were purified by column chromatography unless otherwise stated.

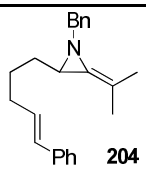
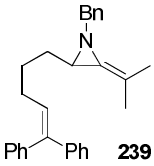
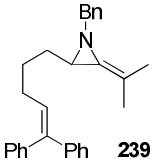
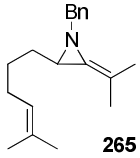
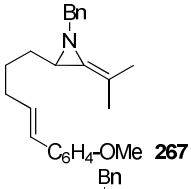
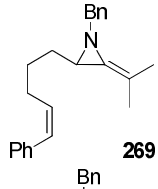
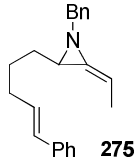
The cyclisations of **265**, **267**, **269** and **275-278** were examined using our best known reaction conditions ($BF_3.OEt_2$ (150 mol%), CH_2Cl_2, -30 °C, 1 h; then room temperature, 15 h), unless otherwise stated. Reaction progress was monitored by TLC and the results summarised in Table 2.6. For comparison, our earlier findings are included (Entries 1-3).

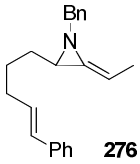
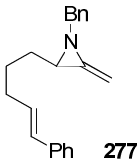
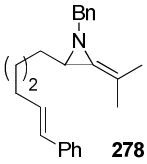
Cyclisation of isopropylideneaziridine **265,** bearing a *gem*-dimethyl acceptor group, required more forcing reaction conditions to drive the reaction to completion. Following reduction, two diastereomers **266a** and **266b** were detected in a crude ratio of 47:53 (Table 2.6, Entry 4). In the reduction of iminium ion **243** (Scheme 2.30) hydride delivery was assumed to occur exclusively from the convex (*Re*) face because the sterically hindered concave (*Si*) face was further obstructed due to incorporation of an additional phenyl substituent at C-5. The diasteromeric ratio obtained upon cycloaddition and reduction of **265** indicates that hydride delivery occurs from both faces of the initially formed iminium ion, since the methyl substituent at C-5 occupies less space than a phenyl substituent.[*] **266a** and **266b** were isolated in a very low combined 10% yield (Table 2.6, Entry

[*] A-values: methyl = 7.14 kJ mol^{-1} *cf.* phenyl = 12.6 kJ mol^{-1}

4). The relative stereochemistry in **266a** and **266b** was deduced using NOE correlation experiments.



Entry	Precursor	R	R^1	R^2	R^3	*n*	dr[a] a:b	Yield (%)
1	 **204**	Me	Me	Ph	H	1	41:59	48
2	 **239**	Me	Me	Ph	Ph	1	0:100	23
3[b]	 **239**	Me	Me	Ph	Ph	1	0:100	27
4[c]	 **265**	Me	Me	Me	Me	1	47:53	10
5	 **267**	Me	Me	C_6H_4-OMe	H	1	40:60	32
6	 **269**	Me	Me	H	Ph	1	-	0
7	 **275**	H	Me	Ph	H	1	-	0

8	 **276**	Me	H	Ph	H	1	-	0
9	 **277**	H	H	Ph	H	1	-	0
10	 **278**	Me	Me	Ph	H	2	-	0

[a] By integration of crude ^{1}H NMR spectrum; [b] $Sc(OTf)_3$ (150 mol%), CH_2Cl_2, -30 °C, 1 h; then rt, 15 h; [c] $BF_3.OEt_2$ (150 mol%), DCE, -30 °C, 1 h; then reflux, 15 h.

Table 2.6.

Cycloaddition and reduction of **267** provided **268a** and **268b** in a crude diastereomeric ratio of 40:60 respectively. Gratifyingly, purification of the major diastereomer **268b** provided crystals suitable for X-ray crystallographic analysis, which unambiguously confirmed the relative configuration of the newly formed stereocentres and the gross structural changes occurring in this remarkable new intramolecular cycloaddition (Figure 2.4).

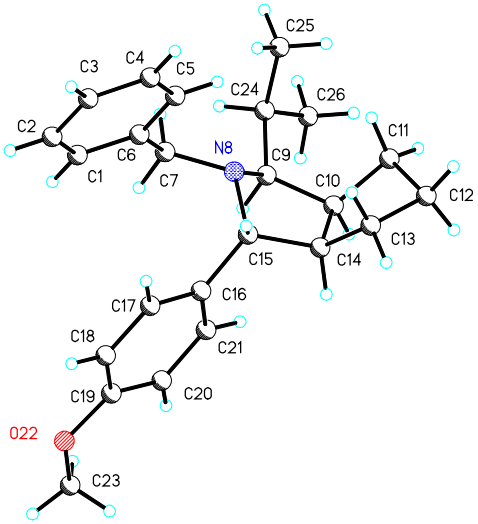
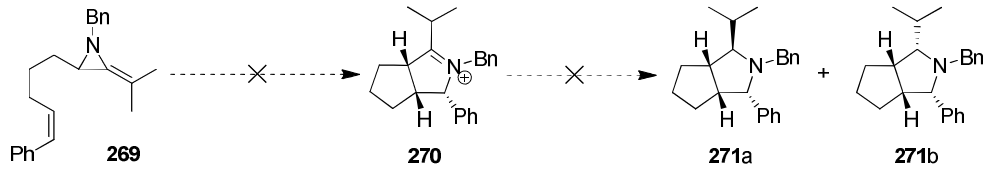


Figure 2.4.

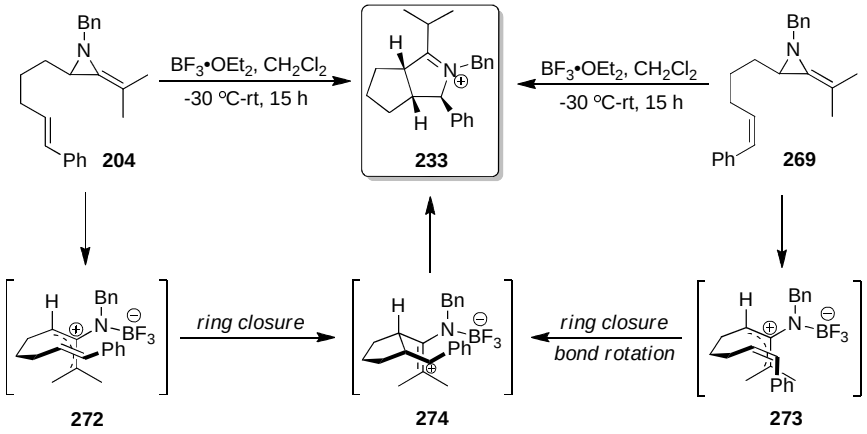
We rationalised that incorporation of a *para*-methoxy substituent within the alkene terminus might increase the electron density of the phenyl ring (without increasing steric bulk), serving to stabilise the intermediate benzylic carbocation, and thus the efficiency of the cyclisation. Unfortunately however, diastereomers **268a** and **268b** were only isolated in a combined 32% yield (Table 2.6, Entry 5).

Having noted that the geometry of the starting alkene acceptor group in **204** was reflected in the relative configuration of the resulting stereocentres in **205a** and **205b** (Scheme 2.25), we wondered whether cyclisation of the corresponding (*Z*)-isomer **269** might provide iminium ion **270** and then cycloadducts **271a** and **271b** as illustrated below (Scheme 2.35).



Scheme 2.35.

However, examination of the crude ^{1}H NMR spectrum following treatment of **269** with $BF_3{\cdot}OEt_2$ showed that the main component was in fact iminium ion **233**, albeit as part of a significantly more complex mixture (Table 2.6, Entry 6 and Scheme 2.36). If we consider plausible transition states for this process, a possible explanation for this phenomenon is revealed.



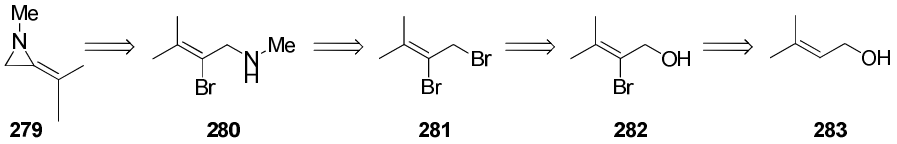
Scheme 2.36.

Ring opening of methyleneaziridines **204** and **269** in the presence of $BF_3{\cdot}OEt_2$ is expected to give rise to 2-aminoallyl cations **272** and **273**. The suggested U-shaped geometry of these cations is based on our analysis of earlier intramolecular (4+3) cycloadditions.[97] In **272** the phenyl group is projected away from the isopropyl group, and initial ring closure onto the presumed 2-aminoallyl cation could give rise to **274** and hence iminium ion **233**, following a second ring closure through nitrogen onto the resulting benzylic carbocation. Ring opening of **269** however, gives rise to a more sterically congested intermediate **273**, in which the phenyl group is eclipsing the isopropyl group. This hindered approach may account for the less clean cyclisation observed for this stereoisomer. Formation of iminium ion **233** from **273** would result from initial ring closure onto the 2-aminoallyl cation, followed by σ-bond rotation to give the energetically more favourable conformer **274**. Due to the complex nature of the crude ^{1}H NMR spectrum following cyclisation of **269**, no attempt was made to reduce the observed iminium ion **233**. The fact that the same iminium ion was detected for

both **204** and **269** provides compelling evidence for the stepwise nature of this sequence.

Disappointingly, we found that intramolecular (3+2) cycloadditions of methyleneaziridines onto alkene acceptors were limited to *gem*-dimethyl isopropylideneaziridines (Table 2.6, Entries 1-6). Treatment of (*E*)- and (*Z*)-ethylideneaziridines **275** and **276**, as well as methyleneaziridine **277** with $BF_3{\cdot}OEt_2$, all resulted in complex mixtures (Table 2.6, Entries 7-9). Furthermore, attempting to extend this methodology to the synthesis of 5,6-fused systems by incorporation of an additional carbon in the linking tether proved unsuccessful. Treatment of **278** with $BF_3{\cdot}OEt_2$ also resulted in complex mixtures (Table 2.6, Entry 10).

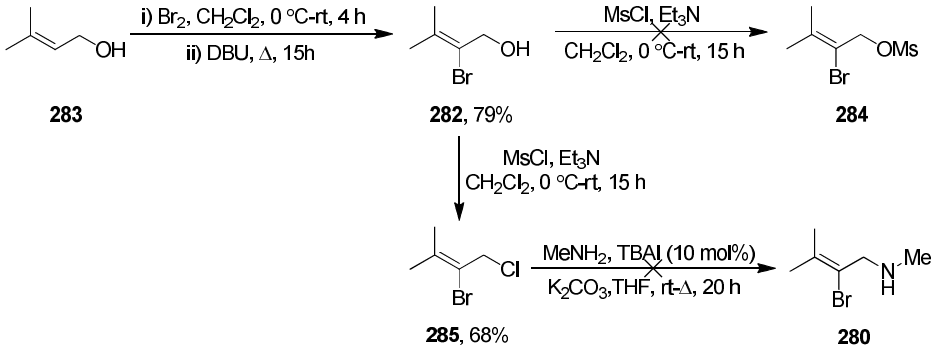
We wondered whether improvements in this chemistry might arise by alteration of the *N*-substituent. Specifically, we hoped that smaller, non-benzylic substituents might lead to improved transformations. To this end, we set about trying to assemble isopropylideneaziridine **279**, which bears a simple *N*-methyl group. The synthesis of 2-bromoallylamine **280** by direct ring opening of 1,1-dibromo-2,2-dimethylcyclopropane **173**[112] with methylamine[140] was discounted due to the high temperatures and long reaction times required for this transformation. Thus, we imagined we might be able to access **279** from commercially available 3-methylbut-2-enol **283**, according to the retrosynthesis detailed below (Scheme 2.37).



Scheme 2.37.

Indeed bromination of **283**, followed by base treatment (DBU) afforded 2-bromo-3-methylbut-2-en-1-ol **282**[100b] in good yield. Treatment of **282** with methanesulfonyl chloride did not provide the expected mesylate **284**. Instead, **285** (presumably formed by displacement of the initially formed mesylate with chloride) was isolated in 68% yield. The structure of **285** was deduced by inspection of its ^{1}H and ^{13}C NMR spectra. The presence of an MH^{+} ion (*m*/*z*=184) in the mass spectrum was also consistent with chloride **285**.

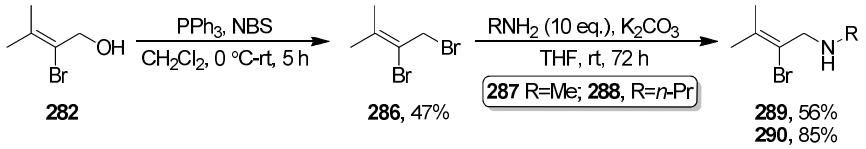
By treatment of **285** with methylamine in the presence of K_2CO_3 and catalytic TBAI, we hoped we might still be able to access 2-bromoallylamine **280**, but unfortunately this proved unsuccessful (Scheme 2.38).



Scheme 2.38.

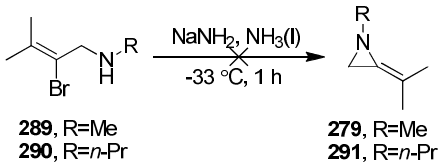
Thus, an alternative method for the conversion of **282** to **280** was required. Gratifyingly, treatment of 2-bromo-3-methylbut-2-en-1-ol **282** with PPh_3 and NBS

provided 1,2-dibromo-3-methylbut-2-ene **286**,[100b] which was further converted to2-bromoallylamine **289** by its reaction with 10 equivalents[141] of methylamine **287** in the presence of K_2CO_3 (Scheme 2.39).



Scheme 2.39.

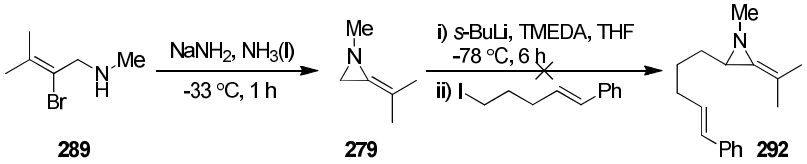
Unfortunately treatment of 2-bromoallylamine **289** with sodium amide in liquid ammonia at -33 °C according to standard protocol[99] failed to provide isopropylideneaziridine **279** (Scheme 2.40). Notably, starting with 500 mg of **289**, less than 30 mg of a malodorous product was isolated. Despite our best efforts to minimise loss during work up, we were never able to detect **279** in any appreciable quantity. Unfortunately, the same problems were encountered attempting to convert *N*-propyl-2-bromoallylamine **290** to the corresponding isopropylideneaziridine **291** under the same reaction conditions.



Scheme 2.40.

Wondering if volatility might be an issue, we attempted to perform the lithiation/alkylation sequence directly on the cyclisation product **279** (Scheme 2.41). Thus, 2-bromoallylamine **289** was treated with sodium amide in liquid ammonia at -33 °C for 1 hour and then quenched and worked up according to

standard protocol. The solvent (Et_2O) was removed by distillation at atmospheric pressure until only 2-3 mL remained, whereupon anhydrous THF was added and the remaining Et_2O removed by distillation at atmospheric pressure. Treatment of the resulting THF solution with *s*-BuLi/TMEDA at -78 °C for 6 hours, followed by addition of 1-((*E*)-5-iodopent-1-enyl)benzene **232** however, failed to provide the required methyleneaziridine **292**.

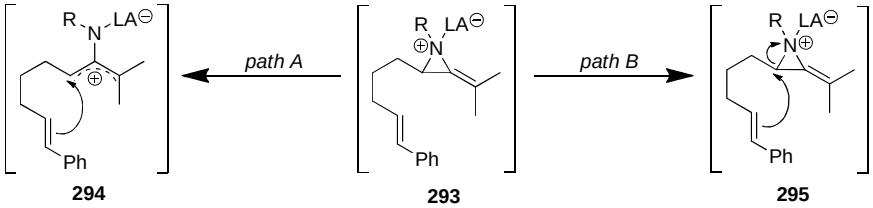


289 279 292

Scheme 2.41.

2.2.2.1. Mechanistic study

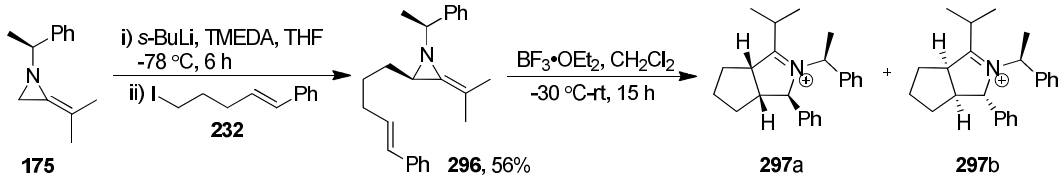
We considered that aziridine ring opening may occur in one of two ways. Either, $BF_3{\cdot}OEt_2$ complexation induces spontaneous ring opening to produce the corresponding 2-aminoallyl cation **294** (path A, Scheme 2.42), or complexation of the Lewis acid merely serves to polarise the aziridine C-N bond, and facilitates ring opening by the appended π-bond *via* S_N2 attack (path B, Scheme 2.42).



294 293 295

Scheme 2.42.

In order to gain insight into the likely reaction pathway, we examined the cyclisation of diastereomerically pure isopropylideneaziridine **296**. We reasoned that cyclisation *via* a 2-aminoallyl cation would result in loss of stereochemical integrity at C-3, while cyclisation *via* an S_N2 pathway would result in inversion of stereochemistry at C-3. Hence, the number of stereoisomeric iminium ions produced from **296** would indicate the mode of aziridine opening. The synthesis of this substrate was achieved by lithiation and subsequent alkylation of **175** with excess 1-((*E*)-5-iodopent-1-enyl)benzene **232**, which provided **296** as a 91:9 mixture of diastereomers. The major diastereomer was isolated in 56% yield and assigned the (*S*,*R*)-stereochemistry by analogy with literature precedent (Scheme 2.43).[111]



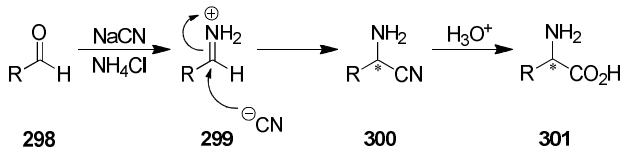
Scheme 2.43.

Crucially, treatment of **296** with $BF_3{\cdot}OEt_2$ resulted in the formation of two iminium ion as a 64:36 mixture of diastereomers, tentatively assigned as **297a** and **297b**. Such an observation is consistent with the formation of a planar achiral intermediate such as **294**, which cyclises with modest levels of diastereoselectivity.

2.2.2.2. Increased structural diversity by HCN addition

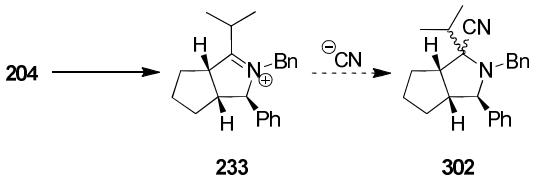
Having established the scope and limitations of a new intramolecular (3+2) cycloaddition reaction involving methyleneaziridines, we hoped to determine if increased structural diversity might be achieved by alternative manipulations of the intermediate iminium ion.

Cyanide will react with iminium ions to form α-amino nitriles **300**, which can be subsequently converted into α-amino acids **301** by incorporation of a simple hydrolysis step. This classical route to amino acids is known as the Strecker synthesis (Scheme 2.44). The reaction is promoted by acid, and HCN must be supplied or generated *in situ* from cyanide salts. By incorporation of a chiral auxiliary on the nitrogen, or through the use of asymmetric catalysts, enantiocontrol can be achieved.



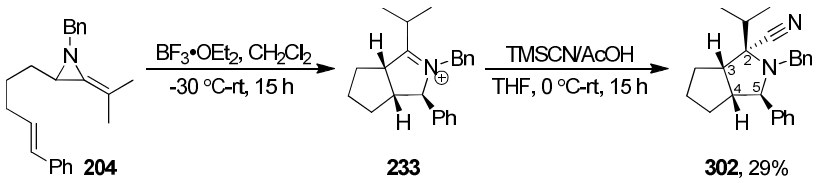
Scheme 2.44.

Thus, we sought to determine if the addition of cyanide to iminium ions such as **233**, derived from the $BF_3{\cdot}OEt_2$-promoted cyclisation of isopropylideneaziridine **204** onto an alkene acceptor, might provide the corresponding α-amino nitrile **302** depicted below (Scheme 2.45).



Scheme 2.45.

We were delighted to find that treatment of isopropylideneaziridine **204** with $BF_3{\cdot}OEt_2$ and further treatment with trimethylsilyl cyanide in the presence of glacial AcOH, afforded α-amino nitrile **302** as a single diastereomer (Scheme 2.46). No attempt was made to convert **302** to the corresponding α-amino acid.



Scheme 2.46.

The gross structure of **302** was assigned by examination of its ^{1}H NMR spectrum. Two doublets at 0.98 and 0.84 ppm which coupled to a multiplet at 1.66 ppm were consistent with an isolated isopropyl group. The signal corresponding to H-4 at 2.47 ppm coupled to H-3 at 2.64 ppm as well as H-5 at 3.30. Coupling of H-3 and H-4 to the cyclopentyl ring hydrogens was also observed. The presence of an MH^+ ion (m/z = 345) was also consistent with α-amino nitrile **302**. The relative stereochemistry of **302** was deduced using NOESY correlation experiments, which revealed a *cis*-relationship between the isopropyl group and H-3, H-4 and the phenyl group at C-5. No correlation between H-3 or H-4 and H-5 was observed (Figure 2.5).

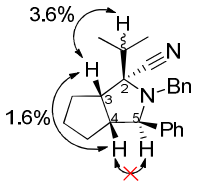
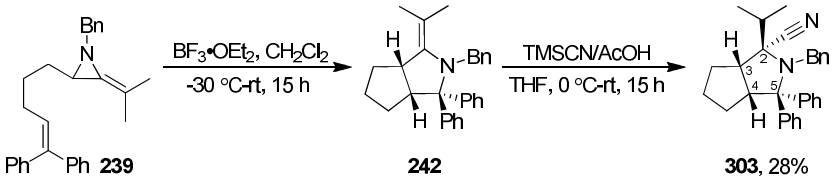


Figure 2.5.

We were initially surprised at this stereochemical outcome, since hydride delivery onto the same iminium ion **233** favoured attack from the convex (*Re*) face of the molecule, while cyanide delivery appeared to have occurred exclusively onto the concave (*Si*) face.

To probe this matter further we examined the same transformation, using precursor **239**, which had shown a preference for diastereoselective addition of hydride from the convex (*Re*) face. Thus, treatment of **239** with $BF_3{\cdot}OEt_2$ provided enamine **242**, which was further treated with trimethylsilyl cyanide in the presence of glacial AcOH, to afford the corresponding α-amino nitrile **303**, again as a single diastereomer (Scheme 2.47).



Scheme 2.47.

NOESY correlation experiments, again confirmed a *cis*-relationship between the isopropyl group and H-3 and H-4, revealing the same stereochemical bias in this addition (Figure 2.6).

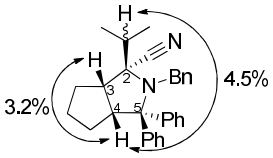
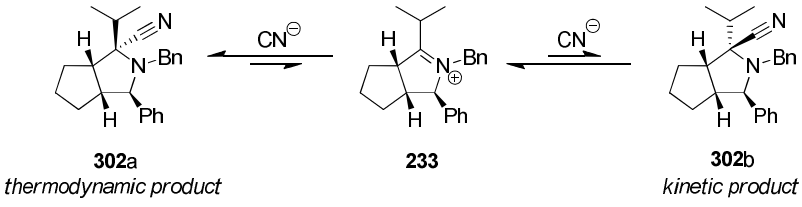


Figure 2.6.

If we consider the relative leaving group ability of hydride ($H^{\ominus}$) versus cyanide ($CN^{\ominus}$), a possible explanation for the observed stereochemical outcome for these transformations is revealed. In the case of iminium ion **233**, we argued that the major diastereomer **205b** was formed as a result of preferential hydride delivery onto the least hindered convex (*Re*) face of the molecule. It is likely that delivery of cyanide onto **233** also occurs preferentially from the convex face, resulting initially in the kinetic product **302b**, but since cyanide is a good leaving group, the addition process is likely to be reversible. Thus, we believe that the observed stereoisomer **302a**, is the more stable thermodynamic product derived from equilibration of **233** and **302b** (Scheme 2.48). The same argument can also be used to rationalise the observed stereochemical outcome upon cyanation of enamine **242**.



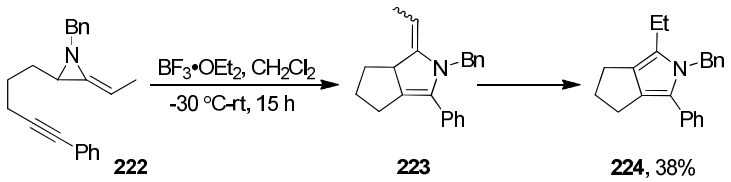
Scheme 2.48.

No attempts were made to further test this hypothesis. However, by quenching the reaction at timed intervals directly after addition of TMSCN, it might be possible to detect the kinetic product **302b**.

2.3. Conclusions

In summary, a novel Lewis acid promoted intramolecular (3+2) cycloaddition reaction of methyleneaziridines onto alkyne and alkene acceptors has been discovered and developed. Both inter- and intramolecular variants of this methodology have been examined, although success was only realised using intramolecular examples. The latter substrates are readily assembled by functionalisation of the parent methyleneaziridines through a simple, one-step lithiation/alkylation sequence.

With alkyne acceptors, the outcome of the reaction was sensitive to the substitution pattern of the methyleneaziridine exocyclic double bond. Most notably, Lewis acid promoted (3+2) cycloaddition of (*Z*)-ethylideneaziridine **222**, resulted in spontaneous aromatisation of the initially formed enamine **223** to give the corresponding pyrrole **224** in 38% yield (Scheme 2.49).

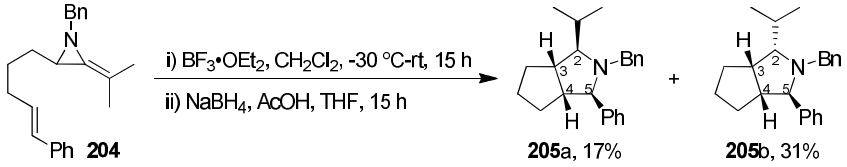


222 **223** **224**, 38%

Scheme 2.49.

Intramolecular cyclisation of isopropylideneaziridines onto alkene acceptors provided the corresponding pyrrolidines, following reduction of the initially

formed bicyclic products with $NaBH_4$/AcOH. The best yield was obtained using isopropylideneaziridine **204**, with $BF_3{\cdot}OEt_2$ in CH_2Cl_2, which gave pyrrolidine **205**, as a 41:59 crude diastereomeric mixture, in 48% yield as two separable diastereomers (Scheme 2.50). Impressively, this reaction results in the production of four contiguous stereocentres in the minimum of chemical operations.

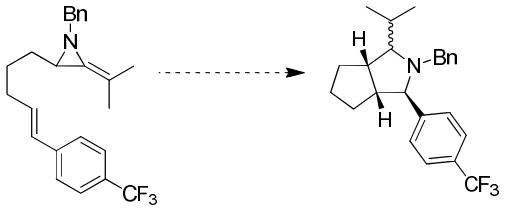


Scheme 2.50.

In a limited Lewis acid screen, $Sc(OTf)_3$, $SnCl_4$ and $AgSbF_6$ were also shown to be moderately effective (Table 2.4, Entries 1-4). In contrast, Brønsted acids led to decomposition (Table 2.4, Entries 5-6). $Sc(OTf)_3$ (150 mol%) gave the cleanest conversion and resulted in slightly improved yields, at least in the context of one substrates tested (Table 2.4, Entry 2). Despite the slight improvement in yield however, its use was disregarded on the grounds of cost effectiveness in comparison with $BF_3{\cdot}OEt_2$.

Attempts to further improve the diastereoselectivity for the reduction of iminium ion **233** were not fruitful, with only poor levels of stereocontrol at C-2 (Table 2.3, Entries 2-4). Attempts to extend the scope of this cycloaddition to include ethylideneaziridines **275** and **276**, methyleneaziridine **277** and isopropylideneaziridines bearing an additional carbon in the linking tether **278** also met with failure (Table 2.6, Entries 7-10).

Although, incorporation of a *para*-electron donating group within the alkene acceptor group failed to improve the efficiency of the reaction, crystals suitable for X-ray crystallographic analysis were obtained, unambiguously confirming the gross skeletal changes and relative stereochemistry of the major diastereomer **268b** (Table 2.6, Entry 5 and Figure 2.4). In view of the fact that the introduction of an electron donating group led to a reduction in yield, further work aimed at examining the cycloaddition reactions of related systems such as **304** bearing *para*-electron donating groups, *e.g.* CF_3, within the alkene acceptor group is merited (Scheme 2.51).



304 **305**

Scheme 2.51.

We have acquired experimental evidence which suggests that Lewis acid complexation results in the formation of a planar 2-aminoallyl cation. Cycloaddition is then likely to proceed in a stepwise manner, by nucleophilic addition of the appended alkene (or alkyne) onto the 2-aminoallyl cation, and subsequent ring closure through nitrogen onto the resultant carbocation.

Interception of the iminium ion **233** by cyanide addition was achieved. This allows greater structural diversity to be introduced into the products of this new cycloaddition reaction (Scheme 2.46 and 2.47). Analysis of the stereochemical outcome of these reactions suggests that hydride reduction is irreversible

providing predominantly, if not exclusively, the products derived from attack on the convex face, while hydrocyanation is reversible, providing products that seemingly appear to derive from nucleophilic attack from the more sterically encumbered concave face. The low yields observed in the successful cycloadditions, and the failure witnessed with further substrates (**275**-**278**), indicates that this reaction is highly sensitive to substrate structure.

To conclude, this chapter describes a new Lewis acid promoted intramolecular (3+2) cycloaddition involving methyleneaziridines, which provides a powerful new approach to fused bicyclic systems, including highly functionalised pyrroles and pyrrolidines. Remarkably, it enables the formation of up to four contiguous stereocentres in as little as two chemical steps. Further optimisation may be warranted to extend the scope of this methodology in order to access a broader range of cycloadducts.

Chapter 3:

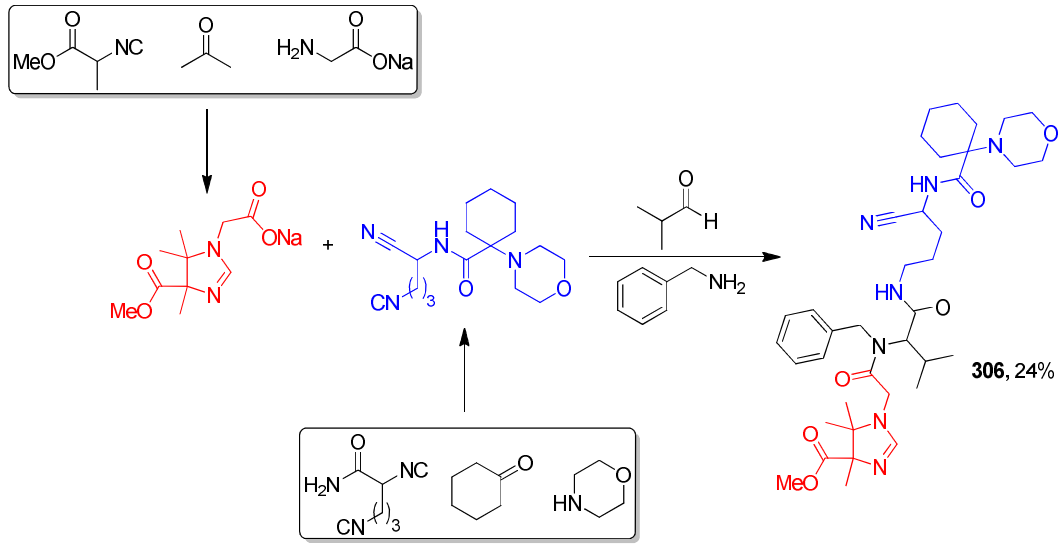
Towards New Multi-component Reactions involving Methyleneaziridines

3.1. Introduction to multi-component reactions

Multi-component reactions (MCRs)[142] are rapidly emerging as an attractive alternative to conventional synthetic methods for the construction of target molecules. An idealised MCR is a 'one-pot' process in which three or more components combine in an orchestrated manner to form a single product, which contains substantial elements of all the reactants.[142a] Famous MCRs include the Biginelli,[143] Mannich,[144] Passerini,[145] Pauson-Khand,[146] Strecker[147] and Ugi[148] reactions. The multi-component approach offers several advantages over traditional, linear methods to molecular construction. First and foremost, MCRs are highly convergent and since the resultant synthesis requires fewer steps, considerable savings in terms of time and cost accumulate. Moreover, the environmental impact of these reactions is greatly reduced since fewer solvents and reagents are required. Comprehensive coverage of multicomponent reactions can be found in a number of reviews.[142]

Taking MCRs to the next level, Orru, Ruijter and co-workers recently described the efficient one-pot reaction of up to eight components, combining three different MCRs and forming nine new bonds in a single step (Scheme 3.1).[149]

The 3-component condensation between an α-acidic isocyanide, acetone and sodium glycinate forms a substituted 2-imidazoline (*red*),[150] then the components for the second 3-component reaction (an isocyanide, cyclohexanone and morpholine) are added to form an *N*-(cyanomethyl)amide (*blue*).[151] Finally, the two halves are united by isobutyraldehyde and benzylamine in an Ugi 4-component reaction, providing **306** in 24% yield.

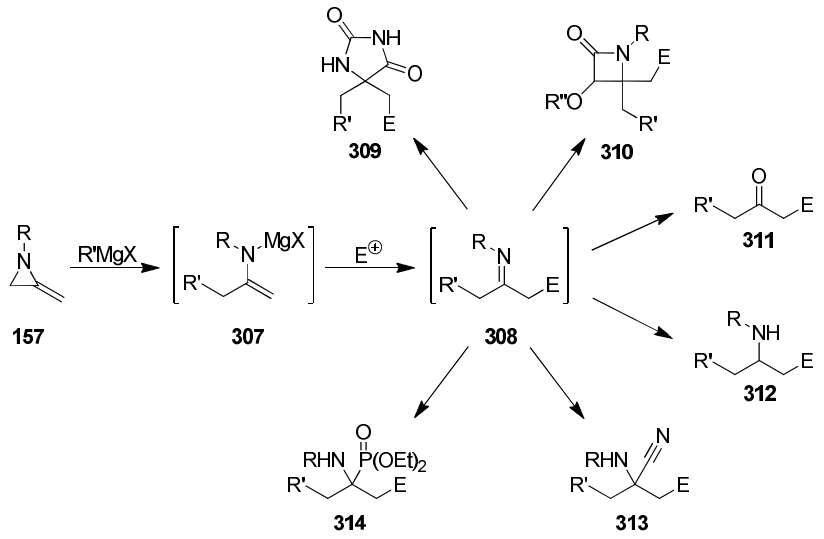


Scheme 3.1.

The overall efficiency of the reaction (85% per bond formation) is thought to arise from the fact that the first two MCRs go to completion with exactly 1:1:1 reactant ratios, so there are no residual components to interfere with the later steps. The described approach provides access to extremely complex and diverse drug-like compounds in a single, simple operation.[149]

3.2. Multi-component reactions involving methyleneaziridines

In recent years, Shipman and co-workers have developed a variety of multi-component reactions based upon the ring-opening reactions of methyleneaziridines **157** with Grignard reagents.[89,152,153] These multi-component processes all involve *in situ* generation of ketimines **308** by nucleophilic ring-opening of **157**, followed by capture of the resulting metalloenamine **307** with carbon-based electrophiles (Scheme 3.2).



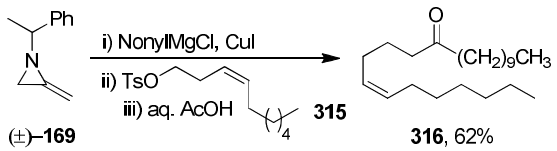
Scheme 3.2.

By further manipulation of the highly reactive ketimine functional group **308**using known chemistry, this methyleneaziridine-based technology has been successfully exploited to access a range of important compound classes including hydantoins **309**,[152] β-lactams **310**,[153] 1,3-disubstituted propanones **311**,[154] achiral[155] and chiral amines **312**,[107] α-amino nitriles **313**[155] and α-amino phosphonates **314**.[156] The multi-component synthesis of 1,3-disubstituted propanones on solid supports has also been described.[106]

These sequential multi-component processes accommodate considerable variation with respect to the nature of both the nucleophile (simple aryl, benzylic, primary and secondary alkyl Grignard reagents are tolerated), and the electrophile (alkyl, allylic and benzylic halides/tosylates, epoxides and aldehydes can be used). Thus, enormous structural diversity can be introduced into the ring-opened products.

The synthetic potential of this methodology was demonstrated by its application to the synthesis of (*Z*)-6-heneicosen-11-one **316**, a sex pheromone on the Tussock

moth, in a single chemical operation (Scheme 3.3).[154b,157] Treatment of (±)-**169** with nonylmagnesium chloride in the presence of copper(I) iodide (20 mol%) then tosylate **315,** provided **316** in good yield, following acidic hydrolysis.



Scheme 3.3.

Previous related research in the area of MCRs is extensive and well-established. However, the opportunity to further extend this methodology for the synthesis of other important compound classes still exists.

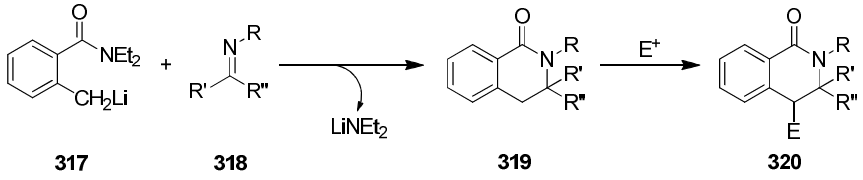
Despite the many advantages that MCRs offer, their development into robust, high yielding chemical processes is not trivial, primarily because it is extremely difficult to design reactions where three or more components combine to form one product exclusively. Nevertheless, the rational design of new MCRs continues apace today and represents an important and timely challenge for the future of chemical synthesis. The remainder of this thesis details our efforts towards realising new MCRs involving methyleneaziridines.

3.3. Attempted MCR to 3,4-dihydro-1(*2H*)-isoquinolones

3.3.1. Introduction

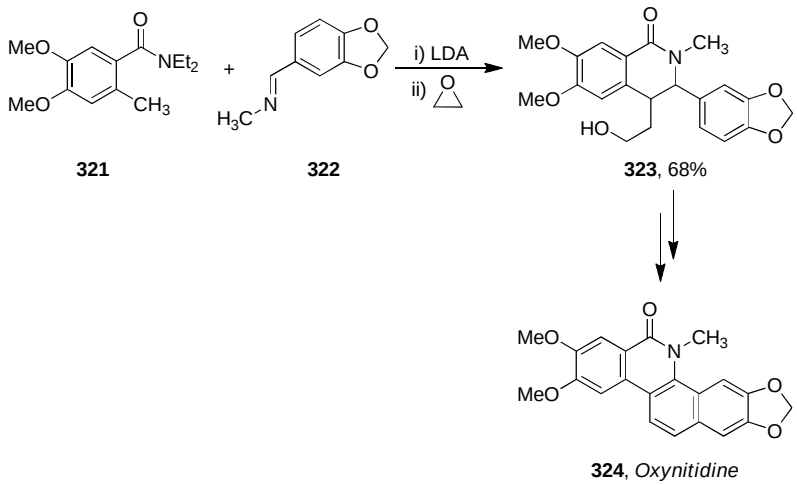
The condensation of lithiated *N*,*N*-diethyl-2-methylbenzamide **317**[158] with imines **318** is known to provide 3,4-dihydro-1(*2H*)-isoquinolones **319** *via* nucleophilic addition to the C=N bond and subsequent ring closure.[159]

Further functionalisation of the initially formed 3,4-dihydro-l(*2H*)-isoquinolones **319** can be achieved by deprotonation at the 4-position by one equivalent of lithium diethylamide, generated *in situ* upon ring closure, and subsequent alkylation with a suitable electrophile (Scheme 3.4).



Scheme 3.4.

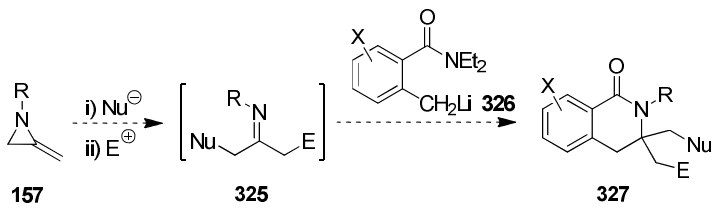
The synthetic utility of this methodology was demonstrated by its incorporation as a key step in the total synthesis of oxynitidine **324**, in which condensation of readily accessible amide **321** with aldimine **322**, followed by ethylene oxide addition, provided alcohol **323** in good yield (Scheme 3.5).[159b]



Scheme 3.5.

Noting that this chemistry was shown to accommodate a limited number of cyclic ketimines, including *N*-cyclohexylidenebutan-1-amine,[159a,c] we hoped, by

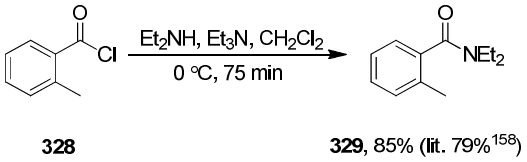
incorporation of our methyleneaziridine-based MCR technology, a new 'one-pot' synthesis of 3,3-disubstituted 3,4-dihydro-1(*2H*)-isoquinolones **327** might be realised. We envisaged that ketimines such as **325** generated by nucleophilic ring-opening of methyleneaziridines **157**, followed by alkylation with suitable electrophiles might provide **327** upon further addition of **326** to the reaction vessel. By making subtle structural changes with respect to the toluamide, Grignard reagent and electrophile, the proposed new 4-CR might provide access to a diverse set of 3,4-dihydro-1(*2H*)-isoquinolones **327** (Scheme 3.6).



Scheme 3.6.

To explore this idea, we first decided to assess whether we could perform this reaction using a preformed 'acyclic' ketimine, which might be expected from our MCR methodology. At the outset, we were concerned that such imines might be too sterically hindered to undergo the required nucleophilic addition.

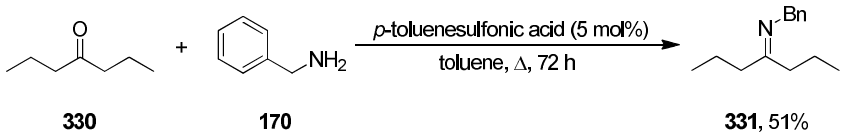
In preparation for this model study, *N*,*N*-diethyl-2-methylbenzamide **329** was synthesised in good yield by treatment of commercially available 2-methylbenzoyl chloride **328** with Et_2NH and Et_3N in CH_2Cl_2 at 0 °C (Scheme 3.7).



328 **329**, 85% (lit. 79%[158])

Scheme 3.7.

Synthesis of ketimine **331** was achieved by condensation of 4-heptanone **330** with benzylamine **170** in refluxing toluene for 72 hours (Scheme 3.8).[160]



330 **170** **331**, 51%

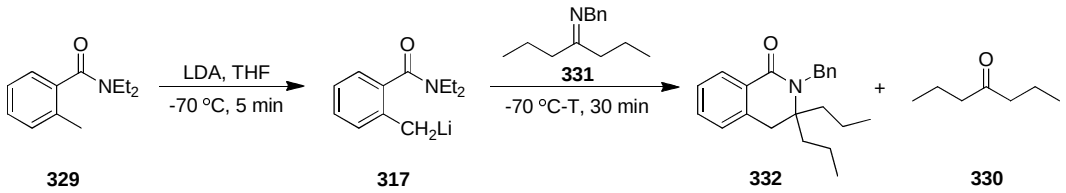
Scheme 3.8.

3.3.2. Initial model reactions

As a starting point, the reaction was conducted at -70 °C by addition of the ketimine **331** to a preformed solution of lithiated *N*,*N*-diethyl-2-methylbenzamide **317** (LDA, 1.1 eq.) in THF. The resulting solution was then stirred at -70 °C for 30 minutes and quenched by addition of dilute aqueous HCl.[161] Unfortunately, examination of the ^{1}H NMR spectrum following work-up, showed the reaction to be incomplete, *i.e.* the crude mixture comprised unreacted starting material **329**, ketone **330** (derived from hydrolysis of ketimine **331**) and the expected product **332** in a ratio of 45:38:17 respectively. The presence of all three components in the crude mixture was also confirmed by GCMS analysis (Table 3.1, Entry 1).

Undeterred by this, we hoped to improve conversion to **332** by quenching the reaction at higher temperature. The outcome of each reaction was determined by

examination of the crude ^{1}H NMR spectra and the results summarised below (Table 3.1).



329 **317** **332** **330**

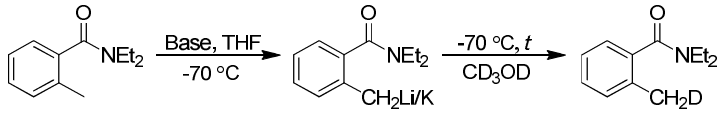
Entry	Quench, T (°C)	Product Ratio[a]		
		329	**330**	**332**
1	-70	45	38	17
2	-30	48	32	20
3	0	43	6	51
4	25	45	5	50
5[b]	0	33	9	58

[a] Determined by integration of crude ^{1}H NMR spectra; [b] Using repurified diisopropylamine.

Table 3.1.

Quenching the reaction at ≥0 °C gave a more favourable product distribution but did not result in complete consumption of the starting materials (Entries 3-5). Thus, we became concerned that *N*,*N*-diethyl-2-methylbenzamide **329** was not being fully converted to the corresponding lithiated species **317** under the stated reaction conditions (*vide supra*).

Hoping to identify optimum conditions for deprotonation of **329**, we conducted a series of experiments in which the lithiated species **317** was intercepted by addition of excess d_4-MeOH. The extent of deuterium incorporation was calculated by integration of the crude ^{1}H NMR spectra. The results are summarised below (Table 3.2).



329 **317** **333**

Entry	Base	Eq.	*t* (min)	Product Ratio[a]	
				329	**333**
1	LDA	1.1	5	53	47
2	LDA	1.1	10	44	56
3	LDA	1.1	20	61	39
4	LDA	1.3	5	64	36
5	LDA	1.5	5	50	50
6	LDA	1.7	5	45	55
7	LDA	1.9	5	46	54
8	LDA	2.1	5	54	46
9	LDA	3.0	5	49	51
10	LiHMDS	1.1	5	100	0
11	KHMDS	1.1	5	100	0
12	*n*-BuLi	1.1	5	11	89
13	*n*-BuLi	1.3	5	4	96
14	*n*-BuLi	1.5	5	6	94
15	*s*-BuLi	1.1	5	6	94

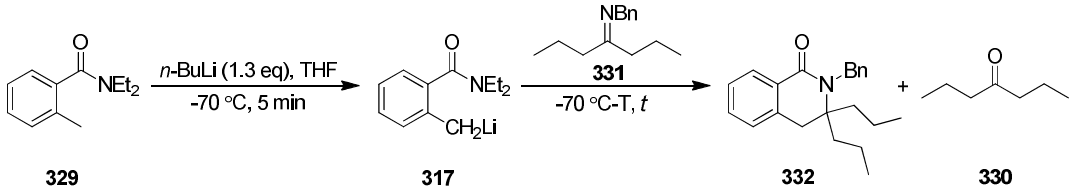
[a] Determined by integration of crude ^{1}H NMR spectra.

Table 3.2.

Prolonging the reaction time or by using increasing molar quantities of LDA, had little or no effect on the conversion of **329** to **333** (Entries 1-9), while using lithium or potassium hexamethyldisilazide, no deuterium incorporation was detected at all (Entries 10-11). The best conversion was observed using 1.3 equivalents of *n*-BuLi, which resulted in 96% deuterium incorporation (Entry 13).

s-BuLi gave comparable conversion, but also resulted in a more complex mixture and was therefore disregarded (Entry 15).

Having identified a base that gave almost complete lithiation of **329**, we next applied these conditions to the condensation of *N*,*N*-diethyl-2-methylbenzamide **329** and ketimine **331**, hoping to observe improved conversion to the desired product **332**. Thus, the reaction was conducted at -70 °C by addition of the ketimine **331** to a preformed solution of lithiated *N*,*N*-diethyl-2-methylbenzamide **317** (*n*-BuLi, 1.3 eq.) in THF. The resulting solution was then stirred at -70 °C for 30 minutes and quenched by addition of dilute aqueous HCl. Again however, examination of the ^{1}H NMR spectrum following work-up, showed the reaction to be incomplete and the crude mixture comprised unreacted starting materials **329** and **330** and the expected product **332** in a ratio of 47:32:21 respectively (Table 3.3, Entry 1). Attempts to improve conversion by increasing reaction time and temperature met with failure. In fact, the formation of the desired product was even further diminished (Table 3.3, Entries 2-3).



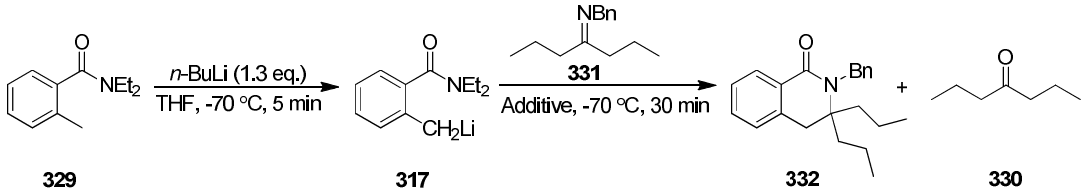
329 **317** **332** **330**

Entry	T (°C)	*t* (min)	Product Ratio[a]		
			329	**330**	**332**
1	-70	30	47	32	21
2	-70	60	51	38	11
3	25	30	77	10	13

[a] Determined by integration of crude ^{1}H NMR spectra.

Table 3.3.

Finally, we examined whether the use of additives would further improve the reaction. We envisaged that TMEDA might enhance the reactivity of lithiated *N*,*N*-diethyl-2-methylbenzamide **317**, while complexation of a suitable Lewis acid might render a more electrophilic and therefore more reactive ketimine. The reactions were conducted at -70 °C by addition of the ketimine and additive (1.0 eq.) to a preformed solution of **317** (*n*-BuLi, 1.3 eq.) in THF. The resulting solution was then stirred at -70 °C for 30 minutes and quenched by addition of dilute aqueous HCl. The results of this study are described in Table 3.4.



329 **317** **332** **330**

Entry	Additive	Eq.	Product Ratio[a]		
			329	**330**	**332**
1	-	-	47	32	21
2	TMEDA	1.0	64	19	17
3	$BF_3{\cdot}OEt_2$	1.0	59	0	41
4	$BF_3{\cdot}THF$	1.0	77	0	23
5	$ZnCl_2$	1.0	82	0	18
6	$CeCl_3$	1.0	88	12	0

[a] Determined by integration of crude ^1H NMR spectra.

Table 3.4.

Disappointingly, only $BF_3{\cdot}OEt_2$ gave improved conversion to **332** (Entry 3 *cf*. Entry 1). All of the other additives gave either comparable or diminished conversion (Entries 2, 4-6 *cf*. Entry 1).

3.3.3. Conclusions

Despite our best efforts, attempts to optimise a model reaction involving condensation of lithiated *N*,*N*-diethyl-2-methylbenzamide **317** with a preformed acyclic ketimine **331** have met with failure. Suspecting that only partial deprotonation of **329** under the original reaction conditions was responsible for incomplete conversion to the desired product **332**, we conducted a deuterium study which revealed that *n*-BuLi (1.3 eq.) gave 96% deprotonation. Application of these conditions to the condensation of **329** and **331** however, failed to improve

conversion, while the use of additives met with only limited success. Possible steric clashing between the *n*-propyl chains in ketimine **331** and the *ortho*-moiety of the lithiated toluamide **317** may, in part, explain the observed poor conversion. Based on our findings, we concluded that acyclic ketimines may be poor substrates for this process and this chemistry was not pursued further.

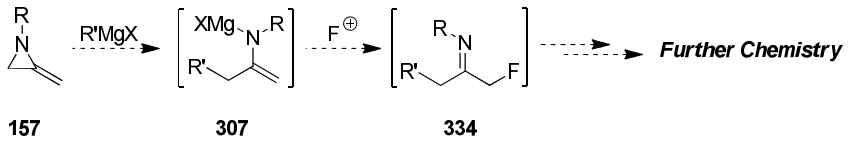
3.4. Electrophilic α-fluorination of methyleneaziridine-derived ketimines

3.4.1. Introduction

Fluorine-containing organic compounds are known to possess unique physical and chemical properties by virtue of the high lipophilicity of the CF bond, and the ability of fluorine to drastically alter the electronic distribution of the molecule without major changes concerning the steric properties of the compound.[162] It is well known that site-specific incorporation of fluorine atoms into biologically-active molecules often causes remarkable modification of their original activities including acidity, metabolic stability, and binding affinity.[163] In this regard, considerable attention has been paid to the development of generally applicable, selective methods for the synthesis of fluorinated organic molecules.[164]

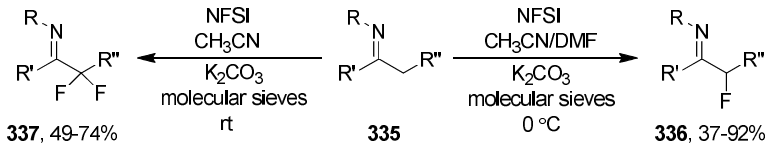
With this in mind, we wondered if it might be possible to access a range of fluorinated compounds by combining our methyleneaziridine-based MCR with a final electrophilic fluorination step. We anticipated that nucleophilic ring-opening of methyleneaziridine **157** and subsequent trapping of the resulting metalloenamine **307** with a suitable source of "$F^{\oplus}$",would provide an α-fluorinated ketimine **334**, which could be further manipulated to access a range of fluorinated azaheterocyclic compounds, α-fluorinated ketones and β-fluorinated

amines, which are of interest in medicinal and agricultural chemistry (Scheme 3.9).[165]



Scheme 3.9.

De Kimpe and co-workers reported a mild and efficient procedure for the synthesis of α-fluoro- and α,α-difluoroketimines from the corresponding acetophenones using the commercially available, easy to use, and stable fluorinating reagent, *N*-fluorobenzenesulfonimide (NFSI). A variety of *N*-alkylketimines **335** were successfully monofluorinated using NFSI in a mixture of CH_3CN and DMF at 0 °C, while the same procedure performed at room temperature without DMF, gave rise to difluorinated ketimines **337** (Scheme 3.10). Additionally, by hydrolysis or reduction of the isolated α-fluorinated ketimines, the corresponding fluorinated ketones and β-fluoroamines were provided respectively, in good yield.[166]

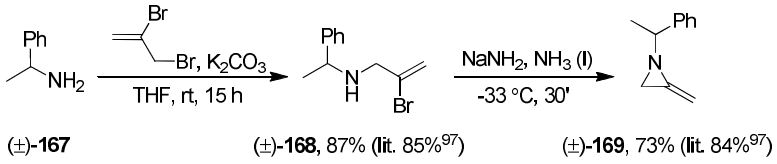


Scheme 3.10.

3.4.2. Initial findings

In order to examine the proposed new MCR, 2-methylene-1-(1-phenylethyl)aziridine (±)-**169**[98] was prepared in two steps from (±)-

phenylethylamine **167**.[89] Alkylation of (±)-phenylethylamine **167** with 2,3-dibromopropene in THF in the presence of K_2CO_3,provided the corresponding 2-bromoallylamine (±)-**168**.[98] Subsequent ring closure with sodium amide, generated *in situ* from sodium, liquid ammonia and catalytic $Fe(NO_3)_3.9H_2O$, afforded methyleneaziridine (±)-**169** in good yield (Scheme 3.11).



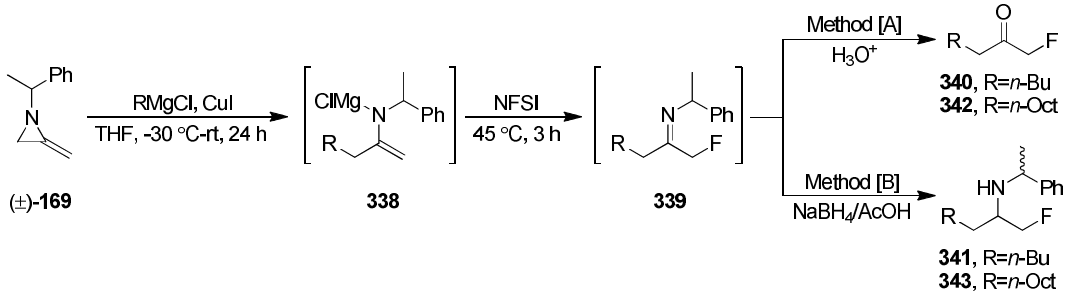
(±)-**167** (±)-**168**, 87% (**lit.** 85%[97]) (±)-**169**, 73% (**lit.** 84%[97])

Scheme 3.11.

With a supply of (±)-**169** in hand, we set about examining whether we could incorporate a final electrophilic fluorination step into the methyleneaziridine-based MCR. Given the success of De Kimpe and co-workers (*vide supra*), NFSI was selected as the fluorinating reagent of choice.

2-Methylene-1-(1-phenylethyl)aziridines (±)-**169** was treated with *n*-butylmagnesium chloride (3.0 eq.) and CuI (20 mol%) according to the normal protocol.[154] Subsequent reaction of the presumed metalloenamine **338** with NFSI (1.1 eq.), followed by imine hydrolysis appeared to provide the corresponding α-fluorinated ketone **340** upon examination of the crude ^{1}H NMR spectrum. Evidence for the formation of **340** came from characteristic splitting of the signal corresponding to the CH_2 directly attached to fluorine (J_{HF} = 48 Hz) in its ^{1}H NMR spectrum. Unfortunately however, problems associated with volatility of this low molecular weight ketone **340** prevented us from isolating a clean sample for full characterisation (Table 3.5, Entry 1). We hoped that by incorporating a

reductive work-up, we might obtain a higher molecular weight β-fluoroamine, however when **339** was treated with $NaBH_4$/AcOH, a complex mixture was obtained (Table 3.5, Entry 2).



Entry	R	Method	Product	Yield (%)
1	*n*-Butyl	[A]	**340**	0
2	*n*-Butyl	[B]	**341**	0
3	*n*-Octyl	[A]	**342**	11
4	*n*-Octyl	[B]	**343**	4*

* 50:50 mixture of diastereomers.

Table 3.5.

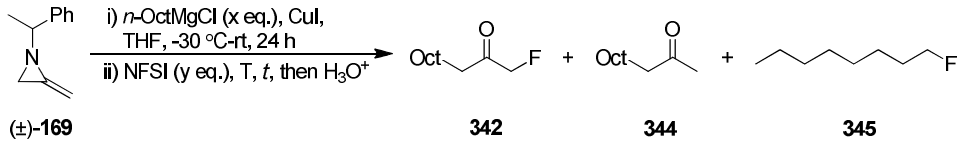
To overcome the problem of volatility, we next investigated the ring opening of (±)-**169** with a Grignard reagent bearing a longer carbon chain, *i.e. n*-octylmagnesium chloride, and were pleased to find that the corresponding α-fluorinated ketone **342** could be isolated in 11% yield, following imine hydrolysis and silica gel chromoatography (Table 3.5, Entry 3). By incorporation of a reductive work-up, β-fluoroamine **343** was also isolated in 4% yield, as a 50:50 mixture of diastereomers (Table 3.5, Entry 4).

Although encouraged by these results, we were obviously disappointed with the very low isolated yields. Suspecting that unwanted side reactions might be

responsible for the observed low yields, we took a closer look at the crude ^{1}H NMR spectra and detected at least two unwanted products, namely undecan-2-one **344** and 1-fluorooctane **345**,[167] which constituted *ca*. 50% of the crude reaction mixture relative to the desired α-fluorinated ketone **342** (Table 3.6, Entry 1). Undecan-2-one **344** is most likely derived from hydrolysis of unreacted metalloenamine **339** in the work-up step, while 1-fluorooctane **345** probably originates from direct reaction of the Grignard reagent with NFSI.

Hoping to improve conversion to the desired product **342** and ultimately improve the isolated yield, we conducted a series of reactions in which the molar quantities of the Grignard and fluorinating reagent were varied, as well as the temperature and time of the electrophilic fluorination step. The results are summarised below (Table 3.6).

Increasing the molar equivalents of NFSI had a detrimental effect on the conversion of (±)-**169** to **342** and in turn the isolated yield (Table 3.6, Entries 1-3), as did decreasing the molar quantities of Grignard reagent (Table 3.6, Entries 4-6). Increasing the time for the fluorination step resulted in a more favourable product distribution but a comparable isolated yield (Table 3.6, Entry 7 *cf*. Entry 1). Performing the fluorination step at low temperature also failed to improve conversion to **342** (Table 3.6, Entry 8).



(±)-**169** **342** **344** **345**

Entry	x eq.	y eq.	T (°C)	*t* (h)	Product Ratio[a]			Yield 342 (%)
					342	344	345	
1	3.0	1.1	45	3	47	51	2	11
2	3.0	2.0	45	3	56	44	0	10
3	3.0	3.0	45	3	19	67	14	3
4	2.0	1.0	45	3	18	79	3	1
5	2.0	2.0	45	3	24	76	0	2
6	2.0	3.0	45	3	17	83	0	4
7	3.0	1.1	45	6	76	23	1	8
8	3.0	1.1	-78→rt	3	25	74	1	-

[a] Determined by integration of crude ^{1}H NMR spectra.

Table 3.6.

Having failed to increase conversion to the desired α-fluoroketone, we wondered if an alternative fluorinating reagent might be more compatible with our reaction conditions. Thus, we briefly investigated the use of Selectfluor® but found that it was only sparingly soluble in THF and none of the desired product was detected when it was used in place of NFSI.

3.4.3. Conclusions

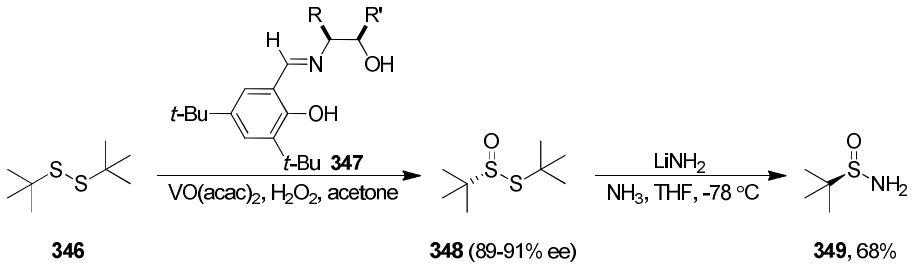
Our attempts at realising a new methyleneaziridine-based MCR incorporating a final electrophilic fluorination step have met with only limited success. Our best yield was obtained when ring-opening was conducted using *n*-octylmagnesium chloride (3.0 eq.) and NFSI (1.1 eq.),[154] whereby the desired α-fluorinated ketone

342 was isolated in 11% yield. We also successfully isolated the corresponding β-fluoroamine **343**, albeit in very poor yield, by incorporation of a reductive work-up. By varying the molar quantities of Grignard and fluorinating reagent and the reaction temperature, no improvement in conversion was observed. It is possible that the use of other fluorinating reagents might improve the efficiency of this reaction but we were somewhat limited in choice as most alternatives were either commercially unavailable and/or hazardous to synthesise or prohibitively expensive. Selectfluor® failed to give any of the desired fluorinated products. Due to time constraints and the lack of progression, this chemistry was not pursued further.

3.5. Towards *N*-*t*-butylsulfinyl ketimines from methyleneaziridines

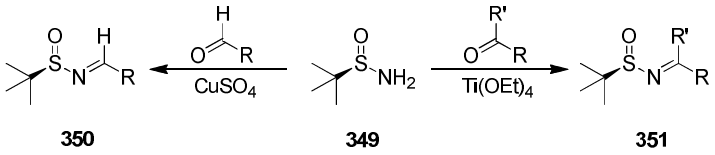
3.5.1. Introduction

In 2003, Jonathan Ellman reported the successful application of *t*-butylsulfinamide **349** in the asymmetric synthesis of amines.[168] The synthesis of enantiomerically pure *t*-butylsulfinamide **349** was achieved in two steps, using catalytic enantioselective methods, from *t*-butyl disulfide **346** - an extremely inexpensive oil waste by-product. Oxidation of **346** was accomplished using H_2O_2 as an inexpensive stoichiometric oxidant, $VO(acac)_2$ (0.25 mol%) and a chiral ligand **347**, derived from *cis*-1,2-aminoindanol. Addition of $LiNH_2$ in ammonia to the intermediate *t*-butylthiosulfanate **348** provided *t*-butylsulfinamide **349** in 68% overall yield after a single crystallisation, with complete inversion of configuration at sulfur (Scheme 3.12).



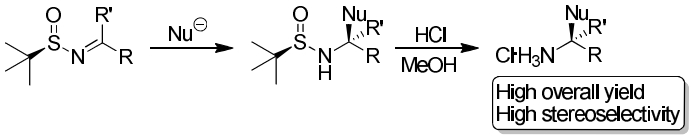
Scheme 3.12.

Direct condensation of *t*-butylsulfinamide **349** with aldehydes and ketones, in the presence of a stoichiometric water scavenger and Lewis acid catalyst, provided the corresponding *t*-butylsulfinyl aldimines **350** and ketimines **351** respectively, in uniformly high yields and purity (Scheme 3.13).



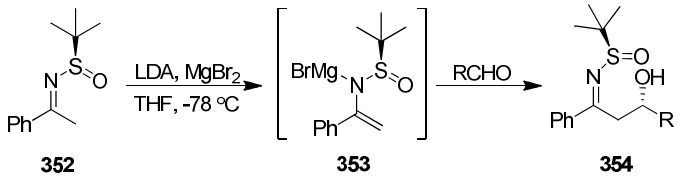
Scheme 3.13.

The *t*-butylsulfinyl group activates the imine and the configurationally stable stereocentre at sulfur provides diastereofacial selectivity for nucleophilic addition reactions. Using this methodology, a number of different classes of enantioenriched amines have been prepared in high overall yields, by the addition of different types of nucleophiles and subsequent cleavage of the *t*-butylsulfinyl group upon treatment with acid (Scheme 3.14).



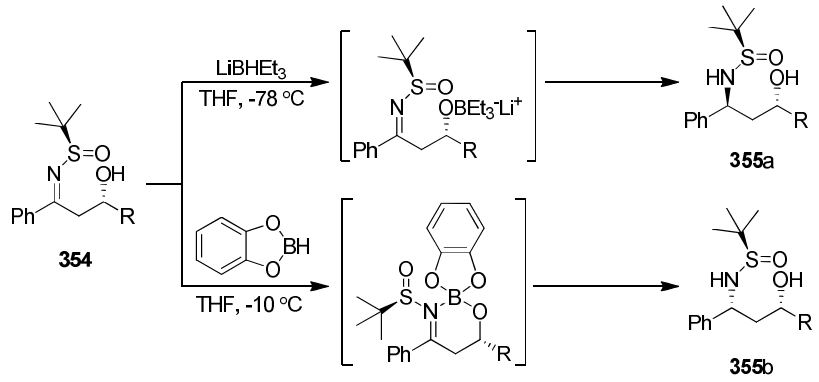
Scheme 3.14.

While nucleophilic additions to sulfinyl imines have been extensively studied,[169] α-deprotonation of *t*-butylsulfinyl ketimines has received significantly less attention. Metalloenamines **353** derived from *t*-butylsulfinyl ketimines **352** were shown to react with aldehydes to provide β-hydroxy *N*-sulfinyl ketimines **354** in high yields and with high diastereoselectivities (Scheme 3.15).



Scheme 3.15.

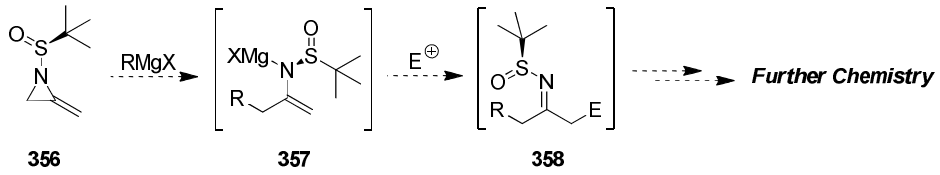
Further diastereoselective reduction of the β-hydroxy *N*-sulfinyl ketimine products **354** with lithium triethylborohydride ($LiBHEt_3$) or catecholborane provided access to the corresponding *anti*- or *syn*-1,3-amino alcohols **355a** or **355b** respectively, with very high diastereomeric ratios (Scheme 3.16).[170]



Scheme 3.16.

Noting the obvious structural similarity between the *t*-butylsulfinyl ketimines formed by direct condensation of *t*-butylsulfinamide with ketones, and the ketimines presumably formed using our methyleneaziridine-based MCR methodology (Scheme 3.2), we were interested to determine if nucleophilic additions to *t*-butylsulfinyl ketimines derived from methyleneaziridines might provide an alternative route to a range of amine containing products. Based upon Ellman's work, this chemistry would have the potential to deliver such products as single enantiomers.

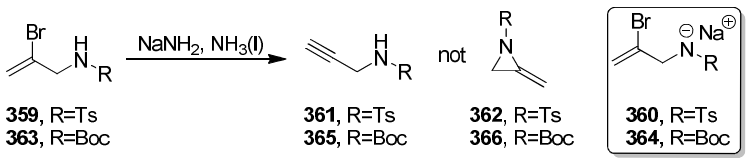
We anticipated that ring opening of *N*-*t*-butylsulfinyl methyleneaziridine **356** with a Grignard reagent might provide a highly reactive *N*-*t*-butylsulfinyl ketimine **358**, following capture of the transient metalloenamine **357** with a suitable external electrophile. Further manipulation of **358**, in the presence of the chiral *t*-butylsulfinyl *N*-substituent, might be expected to provide access to a range of important compound classes in a stereocontrolled manner (Scheme 3.17).



Scheme 3.17.

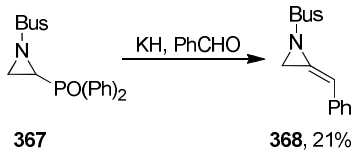
To test this idea, an efficient route to methyleneaziridines bearing an *N*-*t*-butylsulfinyl substituent was required. Incorporation of an electron-withdrawing group within the *N*-substituent is predicted to lower the basicity of the methyleneaziridine nitrogen and increase the polarisation of the C-N bond in comparison to methyleneaziridines featuring simple alkyl substituents, thus leading to enhanced reactivity. However to date, attempts to generate methyleneaziridines bearing electron withdrawing *N*-substituents have met with only limited success.

Attempted ring closure of tosylamine **359** and Boc-amine **363**,[104] returned only starting materials at low molar quantities of $NaNH_2$ (1.1 eq.). While excess $NaNH_2$ (2.1 to 15 eq.), gave clean conversion to the corresponding acetylenes **361** and **365**. Irreversible deprotonation of **359** and **363** (by virtue of the increased acidity of the NH) to form the corresponding sodium anions **360** and **364**, followed by E2-elimination of HBr, is thought to account for the formation of alkynes **361** and **365** (Scheme 3.18).



Scheme 3.18.

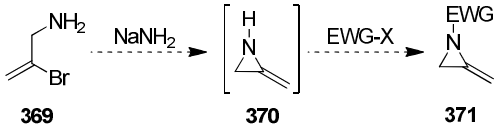
An alternative approach, based upon a Horner-Wadsworth-Emmons[171] type strategy has been examined within the Shipman group. Treatment of aziridine **367** (prepared in three steps from the corresponding vinyl phosphonate) with potassium hydride and benzaldehyde provided the corresponding methyleneaziridine **368** in 21% yield as a single geometrical isomer, as confirmed by X-ray crystallography (Scheme 3.19).[172]



Scheme 3.19.

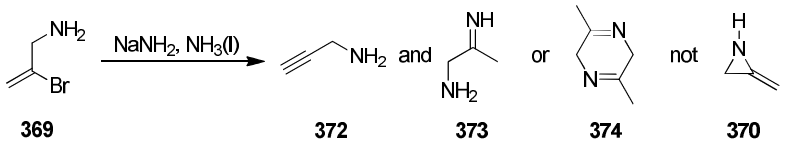
Although encouraging, the length of this sequence and poor yields rendered this methodology unsuitable for its more widespread application to the synthesis of methyleneaziridines featuring electron withdrawing *N*-substituents.

An alternative strategy involving *in situ* generation of *N*-functionalised methyleneaziridines from the parent 2-methyleneaziridine **370** has also been briefly explored (Scheme 3.20).



Scheme 3.20.

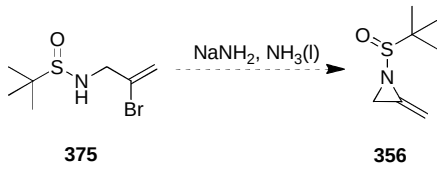
Attempted ring closure of **369** provided only acetylene **372** and a second product, tentatively assigned as imine **373** or diimine **374** with no trace of **370** observed (Scheme 3.21).[173]



Scheme 3.21.

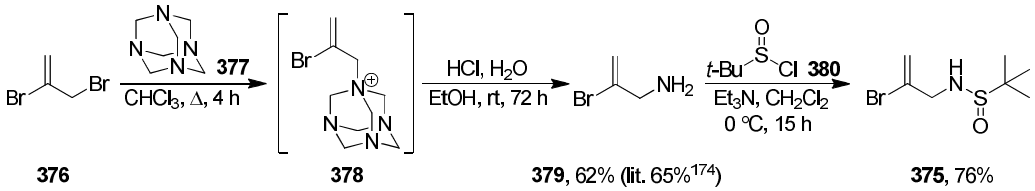
3.5.2. Attempted synthesis of *N*-*t*-butylsulfinyl methyleneaziridines

Since we considered that the NH in *N*-(*t*-butylsulfinyl)-2-bromoprop-2-en-1-amine **375** might be less acidic than in **359** or **363**, ring closure in the presence of $NaNH_2$, might compete favourably with E2-elimination to give methyleneaziridine **356** (Scheme 3.22).



Scheme 3.22.

To explore this idea, we turned our attention to the synthesis of *N*-(*t*-butylsulfinyl)-2-bromoprop-2-en-1-amine **375**, which was made in three steps from commercially available 2,3-dibromopropene **376** (Scheme 3.23). Treatment of **376** with hexamethylenetetramine **377** in refluxing $CHCl_3$ for 4 hours provided quaternary ammonium salt **378**, which was subjected to acid hydrolysis to give 2-bromoprop-2-en-1-amine **379** after distillation.[174] Condensation of **379** with *t*-butylsulfinyl chloride **380**,[175] in the presence of Et_3N, provided **375** in good yield.



Scheme 3.23.

With a supply of **375** in hand, we set about examining whether we could affect ring closure to the corresponding methyleneaziridine **356** under a variety of different reaction conditions. Each reaction was conducted for 60 minutes and the outcome determined by examination of the crude ^{1}H NMR spectra. The results are summarised below (Table 3.7).

Entry	Base	Eq.	Solvent	T (°C)	Product Ratio[a]		
					375	381	356
1	$NaNH_2$	2.5	NH_3	-78	100	0	0
2	$NaNH_2$	2.5	NH_3	-33	86	14	0
3	$NaNH_2$	5.0	NH_3	-33	80	20	0
4	$NaNH_2$	10.0	NH_3	-33	0	100[b]	0
5	$LiNH_2$	10.0	NH_3	-33	3	97	0
6	KNH_2	2.5	NH_3	-33	24	76	0
7	*n*-BuLi	2.5	THF	-70	91	9	0
8	LDA	2.5	THF	-70→rt	66	34	0
9	NaH	2.5	THF	0→rt	89	11	0
10	Cs_2CO_3	2.5	MeCN	0→rt	100	0	0

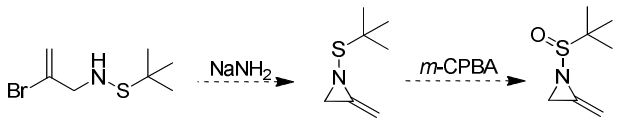
[a] Determined by integration of crude ^{1}H NMR spectra; [b] Acetylene isolated in 57% yield.

Table 3.7.

Using 2.5 equivalents of sodium amide at -78 °C or Cs_2CO_3 at 0 °C→rt, only unconsumed *N*-(*t*-butylsulfinyl)-2-bromoprop-2-en-1-amine **375** was observed (Table 3.7, Entries 1 and 10). By increasing the reaction temperature, molar quantities of $NaNH_2$ or by variation of the base, partial conversion of **375** to acetylene **381** was observed (Table 3.7, Entries 2-3 and 5-9). When the molar equivalents of sodium amide were increased to ten, full consumption of **375** was observed, with only acetylene **381** detected by ^{1}H NMR spectroscopy (Table 3.7, Entry 4). Notably, the desired methyleneaziridine **356** was never detected upon examination of the crude mixtures by ^{1}H NMR spectroscopy.

3.5.3. Attempted synthesis of *N*-*t*-butylsulfenyl methyleneaziridines

We decided to investigate the synthesis and potential ring closure of *N*-(*t*-butylsulfenyl)-2-bromoprop-2-en-1-amine **382**, which we felt might be more likely to provide the corresponding methyleneaziridine **383** than its oxygenated counterpart **375**, by virtue of the lower acidity of the NH. If this cyclisation could be realised, we envisaged *N*-(*t*-butylsulfinyl)-methyleneaziridine **356** could be accessed by selective oxidation of **383** with *m*-CPBA (Scheme 3.24).

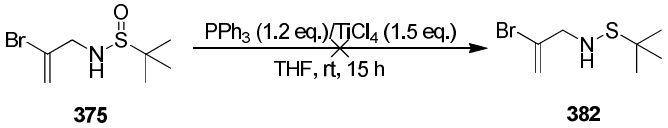


382 **383** **356**

Scheme 3.24.

Hashimoto and co-workers found the combination of $PPh_3/TiCl_4$ was an effective promoter for the deoxygenation of sulfoxides and gave the corresponding sulfides

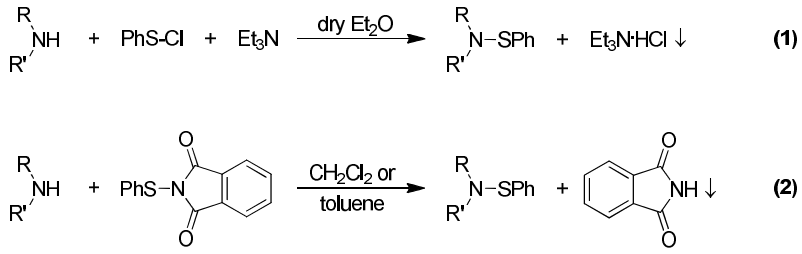
in good yield (up to 97%) under mild conditions.[176] We hoped we might be able to apply these conditions to access **382** directly from *N*-(*t*-butylsulfinyl)-2-bromoprop-2-en-1-amine **375**. Unfortunately however, upon treatment with $PPh_3/TiCl_4$ in THF at rt for 15 hours, **375** was returned unchanged (Scheme 3.25).



375 **382**

Scheme 3.25.

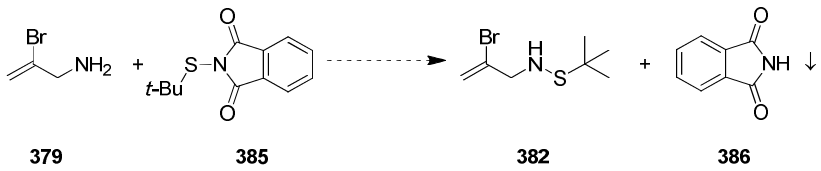
Bowman and co-workers described the efficient synthesis of sulfenamides through the reaction between a variety of amines and benzenesulfonyl chloride in the presence of Et_3N (Scheme 3.26, eq. 1) or *N*-(benzenesulfenyl)phthalimide (Scheme 3.26, eq. 2).[177]



Scheme 3.26.

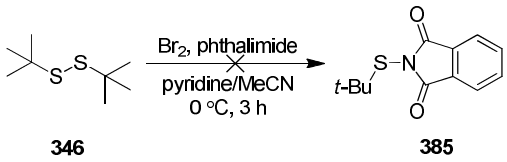
We initially considered that the synthesis of *N*-(*t*-butylsulfenyl)-2-bromoprop-2-en-1-amine **382** might be achieved by direct condensation of 2-bromoprop-2-en-1-amine **379** with *t*-butylsulfenyl chloride **384** in the presence of Et_3N, but **384** was not commercially available, and its synthesis and storage is problematic due to volatility and stability issues.[178] As an alternative, we considered that the

coupling reaction of *N*-(*t*-butylsulfenyl)phthalimide **385** with 2-bromoprop-2-en-1-amine **379** might be more suitable for the synthesis of **382** (Scheme 3.27).



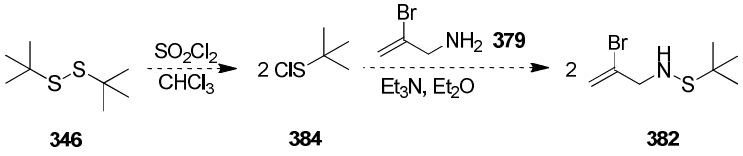
Scheme 3.27.

The synthesis of *N*-(benzenesulfenyl)phthalimide **387** can be achieved in quantitative yield by the reaction of diphenyl disulfide, bromine and phthalimide.[179] Unfortunately however, when diphenyl disulfide was replaced with di-*t*-butyl disulfide **346**, only starting materials were returned unchanged (Scheme 3.28).



Scheme 3.28.

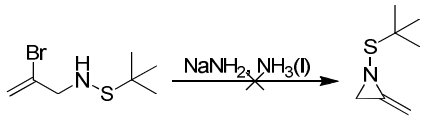
Given our earlier failed attempts, we finally considered *in situ* generation of *t*-butylsulfenyl chloride **384** and its condensation with 2-bromoprop-2-en-1-amine **379**, in the presence of Et_3N (Scheme 3.29).



Scheme 3.29.

A convenient method for the synthesis of sulfenyl halides involves the reaction of disulfides, typically in chlorinated solvents[178] with sulfuryl chloride.[180] Thus, sulfuryl chloride (1 eq.) was added to a solution of di-*t*-butyl disulfide **346** in anhydrous $CHCl_3$ at -20 °C. The conversion of **346** to **384**, which was monitored by ^{1}H NMR spectroscopy, was found to be complete after 1 hour, whereupon the solvent was removed *in vacuo*, at low temperature. Treatment of crude *t*-butylsulfenyl chloride **384** with 2-bromoprop-2-en-1-amine **379** (2 eq.) in anhydrous Et_2O, in the presence of Et_3N, initially at 0 °C with warming to room temperature over 15 hours resulted in 55% conversion to sulfenamide **382**. Conducting the entire reaction in $CHCl_3$ improved conversion to 72%, as assessed by ^{1}H NMR spectroscopy. Finally, we found that use of anhydrous THF in place of Et_2O gave complete conversion to sulfenamide **382**. Unfortunately, attempts to purify **382** met with only limited success. Exposure of **382** to silica gel and bulb-to-bulb distillation at elevated temperature resulted in extensive degradation. Purification on basic alumina provided **382** in sufficient quantity (2%) for characterisation, but insufficient material to take through to the next step. Hence, the decision was made to attempt cyclisation on the crude material.

Frustratingly, upon treatment with $NaNH_2$ (2.5 eq.) in liquid ammonia, *N*-(*t*-butylsulfenyl)-2-bromoprop-2-en-1-amine **382** was returned unchanged. When the molar equivalents of $NaNH_2$ were increased to five, extensive degradation was observed (Scheme 3.30). Importantly, the desired methyleneaziridine **383** was not detected in either case.

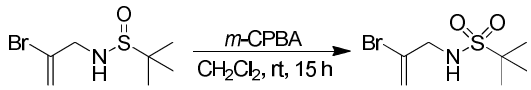


382 **383**

Scheme 3.30.

3.5.4. Attempted synthesis of *N*-*t*-butylsulfonyl methyleneaziridines.

For completeness, we finally examined the ring closure of *N*-(*t*-butylsulfonyl)-2-bromoprop-2-en-1-amine **388**, which was conveniently prepared by oxidation of sulfinamide **375** with *m*-CPBA (Scheme 3.31).[175]

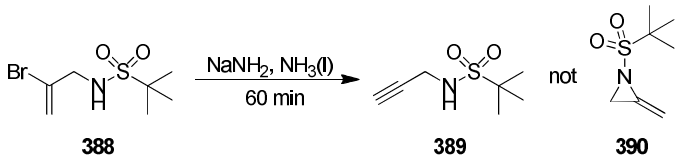


375 **388**, 44%

Scheme 3.31.

In a limited study, the temperature and molar equivalents of sodium amide were varied. Each reaction was conducted for 60 minutes and the outcome determined by examination of the crude ^{1}H NMR spectra. The results are summarised inTable 3.8.

Disappointingly, by using 2.5 equivalents of sodium amide at -78 °C or -33 °C, only unreacted *N*-(*t*-butylsulfonyl)-2-bromoprop-2-en-1-amine **388** was observed (Table 3.8, Entries 1-2). While, increasing the molar equivalents of sodium amide, gave only partial conversion of **388** to the corresponding acetylene **389** (Table 3.8, Entries 3-4). Again, the desired methyleneaziridine **390** was not detected.

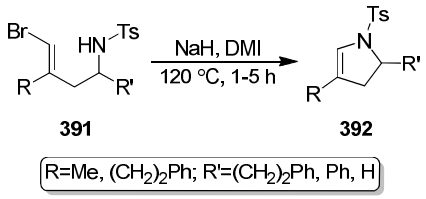


Entry	$NaNH_2$ (eq.)	T (°C)	Product Ratio[a]		
			388	**389**	**390**
1	2.5	-78	100	0	0
2	2.5	-33	100	0	0
3	5.0	-33	42	58	0
4	10.0	-33	7	93	0

[a] Determined by integration of crude ^{1}H NMR spectra.

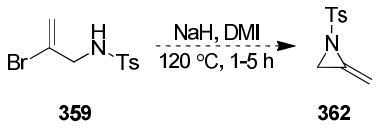
Table 3.8.

Ando, Narasaka and co-workers described the synthesis of a range of *N*-tosyl-pyrrolines **392** from the corresponding vinyl bromides **391** by way of an intramolecular S_N2-type ring closure of the tosylamide moiety onto the appended bromoalkene (Scheme 3.32).[181]



Scheme 3.32.

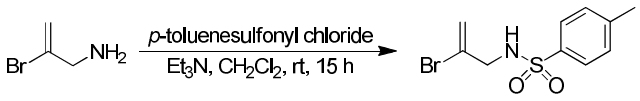
Inspired by this work, we wondered if we might be able to apply the same conditions to affect cyclisation of 2-bromo-*N*-tosylprop-2-en-1-amine **359** to the corresponding methyleneaziridine **362** (Scheme 3.33).



359 **362**

Scheme 3.33.

Thus, **359** was synthesised in moderate yield, by condensation of 2-bromoprop-2-en-1-amine **379** with *p*-toluenesulfonyl chloride in the presence of Et_3N (Scheme 3.34).



379 **359**, 68%

Scheme 3.34.

Unfortunately, treatment of amine **379** with sodium hydride (1.5 eq.) in DMI at 120 °C for 1 hour, resulted only in partial conversion to the corresponding acetylene[182] as assessed by ^{1}H NMR spectroscopy (Table 3.9, Entry 1).

a **b** **c**

Entry	2-Bromoallylamine	R	Product Ratio[a]		
			a	**b**	**c**
1	**379**	*p*-toluenesulfonyl	48	52	0
2	**388**	*t*-butylsulfonyl	100	0	0
3	**168**	(*S*)-CH(CH_3)Ph	0	100	0

[a] Determined by integration of crude ^{1}H NMR spectra.

Table 3.9.

Under the same reaction conditions, *N*-(*t*-butylsulfonyl)-2-bromoprop-2-en-1-amine **388** was returned unchanged (Table 3.9, Entry 2). Notably, vinyl bromide **168**, which is known to provide the corresponding methyleneaziridine **169** in the presence of sodium amide in liquid ammonia, reacted smoothly to give the corresponding acetylene upon treatment under these reaction conditions (Table, 3.9, Entry 3).

3.5.5. Conclusions

Disappointingly, our attempts to form methyleneaziridines bearing a *t*-butylsulfinyl *N*-substituent have proven unsuccessful. Attempted $NaNH_2$-based ring closure of *N*-(*t*-butylsulfinyl)-2-bromoprop-2-en-1-amine **375** and *N*-(*t*-butylsulfonyl)-2-bromoprop-2-en-1-amine **388**, generally led to mixtures of unreacted starting materials and the corresponding acetylenes **381** and **389**, derived from a competitive E2-elimination reaction pathway. A route to *N*-(*t*-butylsulfenyl)-2-bromoprop-2-en-1-amine **382** was achieved, although this material failed to provide access to *N*-*t*-butylsulfenyl methyleneaziridine **383**.

3.6. Summary and future work

Unfortunately, our efforts towards realising new multicomponent reactions involving methyleneaziridines met with only limited success.

A limited model study established that acyclic ketimines such as **331** were poor substrates for the proposed condensation reaction with lithiated *N*,*N*-diethyl-2-methylbenzamide **317**. While, α-fluorinated ketone **342** and β-fluoroamine **343** were isolated, albeit in extremely poor yield, by incorporation of a final

electrophilic fluorination step within our well-established methyleneaziridine-based MCR methodology.

Attempts towards the synthesis of N-*t*-butylsulfinyl methyleneaziridines from the corresponding 2-bromoallylamines met with failure. In general, the corresponding acetylenes (formed by a competitive E2-elimination pathway), or complex mixtures were obtained.

Related research currently being conducted within the Shipman group has moved away from multicomponent reactions based upon the methyleneaziridine nucleus nucleus, specifically focusing on the three-component Passerini reaction of oxetan-3-ones with simple carboxylic acids and isocyanides.

Chapter 4: Experimental

4.1. General Remarks

Anhydrous solvents were purchased in Sure/Seal^{TM} bottles from Sigma-Aldrich. All other solvents and reagents were used as received or purified by standard protocols. Petroleum ether refers to the fraction of petroleum ether having a boiling point between 40-60 °C. All experiments were performed under an inert atmosphere (N_2) and moisture sensitive reactions were conducted in oven- or flame-dried glassware. Where appropriate, reagent transfer was performed using syringe techniques.

Flash chromatography was carried out using Matrex silica 60 unless otherwise stated. Thin layer chromatography was performed on pre-coated aluminium-backed plates (Merck Kieselgel 60 F_{254}) and developed using UV fluorescence (254 nm) and/or potassium permanganate, followed by heating.

Infrared spectra were recorded neat or as thin films on NaCl plates using a PerkinElmer Spectrum One FT-IR spectrometer with internal calibration.

^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Bruker DPX-300; at 400 MHz and 100 MHz respectively on a Bruker DPX-400; at 500 MHz and 125 MHz respectively on a Bruker DRX-500; and at 600 MHz and 150 MHz respectively on a Bruker AV-600 spectrometer at 298K unless otherwise stated. Signals in ^{1}H and ^{13}C spectra are reported as singlets (s), doublets (d), triplets (t), pentets (p) etc, which refer to the observed spin-spin coupling patterns. Chemical shifts (δ) are quoted in parts per million (ppm) relative to TMS (δ = 0 ppm), with the residual solvent as the internal standard.

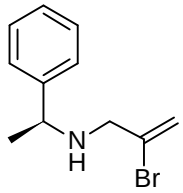
Coupling constants (*J*) were measured in Hertz. Ambiguous signals were assigned using COSY, HMQC, HMBC and NOESY correlation spectroscopy.

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

Melting points were recorded on a Gallenkamp MPD350 apparatus and are reported uncorrected.

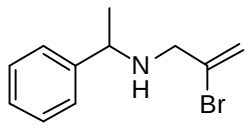
4.2. Preparations

2-Bromo-*N*-((*S*)-1-phenylethyl)prop-2-en-1-amine (*S*)-168[104]



To a stirred suspension of K_2CO_3 (7.06 g, 51.1 mmol) in THF (125 mL) was added (*S*)-(-)-1-phenylethylamine (10.0 mL, 77.5 mmol) and then 2,3-dibromopropene (5.00 mL, 38.7 mmol). The resulting mixture was stirred at room temperature for 15 hours and then partitioned between 10% NaOH solution (100 mL) and Et_2O (200 mL). The aqueous phase was extracted with Et_2O (2 x 200 mL). The combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (1% Et_3N and 10% EtOAc in petroleum ether) afforded 2-bromo-*N*-((*S*)-1-phenylethyl)prop-2-en-1-amine **168** (9.29 g, 38.7 mmol, 100%) as a pale, yellow oil. δ_H (400 MHz, $CDCl_3$) 7.30-7.21 (5H, m, 5 x CH, Ph), 5.66 (1H, s, =CH), 5.54 (1H, s, =CH), 3.79 (1H, q, *J* = 6.6 Hz, CH), 3.35 (1H, d, *J* = 15.2 Hz, C*H*H), 3.24 (1H, d, *J* = 15.2 Hz, CH*H*), 1.73 (1H, br s, NH), 1.35 (3H, d, *J* = 6.6 Hz, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 144.8 (C, Ph), 133.8 (CBr), 128.5 (2 x CH, Ph), 127.1 (CH, Ph), 126.9 (2 x CH, Ph), 118.0 (=CH_2), 55.7 (CH), 55.1 (CH_2), 24.3 (CH_3) ppm.

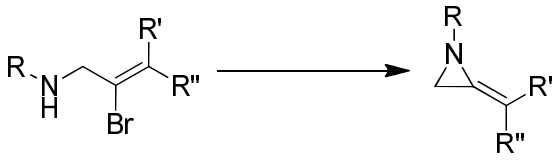
2-Bromo-*N*-(1-phenylethyl)prop-2-en-1-amine (±)-168[98]



To a stirred suspension of K_2CO_3 (4.41 g, 31.9 mmol) in THF (75 mL) was added (±)-phenylethylamine (7.5 mL, 58.5 mmol) and then 2,3-dibromopropene (3.00 mL, 29.0 mmol). The resulting mixture was stirred at room temperature for 15 hours and then partitioned between 10% NaOH solution (60 mL) and Et_2O (100 mL). The aqueous phase was extracted with Et_2O (2 x 100 mL) The combined organic extracts were washed

with brine (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (1% Et_3N and 10% EtOAc in petroleum ether) afforded 2-bromo-*N*-(1-phenylethyl)prop-2-en-1-amine (±)-**168** (6.05 g, 25.19 mmol, 87%) as a pale, yellow oil. δ_H (400 MHz, $CDCl_3$) 7.34-7.20 (5H, m, 5 x CH, Ph), 5.67-5.66 (1H, m, =C*H*H), 5.54-5.53 (1H, m, =CH*H*), 3.79 (1H, q, *J* = 6.5 Hz, CH), 3.35 (1H, d, *J* = 15.3 Hz, NHC*H*H), 3.25 (1H, d, *J* = 15.3 Hz, NHCH*H*), 1.78 (1H, br s, NH), 1.35 (3H, d, *J* = 6.5 Hz, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 144.9 (C, Ph), 133.8 (CBr), 128.5 (2 x CH, Ph), 127.1 (2 x CH, Ph), 126.9 (CH, Ph), 117.8 ($=CH_2$), 55.6 (CH), 55.1 (CH_2), 24.3 (CH_3) ppm.

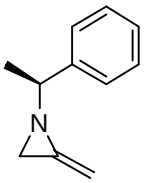
General method A: Dehydrohalogenation of 2-bromoallylamines featuring *in situ* generation of sodium amide.



An oven-dried three-necked flask was fitted with a cold-finger condenser and a gas inlet. Iron(III) nitrate nonahydrate (0.2-0.5 mol%) was added and the system flushed with ammonia. A dry ice/acetone mixture was added to the condenser and ammonia (0.1-0.2 M) was condensed into the flask. Portionwise addition of sodium (2.5-10.0 M equiv) initially resulted in a deep blue colouration, which slowly faded to afford a grey suspension of sodium amide. The mixture was cooled to -78 °C or maintained at -33 °C, whereupon a solution of 2-bromoallylamine (1.0 M equiv) in Et_2O (1:1 w/v) was added slowly. After 30-120 minutes, the mixture was diluted with Et_2O and quenched by the cautious addition of water. After the residual ammonia had evaporated, the mixture was partitioned

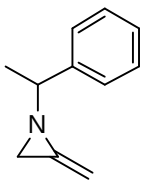
between Et_2O and 10% NaOH solution. The organic phase was separated and washed successively with 0.1 M acetic acid, 10% NaOH solution and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography or bulb-to-bulb distillation afforded the title compounds.

2-Methylene-1-((*S*)-1-phenylethyl)aziridine (*S*)-169[104]



Iron(III) nitrate nonahydrate (17.0 mg, 0.04 mmol), sodium (574 mg, 25.0 mmol) and 2-bromo-*N*-((*S*)-1-phenylethyl)prop-2-en-1-amine (*S*)-**168** (2.00 g, 8.33 mmol) were reacted together in ammonia (50 mL) at -33 °C for 30 minutes, in accordance with general method A. After work-up, purification by bulb-to-bulb distillation (70 °C, 0.4 mmHg) afforded 2-methylene-1-((*S*)-1-phenylethyl)aziridine (*S*)-**169** (0.75 g, 4.71 mmol 57%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.56-7.14 (5H, m, 5 x CH, Ph), 4.66-4.64 (2H, m, $=CH_2$), 2.94 (1H, q, J = 6.6 Hz, CH), 2.11 (1H, s, 1 x aziridine CH), 2.02 (1H, s, 1 x aziridine CH), 1.52 (3H, d, J = 6.6 Hz, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 144.1 (C, Ph), 137.1 (=C-N), 128.4 (2 x CH, Ph), 127.2 (CH, Ph), 126.8 (2 x CH, Ph), 83.1 ($=CH_2$), 68.5 (CH), 29.9 (aziridine CH_2), 23.5 (CH_3) ppm.

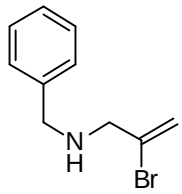
2-Methylene-1-(1-phenylethyl)aziridine (±)-169[98]



Iron(III) nitrate nonahydrate (13.0 mg, 0.03 mmol), sodium (920 mg, 40.0 mmol) and 2-bromo-*N*-(1-phenylethyl)prop-2-en-1-amine (±)-**168** (3.84 g, 16.0 mmol) were reacted together in ammonia (100 mL) at -33 °C for 30 minutes, in accordance with general method A. After work-up, purification by bulb-to-bulb distillation (70 °C, 0.4 mmHg) afforded 2-methylene-

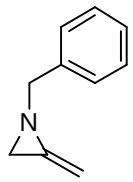
1-(1-phenylethyl)aziridine (±)-**169** (1.85 g, 11.6 mmol 73%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.38-7.29 (4H, m, 4 x CH, Ar), 7.26-7.22 (1H, m, CH, Ph), 4.64-4.62 (2H, m, $=CH_2$), 2.92 (1H, q, J = 6.6 Hz, CH), 2.07 (1H, s, 1 x ring CH), 1.99 (1H, s, 1 x ring CH), 1.50 (3H, d, J = 6.6 Hz, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 144.0 (C, Ph), 137.2 (=C-N), 128.4 (2 x CH, Ph), 127.3 (2 x CH, Ph), 126.8 (CH, Ph), 83.3 ($=CH_2$), 68.6 (CH), 29.9 (ring CH_2), 23.6 (CH_3) ppm.

_N_-Benzyl-2-bromoprop-2-en-1-amine 171[104]



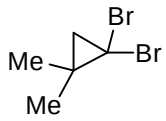
To a stirred suspension of K_2CO_3 (7.06 g, 51.1 mmol) in THF (125 mL) was added benzylamine (10.2 mL, 92.9 mmol) and then 2,3-dibromopropene (6.00 mL, 46.5 mmol). The resulting mixture was stirred at room temperature for 15 hours and then partitioned between water (100 mL) and Et_2O (200 mL). The aqueous phase was extracted with Et_2O (2 x 200 mL). The combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (10% EtOAc in petroleum ether) afforded *N*-benzyl-2-bromoprop-2-en-1-amine **171** (6.49 g, 28.7 mmol, 62%) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 7.35-7.24 (5H, m, 5 x CH, Ph), 5.80-5.79 (1H, m, =C*H*H), 5.60 (1H, m, =CH*H*), 3.74 (2H, s, $PhCH_2$), 3.47 (2H, s, $NHCH_2$), 1.73 (1H, br s, NH), ppm; δ_C (100 MHz, $CDCl_3$) 139.7 (C, Ph), 133.5 (CBr), 128.5 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.1 (CH, Ph), 117.9 ($=CH_2$), 56.7 ($NHCH_2$), 51.6 ($PhCH_2$) ppm.

1-Benzyl-2-methyleneaziridine 172[110]



Iron(III) nitrate nonahydrate (27.0 mg, 0.07 mmol), sodium (763 mg, 33.2 mmol) and *N*-benzyl-2-bromoprop-2-en-1-amine **171** (3.00 g, 13.3 mmol) were reacted together in ammonia (75 mL) at -78 °C for 1 hour, in accordance with general method A. After work-up, purification by bulb-to-bulb distillation (80 °C, 0.4 mmHg) afforded 1-benzyl-2-methyleneaziridine **172** (1.14 g, 7.85 mmol 59%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 7.40-7.24 (5H, m, 5 x CH, Ph), 4.72-4.71 (2H, m, $=CH_2$), 3.68 (2H, s, $PhCH_2$), 2.13 (2H, s, aziridine CH_2) ppm; δ_C (75 MHz, $CDCl_3$) 137.6 (C, Ph), 136.4 (=C-N), 127.8 (2 x CH, Ph), 127.6 (2 x CH, Ph), 126.7 (CH, Ph), 83.0 ($=CH_2$), 62.2 ($PhCH_2$), 30.0 (aziridine CH_2) ppm.

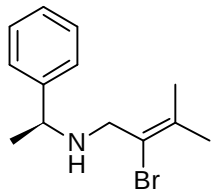
1,1-Dibromo-2,2-dimethylcyclopropane 173[112]



To a three-necked flask equipped with a dry ice condenser and dropping funnel immersed in a dry ice/MeOH bath was added potassium *tert*-butoxide (29.0 g, 0.24 mol). Isobutylene (100 mL) was condensed into the flask with stirring. The bath temperature was adjusted to between -20 and -10 °C, whereupon bromoform (20 mL, 0.22 mol) was added *via* dropping funnel over a 30 minute period. The resulting mixture was stirred for 30 minutes then allowed to return to room temperature. The mixture was partitioned between water (100 mL) and pentane (200 mL). The aqueous layer was extracted with pentane (200 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. Purification by bulb-to-bulb distillation (50 °C, 0.4 mmHg) afforded 1,1-dibromo-2,2-dimethylcyclopropane **173** (33.3 g, 0.15 mol, 66%) as a colourless liquid. δ_H (400

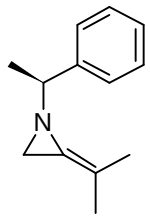
MHz, $CDCl_3$) 1.45 (2H, s, CH_2), 1.41 (6H, s, 2 x CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 39.7 (CBr_2) 35.1 (CH_2) 26.4 ($C(CH_3)_2$) 25.3 (2 x CH_3) ppm.

2-Bromo-3-methyl-*N*-((*S*)-1-phenylethyl)but-2-en-1-amine 174[107]



To a stirred solution of 1,1-dibromo-2,2-dimethylcyclopropane **173** (8.02 g, 35.2 mmol) and K_2CO_3 (4.86 g, 35.2 mmol) in 1,2-dichlorobenzene (65 mL) was added (*S*)-(-)-1-phenylethylamine (10.1 mL, 77.6 mmol). The resulting mixture was heated at 170 °C for 72 hours then cooled to room temperature. The 1,2-dichlorobenzene was removed under reduced pressure (40 °C, 0.4 mmHg) and the resulting residue partitioned between Et_2O (150 mL) and 2M NaOH solution (75 mL). The organic layer was washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (1% Et_3N and 5% EtOAc in petroleum ether) afforded 2-bromo-3-methyl-*N*-((*S*)-1-phenylethyl)but-2-en-1-amine **174** (3.97 g, 14.8 mmol, 42%). δ_H (300 MHz, $CDCl_3$) 7.36-7.20 (5H, m, 5 x CH, Ph), 3.75 (1H, q, *J* = 6.6 Hz, CH), 3.43 (1H, d, *J* = 14.2 Hz, NHC*H*H), 3.33 (1H, d, *J* = 14.2 Hz, NHCH*H*), 1.88 (3H, s, CH_3), 1.87 (1H, br s, NH), 1.55 (3H, s, CH_3), 1.35 (3H, d, *J* = 6.6 Hz, CHCH_3) ppm; δ_C (75 MHz, $CDCl_3$) 145.2 (C, Ph), 133.4 (=$C(CH_3)_2$), 128.4 (2 x CH, Ph), 127.0 (2 x CH, Ph), 126.9 (CH, Ph), 121.8 (CBr), 55.8 (CH), 51.1 (CH_2), 25.5 (CHCH$_3$), 24.8 (CH_3), 20.5 (CH_3) ppm.

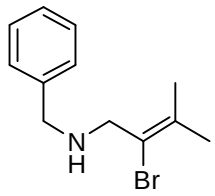
1-((*S*)-1-Phenylethyl)-2-(propan-2-ylidene)aziridine 175[107]



Iron(III) nitrate nonahydrate (29.0 mg, 0.07 mmol), sodium (1.15 g, 50.0 mmol) and 2-bromo-3-methyl-*N*-((*S*)-1-phenylethyl)but-2-en-1-amine **174** (3.83 g, 14.3 mmol) were reacted together in ammonia (125 mL) at -33 °C for 2 hours, in accordance with general method A. After work-

up, purification by bulb-to-bulb distillation (135 °C, 0.4 mmHg) afforded 1-((*S*)-1-phenylethyl)-2-(propan-2-ylidene)aziridine **175** (2.17 g, 11.6 mmol, 81%) as a yellow oil. δ_H (400 MHz, DMSO-d_6 at 90 °C) 7.40-7.32 (4H, m, 4 x CH, Ph), 7.28-7.24 (1H, m, CH, Ph), 3.07 (1H, q, *J* = 6.6 Hz, CH), 2.03 (1H, s, 1 x aziridine CH), 1.95 (1H, s, 1 x aziridine CH), 1.71 (3H, s, CH_3), 1.43 (3H, d, *J* = 6.6 Hz, CHCH_3), 1.42 (3H, s, CH_3) ppm; δ_C (125 MHz, DMSO-d_6 at 90 °C) 145.4 (C, Ph), 128.5 (2 x CH, Ph), 127.3 (2 x CH, Ph), 127.3 (CH, Ph), 125.2 (=C-N),101.9 ($C(CH_3)_2$), 67.4 (PhCH), 29.5 (aziridine CH_2), 23.6 (CH_3), 21.0 (CH_3), 19.4 (CHCH_3) ppm.

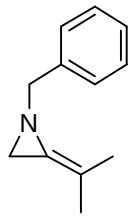
_N_-Benzyl-2-bromo-3-methylbut-2-en-1-amine 176[111]



To a stirred solution of 1,1-dibromo-2,2-dimethylcyclopropane **173** (8.00 g, 35.1 mmol) and K_2CO_3 (5.09 g, 36.9 mmol) in 1,2-dichlorobenzene (65 mL) was added benzylamine (8.50 mL, 77.2 mmol). The resulting mixture was heated at 170 °C for 72 hours then cooled to room temperature. The 1,2-dichlorobenzene was removed under reduced pressure (40 °C, 0.4 mmHg) and the resulting residue partitioned between Et_2O and 2M NaOH solution. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (0.5% Et_3N and 10% EtOAc in petroleum ether) afforded *N*-benzyl-2-bromo-3-methylbut-2-en-1-amine **176** (5.35 g, 21.1 mmol, 60%). δ_H (400 MHz, $CDCl_3$) 7.36-7.23 (5H, m, 5 x CH, Ph), 3.70 (2H, s, $PhCH_2$), 3.56 (2H, s, $NHCH_2$), 1.93 (3H, s, CH_3), 1.83 (1H, br s, NH), 1.75 (3H, s, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 140.0 (C, Ph), 133.7 (=$C(CH_3)_2$), 128.4 (2 x CH, Ph), 128.3 (2 x

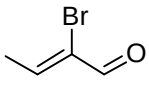
CH, Ph), 127.0 (CH, Ph), 121.5 (CBr), 52.6 ($PhCH_2$), 51.5 ($NHCH_2$), 25.6 (CH_3), 20.7 (CH_3) ppm.

1-Benzyl-2-(propan-2-ylidene)aziridine 177[111]



Iron(III) nitrate nonahydrate (12.0 mg, 0.04 mmol), sodium (633 mg, 27.5 mmol) and *N*-benzyl-2-bromo-3-methylbut-2-en-1-amine **176** (2.00 g, 7.87 mmol) were reacted together in ammonia (50 mL) at -78 °C for 1 hour, in accordance with general method A. After work-up, purification on silica (0.5% Et_3N and 5% EtOAc in petroleum ether) afforded 1-benzyl-2-(propan-2-ylidene)aziridine **177** (576 mg, 3.33 mmol, 42%) as a pale, yellow oil. δ_H (400 MHz, DMSO-d_6 at 90 °C) 7.39-7.26 (5H, m, 5 x CH, Ph), 3.66 (2H, s, CH_2), 2.09 (2H, s, aziridine CH_2), 1.76 (3H, s, CH_3), 1.69 (3H, s, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 138.9 (C, Ph), 128.4 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.2 (CH, Ph), 124.2 (=C-N), 104.2 (=*C*$(CH_3)_2$), 62.4 ($PhCH_2$), 31.7 (aziridine CH_2), 20.4 (CH_3), 19.2 (CH_3) ppm.

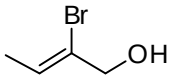
(*Z*)-2-Bromobut-2-enal 179[113]



A solution of Br_2 (3.20 mL, 62.1 mmol) in CH_2Cl_2 (4 mL) was added to a stirred solution of crotonaldehyde (5.00 mL, 59.1 mmol) in CH_2Cl_2 (100 mL) at -78 °C and the resulting mixture was stirred for 1 hour. A solution of triethylamine (12.0 mL, 85.7 mmol) in CH_2Cl_2 (12 mL) was added and the mixture was stirred at -78 °C for a further hour and then allowed to warm to room temperature. The mixture was washed successively with saturated, aqueous Na_2SO_3 (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and water (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford (*Z*)-2-bromobut-2-enal **179** (6.68 g, 44.8 mmol, 76%) as a dark brown oil. The crude oil was

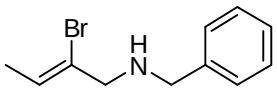
characterised and used without further purification. δ_H (600 MHz, $CDCl_3$) 9.22 (1H, s, CHO), 7.26 (1H, q, *J* = 6.8 Hz, =CH), 2.16 (3H, d, *J* = 6.8 Hz, CH_3) ppm; δ_C (150 MHz, $CDCl_3$) 186.1 (C=O), 150.9 (=CH), 130.2 (CBr), 18.0 (CH_3) ppm.

(*Z*)-2-Bromobut-2-en-1-ol 180[114]



To a stirred suspension of $NaBH_4$ (3.51 g, 90.8 mmol) in THF (15 mL) and water (15 mL) at -30 °C was added a solution of (*Z*)-2-bromobut-2-enal **179** (6.60 g, 44.3 mmol) in THF (15 mL). The resulting mixture was allowed to warm to 0 °C over a 1 hour period and then stirred at this temperature for a further 30 minutes. The mixture was partitioned between EtOAc (30 mL) and 10% NaOH solution (20 mL). The organic phase was washed with 10% NaOH solution (2 x 20 mL) and then brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford (*Z*)-2-bromobut-2-en-1-ol **180** (4.17 g, 27.6 mmol, 62%) as a dark, brown oil. The crude oil was characterised and used without further purification. δ_H (400 MHz, $CDCl_3$) 6.08 (1H, q, *J* = 6.6 Hz, =CH), 4.25 (2H, s, CH_2), 2.06 (1H, br s, OH), 1.78 (3H, d, *J* = 6.6 Hz, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 127.2 (CBr), 124.7 (=CH), 67.9 (CH_2), 15.8 (CH_3) ppm.

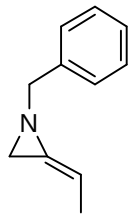
(*Z*)-*N*-Benzyl-2-bromobut-2-en-1-amine 181[108]



Triethylamine (9.50 mL, 97.9 mmol) was added to a stirred solution of (*Z*)-2-bromobut-2-en-1-ol **180** (4.10 g, 27.2 mmol) in THF (45 mL) at -30 °C. Methanesulfonyl chloride (2.21 mL, 28.5 mmol) was added to the cooled mixture followed by benzylamine (5.98 mL, 54.3 mmol). The mixture was heated at reflux temperature for 15 hours and then cooled to room temperature. The mixture was partitioned between Et_2O (80 mL) and 10% NaOH solution (40 mL). The organic phase was washed with 10%

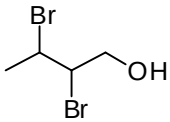
NaOH solution (40 mL) then brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (15% EtOAc in petroleum ether) afforded (*Z*)-*N*-benzyl-2-bromobut-2-en-1-amine **181** (3.26 g, 13.6 mmol, 50%) as an orange oil. δ_H (300 MHz, $CDCl_3$) 7.35-7.21 (5H, m, 5 x CH, Ph), 5.92 (1H, tq, *J* = 0.9, 6.5 Hz, =CH), 3.70 (2H, s, $PhCH_2$), 3.48 (2H, t, *J* = 1.0 Hz, $NHCH_2$), 1.82 (1H, br s, NH), 1.79 (3H, dt, *J* = 6.5, 1.0 Hz, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 139.3 (C, Ph), 128.2 (CBr), 127.8 (2 x CH, Ph), 127.7 (2 x CH, Ph), 126.4 (CH, Ph), 125.0 (=CH), 56.5 ($NHCH_2$), 50.8 ($PhCH_2$), 16.0 (CH_3) ppm.

(*E*)-1-Benzyl-2-ethylideneaziridine 182[108]



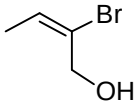
Iron(III) nitrate nonahydrate (24.0 mg, 0.06 mmol), sodium (805 mg, 35.0 mmol) and (*Z*)-*N*-benzyl-2-bromobut-2-en-1-amine **181** (2.80 g, 11.7 mmol) were reacted together in ammonia (75 mL) at -78 °C for 1 hour, in accordance with general method A. After work-up, purification on silica (0.5% Et_3N and 5% Et_2O in petroleum ether) afforded **(***E***)**-1-benzyl-2-ethylideneaziridine **182** (390 mg, 2.45 mmol 21%) as a pale, yellow oil. δ_H (400 MHz, $CDCl_3$) 7.37-7.25 (5H, m, 5 x CH, Ph), 5.17 (1H, qt, *J* = 6.7, 1.2 Hz, =CH), 3.62 (2H, s, CH_2), 2.12 (2H, br s, aziridine CH_2), 1.75 (3H, d, *J* = 6.7 Hz, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 138.7 (C, Ph), 130.2 (=C-N), 128.4 (2 x CH, Ph), 128.2 (2 x CH, Ph), 127.2 (CH, Ph), 94.9 (=CH), 63.4 (CH_2), 30.3 (aziridine CH_2), 14.2 (CH_3) ppm.

2,3-Dibromobutan-1-ol 184[115]



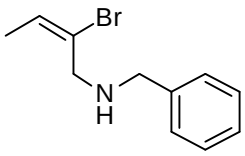
To a vigorously stirred solution of Br_2 (4.14 mL, 80.0 mmol) in CH_2Cl_2 (4 mL) was added a solution of crotyl alcohol (7.00 mL, 80.0 mmol) in CH_2Cl_2 (36 mL) at -78 °C. The mixture was allowed to warm to room temperature and stirred for 1 hour. The organic phase was decolourised with 10% aqueous $Na_2S_2O_3$ solution and then washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 2,3-dibromobutan-1-ol **184** (16.7 g, 77.3 mmol, 97%) as a pale, yellow oil. The crude oil was characterised and used without further purification. δ_H (400 MHz, $CDCl_3$) 4.37 (1H, dq, *J* = 9.3, 6.6 Hz, C*H*CH_3), 4.26-4.22 (1H, m, C*H*CH_2), 4.08-4.06 (2H, m, CH_2), 2.22 (1H, br s, OH), 1.90 (3H, d, *J* = 6.6 Hz, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 66.1 (CH_2), 62.3 (*C*HCH_2), 47.7 (*C*HCH_3), 25.5 (CH_3) ppm.

(*E*)-2-Bromobut-2-en-1-ol 185[115]



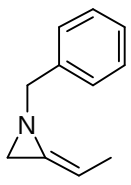
A solution of 2,3-dibromobutan-1-ol **184** (16.6 g, 75.8 mmol) in Et_2O (16 mL) was added to a stirred suspension of powdered KOH (9.78 g, 0.17 mol) in Et_2O (38 mL) at a rate that permitted the mild reflux of the reaction mixture. After the addition was complete, the mixture was heated at reflux temperature for 15 hours. The cooled mixture was washed successively with water then brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (5-10% EtOAc in petroleum ether) afforded (*E*)-2-bromobut-2-en-1-ol **185** (1.85 g, 12.3 mmol, 16%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 6.08 (1H, q, *J* = 7.3 Hz, =CH), 4.32 (2H, d, *J* = 6.5 Hz, CH_2), 2.12 (1H, t, *J* = 6.5 Hz, OH), 1.74 (3H, d, *J* = 7.3 Hz, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 129.7 (=CH), 124.6 (CBr), 62.3 (CH_2), 15.1 (CH_3) ppm.

(*E*)-*N*-Benzyl-2-bromobut-2-en-1-amine 186[108]



Triethylamine (4.13 mL, 29.5 mmol) was added to a stirred solution of (*E*)-2-bromobut-2-en-1-ol **185** (1.78 g, 11.8 mmol) in THF (20 mL) at -30 °C. Methanesulfonyl chloride (0.96 mL, 12.4 mmol) was added to the cooled mixture followed by benzylamine (2.60 mL, 23.6 mmol). The mixture was heated at reflux temperature for 15 hours and then cooled to room temperature. The mixture was partitioned between Et_2O (40 mL) and 10% NaOH solution (20 mL). The organic phase was washed with 10% NaOH solution (20 mL) and then brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (10% EtOAc in petroleum ether) afforded (*E*)-*N*-benzyl-2-bromobut-2-en-1-amine **186** (2.23 g, 9.29 mmol, 79%) as an orange oil. δ_H (400 MHz, $CDCl_3$) 7.37-7.31 (4H, m, 4 x CH, Ph), 7.27-7.23 (1H, m, CH, Ph), 6.13 (1H, q, *J* = 7.2 Hz, =CH), 3.72 (2H, s, $PhCH_2$), 3.51 (2H, s, $NHCH_2$), 1.78 (1H, br s, NH), 1.61 (3H, d, *J* = 7.2 Hz, CH_3), ppm; δ_C (100 MHz, $CDCl_3$) 139.8 (C, Ph), 129.6 (=CH), 128.4 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.1 (CH, Ph), 125.4 (CBr), 51.3 ($NHCH_2$), 50.1 ($PhCH_2$), 15.1 (CH_3) ppm.

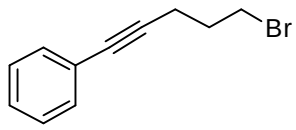
(*Z*)-1-Benzyl-2-ethylideneaziridine 187[108]



An oven-dried three-necked flask was fitted with a cold-finger condenser and a gas inlet. Sodium amide (5.69 g, 0.14 mol) was added and the system flushed with ammonia. A dry ice/acetone mixture was added to the condenser and ammonia (75 mL) was condensed into the flask. After cooling to -78 °C, a solution (*E*)-*N*-benzyl-2-bromobut-2-en-1-amine **186** (2.22 g, 9.24 mmol) in Et_2O (2 mL) was added slowly. After 1 hour, the mixture was

diluted with Et_2O (30 mL) and quenched by the cautious addition of water (20 mL). After the residual ammonia had evaporated, the mixture was partitioned between Et_2O (100 mL) and 10% NaOH solution (75 mL). The organic phase was separated and washed successively with 0.1 M acetic acid (75 mL), 10% NaOH solution (75 mL) and brine (75 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by bulb-to-bulb distillation (90 °C, mmHg) afforded (*Z*)-1-benzyl-2-ethylideneaziridine **187** (1.06 g, 6.66 mmol, 72%). δ_H (400 MHz, $CDCl_3$) 7.39-7.26 (5H, m, 5 x CH, Ph), 5.11 (1H, q, *J* = 6.8 Hz, =CH), 3.72 (2H, br s, CH_2), 2.10 (2H, br s, aziridine CH_2), 1.70 (3H, d, *J* = 6.8 Hz, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 138.5 (C, Ph), 129.9 (=C-N), 128.4 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.3 (CH, Ph), 95.2 (=CH), 62.1 (CH_2), 31.3 (aziridine CH_2), 13.3 (CH_3) ppm.

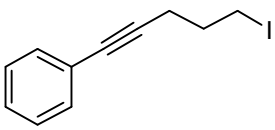
1-(5-Bromopent-1-ynyl)benzene 212[119]



To a stirred solution of phenylacetylene (1.10 mL, 9.82 mmol) in THF (10 mL) at -78 °C was added a 1.6 M solution of *n*-BuLi in hexanes (6.13 mL, 9.82 mmol) dropwise. The resulting mixture was stirred at -78 °C for 1 hour whereupon the solution of lithium phenylacetylide was added *via* canula to a stirred solution of 1,3-dibromopropane (1.01 mL, 9.82 mmol) in THF (1 mL) at 0 °C. The resulting mixture was heated at reflux temperature for 3 hours, then cooled to room temperature and carefully hydrolysed with water. The mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (100% petroleum ether) afforded 1-(5-bromopent-1-ynyl)benzene **212** (860 mg,

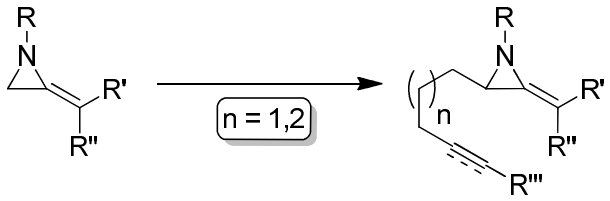
3.85 mmol, 39%) as a pale, yellow oil.δ_H (300 MHz, $CDCl_3$) 7.43-7.37 (2H, m, 2 x CH, Ph), 7.33-7.26 (3H, m, 3 x CH, Ph), 3.59 (2H, t, *J* = 6.5 Hz, CH_2Br), 2.61 (2H, t, *J* = 6.8 Hz, ≡CC*H*$_2$), 2.14 (2H, t, *J* = 6.6 Hz, ≡CCH_2CH_2) ppm; δ_C (75 MHz, $CDCl_3$) 131.0 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.2 (CH, Ph), 122.9 (C, Ph), 87.3 (C≡), 81.0 (C≡), 31.9 (CH_2Br), 30.9 (≡CCH_2CH_2), 17.5 (≡C*C*H$_2$) ppm.

1-(5-Iodopent-1-ynyl)benzene 215[120]



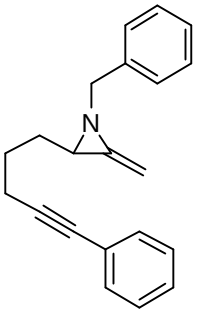
To a stirred solution of phenylacetylene (11.0 mL, 98.2 mmol) in THF (100 mL) at -78 °C was added a 1.6 M solution of *n*-BuLi in hexanes (61.3 mL, 98.2 mmol) dropwise. The resulting mixture was stirred at -78 °C for 1 hour whereupon the solution of lithium phenylacetylide was added *via* canula to a stirred solution of 1,3-diiodopropane (8.25 mL, 70.7 mmol) in THF (10 mL) at 0°C. The resulting mixture was heated at reflux temperature for 3 hours, then cooled to room temperature and carefully hydrolysed with water. The mixture was extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (100% petroleum ether) afforded 1-(5-iodopent-1-ynyl)benzene **215** (9.44 g, 35.0 mmol, 49%) as a pale, yellow oil.δ_H (400 MHz, $CDCl_3$) 7.42-7.37 (2H, m, 2 x CH, Ph), 7.30-7.27 (3H, m, 3 x CH, Ph), 3.37 (2H, t, *J* = 6.8 Hz, CH_2I), 2.56 (2H, t, *J* = 6.7 Hz, ≡CC*H*$_2$), 2.09 (2H, t, *J* = 6.8 Hz, ≡CCH_2CH_2) ppm; δ_C (100 MHz, $CDCl_3$) 131.6 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.8 (CH, Ph), 123.6 (C, Ph), 87.8 (C≡), 81.7 (C≡), 32.2 (≡CCH_2CH_2), 20.5 (≡C*C*H$_2$), 5.5 (CH_2I) ppm.

General method B: Lithiation/electrophile trapping of methyleneaziridines.



To a stirred solution of the methyleneaziridine (1.0 M equiv) in THF at -78 °C, was added TMEDA (1.2 M equiv) and *s*-BuLi (1.9 M equiv) dropwise. The reaction was stirred at -78 °C for 6 hours, then quenched with a solution of the electrophile (0.95-2.0 M equiv) in THF and allowed to warm to room temperature for 15 hours. Water was added, the layers separated, and the aqueous phase extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography or removal of unreacted methyleneaziridine by bulb-to-bulb distillation followed by filtration through a short plug of basic alumina (Et_2O) afforded the title compounds.

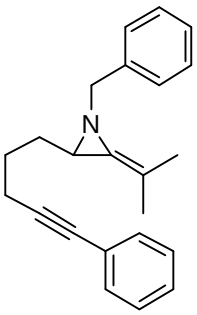
1-Benzyl-2-methylene-3-(5-phenylpent-4-ynyl)aziridine 217



1-Benzyl-2-methyleneaziridine **172** (212 mg, 1.46 mmol) was reacted with TMEDA (0.27 mL, 1.75 mmol) and *s*-BuLi (1.98 mL, 2.77 mmol) in THF (12 mL) in accordance with general method B, then a solution of 1-(5-iodopent-1-ynyl)benzene **215** (375 mg, 1.39 mmol) in THF (3 mL) was added. After work-up, the unreacted methyleneaziridine was removed by bulb-to-bulb distillation (80 °C, 0.4 mmHg), and the residue passed through a short plug of basic alumina (Et_2O) to afford 1-benzyl-2-methylene-3-(5-phenylpent-4-ynyl)aziridine **217** (139 mg,

0.48 mmol, 35% based on electrophile) as a yellow oil. R_f = 0.22 (5% EtOAc in petroleum ether); ν_{max} (film) 2934, 1772, 1643, 1490, 1453, 1157, 756, 652 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.42-7.25 (10H, m, 10 x CH, Ph) 4.70 (2H, d, *J* = 14.3 Hz, $=CH_2$), 3.93 (1H, d, *J* = 13.2 Hz, PhC*H*H), 3.53 (1H, d, *J* = 13.2, PhCH*H*), 2.37 (2H, t, *J* = 7.0 Hz, $\equiv CCH_2$), 2.07 (1H, t, *J* = 5.8 Hz, aziridine CH), 1.80-1.58 (4H, m, 2 x CH_2) ppm; δ_C (100 MHz, $CDCl_3$) 142.5 (=C-N), 138.9 (C, Ph), 132.1 (C, Ph), 131.6 (2 x CH, Ph), 128.4 (2 x CH, Ph), 128.4 (2 x CH, Ph), 128.2 (2 x CH, Ph), 127.6 (CH, Ph), 127.3 (CH, Ph), 90.2 (C≡), 83.3 ($=CH_2$), 81.2 (C≡), 62.3 ($PhCH_2$), 42.3 (aziridine CH), 30.9 ($CHCH_2$), 26.2 ($\equiv CCH_2$), 19.0 ($\equiv CCH_2CH_2$) ppm; MS (ES^+) *m/z* 288 [MH^+]; HRMS (ES^+) calcd. for $C_{21}H_{22}N$ [MH^+]: 288.1747; found 288.1751.

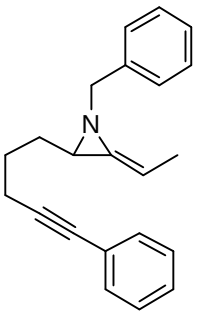
1-Benzyl-2-(5-phenylpent-4-ynyl)-3-(propan-2-ylidene)aziridine 219



1-Benzyl-2-(propan-2-ylidene)aziridine **177** (202 mg, 1.17 mmol) was reacted with TMEDA (0.21 mL, 1.40 mmol) and *s*-BuLi (1.57 mL, 2.19 mmol) in THF (9 mL) in accordance with general method B, then a solution of 1-(5-iodopent-1-ynyl)benzene **215** (374 mg, 1.39 mmol) in THF (1 mL) was added. After work-up, purification on silica (0.5% Et_3N and 5% EtOAc in petroleum ether) afforded 1-benzyl-2-(5-phenylpent-4-ynyl)-3-(propan-2-ylidene)aziridine **219** (198 mg, 0.63 mmol, 54%) as a pale, yellow oil. R_f = 0.30 (10% EtOAc in petroleum ether); ν_{max} (neat) 3028, 2923, 2361, 1796, 1598, 1490, 1452, 755, 693 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.25 (10H, m, 10 x CH, Ph), 4.18 (1H, d, *J* = 13.3 Hz, 1 x PhC*H*H), 3.19 (1H, d, *J* = 13.3 Hz, 1 x PhCH*H*), 2.31 (2H, t, *J* = 7.0 Hz, $\equiv CCH_2$), 2.06 (1H, t, *J* = 5.7 Hz, aziridine CH), 1.78 (3H,

s, CH_3), 1.74 (3H, s, CH_3), 1.67-1.48 (4H, m, 2 x CH_2) ppm; δ_C (100 MHz, $CDCl_3$) 139.1 (C, Ph), 131.6 (2 x CH, Ph), 129.7 (C, Ph), 128.5 (2 x CH, Ph), 128.4 (2 x CH, Ph), 128.2 (2 x CH, Ph), 127.5 (CH, Ph), 127.2 (CH, Ph), 124.0 (=C-N) 104.2 (*C*$(CH_3)_2$), 89.9 (C≡), 80.8 (C≡), 62.1 (Ph*C*H_2), 43.7 (aziridine CH), 31.4 (CH*C*H_2), 26.5 (≡C*C*H_2), 20.7 (CH_3), 19.1 (CH_3), 19.1 (≡CCH_2*C*H_2) ppm; MS (ES^+) *m/z* 316 [MH^+]; HRMS (ES^+) calcd. for $C_{23}H_{26}N$ [MH^+]: 316.2060; found 316.2061.

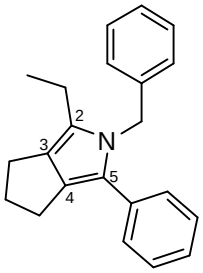
(*Z*)-1-Benzyl-2-ethylidene-3-(5-phenylpent-4-ynyl)aziridine 222



(*Z*)-1-Benzyl-2-ethylideneaziridine **187** (212 mg, 1.33 mmol) was reacted with TMEDA (0.24 mL, 1.60 mmol) and *s*-BuLi (1.80 mL, 2.53 mmol) in THF (11 mL) in accordance with general method B, then a solution of 1-(5-iodopent-1-ynyl)benzene **215** (431 mg, 1.60 mmol) in THF (2 mL) was added. After work-up, purification on silica (0.5% Et_3N and 0-1% EtOAc in petroleum ether) afforded (*Z*)-1-benzyl-2-ethylidene-3-(5-phenylpent-4-ynyl)aziridine **222** (125 mg, 0.41 mmol, 31%) as a yellow oil. R_f = 0.21 (5% EtOAc in petroleum ether); ν_{max} (film) 2936, 1780, 1598, 1490, 1454, 1303, 1130, 756, 692 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39-7.23 (10H, m, 10 x CH, Ph), 5.12 (1H, q, *J* = 6.7 Hz, =CH), 4.20 (1H, d, *J* = 13.4 Hz, PhC*H*H), 3.29 (1H, d, *J* = 13.4 Hz, PhCH*H*), 2.32 (2H, t, *J* = 7.0 Hz, ≡CCH_2), 2.03 (1H, t, *J* = 5.9 Hz, aziridine CH), 1.78-1.47 (7H, m, 2 x CH_2 and CH_3), ppm; δ_C (100 MHz, $CDCl_3$) 138.7 (C, Ph), 135.3 (=C-N), 131.6 (2 x CH, Ph), 128.5 (2 x CH, Ph), 128.4 (2 x CH, Ph), 128.2 (2 x CH, Ph), 127.5 (CH, Ph), 127.3 (CH, Ph), 124.0 (C, Ph), 94.9 (=CH), 89.9 (C≡), 80.9 (C≡), 61.8 (PhCH_2), 42.9 (aziridine CH), 31.2 (CH*C*H_2), 26.3

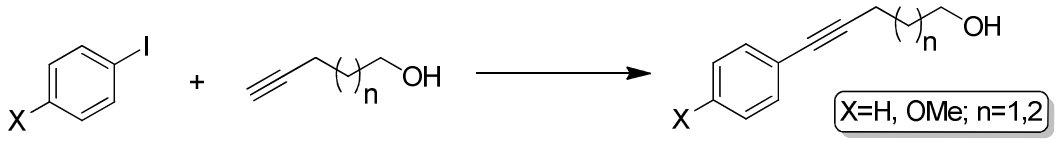
(≡C*C*H_2), 19.0 (≡CCH$_2$*C*H$_2$), 13.3 (CH_3) ppm; MS (ES^+) *m/z* 302 [MH^+]; HRMS (ES^+) calcd. for $C_{22}H_{24}N$ [MH^+]: 302.1903; found 302.1906.

2-Benzyl-1-ethyl-2,4,5,6-tetrahydro-3-phenylcyclopenta[*c*]pyrrole 224



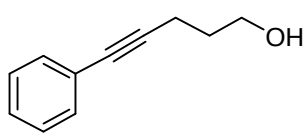
To a stirred solution of (*Z*)-1-benzyl-2-ethylidene-3-(5-phenylpent-4-ynyl)aziridine **222** (118 mg, 0.39 mmol) in CH_2Cl_2 (8 mL) at -30 °C was added $BF_3{\cdot}OEt_2$ (0.07 mL, 0.59 mmol). The resulting mixture was allowed to warm slowly to room temperature for 15 hours, and then quenched by the addition of saturated $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (0-2% Et_2O in petroleum ether) afforded 2-benzyl-1-ethyl-2,4,5,6-tetrahydro-3-phenylcyclopenta[*c*]pyrrole **224** (45.0 mg, 0.15 mmol, 38%) as a yellow oil. R_f = 0.35 (2% Et_2O in petroleum ether); ν_{max} (film) 2940, 1596, 1494, 1453, 1352, 701 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.30-7.14 (8H, m, 8 x CH, Ph), 6.98 (2H, d, *J* = 7.4 Hz, 2 x CH, Ph), 5.10 (2H, s, $PhCH_2$), 2.76-2.72 (4H, m, 2 x cp ring CH_2), 2.44 (2H, q, *J* = 7.6 Hz, C*H*$_2$CH$_3$), 2.37-2.33 (2H, m, cp ring CH_2), 1.18 (3H, t, *J* = 7.6 Hz, CH_2CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 139.9 (C, Ph and C-5), 133.8 (C, Ph), 129.5 (C-2), 128.6 (2 x CH, Ph), 128.4 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.1 (C-4), 126.8 (CH, Ph), 125.8 (3 x CH, Ph), 124.7 (C-3), 48.0 ($PhCH_2$), 31.1 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 19.9 (*C*H$_2$CH$_3$), 12.9 (CH_2CH_3) ppm; MS (ES^+) *m/z* 302 [MH^+]; HRMS (ES^+) calcd. for $C_{22}H_{24}N$ [MH^+]: 302.1903; found 302.1905.

General method C: Sonogashira coupling of terminal acetylenes with aryl iodides.



To tetrakis(triphenylphosphine)palladium(0) (2 mol%) under N_2, was added THF (0.5 M) then successively, terminal acetylene (1.0 M equiv), aryl iodide (2.0 M equiv) and diisopropylamine (6.2 M equiv). The resulting mixture was stirred at room temperature for 20 minutes whereupon copper iodide (1 mol%) was added. The reaction mixture was stirred at room temperature for 15 hours. The resulting suspension was concentrated *in vacuo*, taken up in EtOAc and passed through a plug of Celite®. The solvent was removed *in vacuo* to give the crude product. Purification by column chromatography afforded the title compounds.

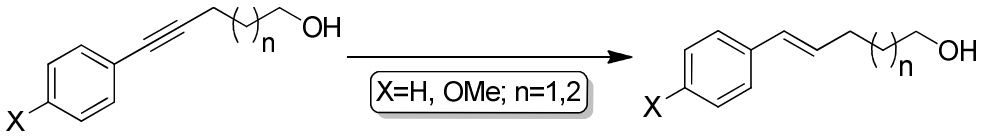
5-Phenylpent-4-yn-1-ol 229[123]



Tetrakis(triphenylphosphine)palladium(0) (563 mg, 0.48 mmol), 4-pentynol (2.30 mL, 24.1 mmol), iodobenzene (5.50 mL, 48.2 mmol), diisopropylamine (21.0 mL, 0.15 mol) and CuI (46.0 mg, 0.24 mmol) were reacted together in THF (52 mL), in accordance with general method C. After work-up, purification on silica gel (25% EtOAc in petroleum ether) afforded 5-phenylpent-4-yn-1-ol **229** (3.51 g, 21.9 mmol, 91%) as an orange oil. δ_H (400 MHz, $CDCl_3$) 7.36-7.41 (2H, m, 2 x CH, Ph), 7.24-7.29 (3H, m, 3 x CH, Ph), 3.81 (2H, br q, J = 5.6 Hz, CH_2OH), 2.53 (2H, t, J = 7.0 Hz, $\equiv CCH_2$), 1.85 (2H, p, J = 6.6 Hz, $\equiv CCH_2CH_2$), 1.81 (1H, br t, J = 4.7 Hz, OH) ppm; δ_C (100 MHz, $CDCl_3$), 131.6 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.7 (CH,

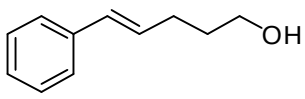
Ph), 123.8 (C, Ph), 89.4 (C≡), 81.2 (C≡), 61.8 (CH_2OH), 31.4 (≡CCH_2CH_2), 16.0 (≡CCH_2) ppm.

General method D: Lithium aluminium hydride reduction of acetylenes.



A solution of acetylene (1.0 M equiv) in THF was added dropwise to $LiAlH_4$ (3.5 M equiv) in THF (0.5 M) under N_2 at 0 °C. The resulting mixture was heated at reflux temperature for 15 hours then cooled to room temperature, whereupon the reaction was hydrolysed cautiously with a saturated, aqueous solution of potassium sodium tartrate. The mixture was extracted twice with EtOAc, and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography afforded the title compounds. Where appropriate, the crude products were characterised and used without further purification.

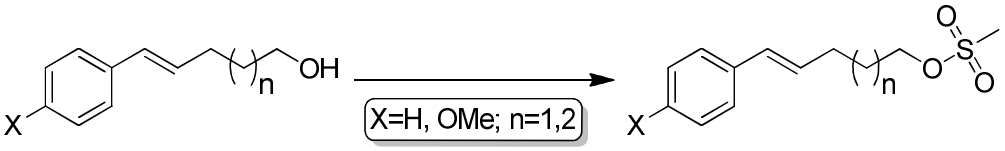
(*E*)-5-Phenylpent-4-en-1-ol 230[124]



5-Phenylpent-4-yn-1-ol **229** (3.00 g, 18.7 mmol) in THF (10 mL) was reacted with $LiAlH_4$ (2.50 g, 65.5 mmol) in THF (27 mL), in accordance with general method D. After work-up, (*E*)-5-phenylpent-4-en-1-ol **230** (3.04 g, 18.7 mmol, 100%) was isolated as an orange oil, as an inseparable 99:1 (*E*:*Z*) mixture of geometrical isomers. **230** was characterised and used without further purification. δ_H (400 MHz, $CDCl_3$) 7.35-7.26 (4H, m, 4 x CH, Ph), 7.21-7.17 (1H, m, CH, Ph), 6.41 (1H, d, *J* = 15.8 Hz,

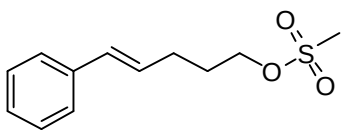
PhCH=), 6.22 (1H, dt, *J* = 15.8, 6.9 Hz, PhCH=C*H*), 3.68 (2H, t, *J* = 6.5 Hz, CH_2OH), 2.30 (2H, dq, *J* = 1.3, 7.2 Hz, =CHCH_2), 1.74 (2H, p, *J* = 6.9 Hz, CH_2), 1.62 (1H, br s, OH), ppm; δ_C(100 MHz, $CDCl_3$) 137.7 (C, Ph), 130.4 (PhCH=), 130.1 (PhCH=*C*H), 128.5 (2 x CH, Ph), 127.0 (CH, Ph), 126.0 (2 x CH, Ph), 62.4 (CH_2OH), 32.3 (CH_2), 29.4 (=CH*C*H_2) ppm.

General method E: Mesylation of primary alcohols.



To a stirred solution of the primary alcohol (1.0 M equiv) and Et_3N (2.0 M equiv) in CH_2Cl_2 (0.3 M) was added methanesulfonyl chloride (1.5 M equiv). The resulting mixture was stirred at room temperature for 15 hours, whereupon the solvent was removed *in vacuo*. The mixture was hydrolysed with water and then extracted twice with EtOAc. The combined organic extracts were washed with 0.2 M HCl, and then brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography afforded the title compounds. Where appropriate, the crude products were characterised and used without further purification.

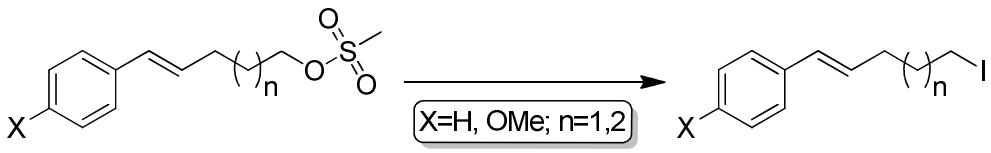
(*E*)-5-Phenylpent-4-enyl methanesulfonate 231



(*E*)-5-Phenylpent-4-en-1-ol **230** (2.60 g, 16.0 mmol), Et_3N (4.50 mL, 32.1 mmol) and methanesulfonyl chloride (1.90 mL, 24.0 mmol) were reacted together in CH_2Cl_2 (50 mL), in accordance with general method E. After work-up, purification on silica gel (20% EtOAc in petroleum ether) afforded (*E*)-5-phenylpent-4-enyl methanesulfonate

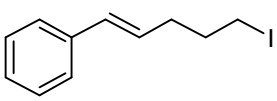
231 (2.83 g, 11.8 mmol, 73%) as a yellow oil. R_f = 0.29 (40% EtOAc in petroleum ether); ν_{max} (neat) 3381, 2940, 1732, 1467, 1349, 1170, 924, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36-7.18 (5H, m, 5 x CH, Ph), 6.43 (1H, d, *J* = 15.8 Hz, PhCH=) 6.17 (1H, dt, *J* = 15.8, 6.9 Hz, PhCH=C*H*), 4.29-4.25 (2H, m, CH_2OMs), 2.99 (3H, s, CH_3), 2.39-2.31 (2H, m, =CHCH_2), 1.98-1.88 (2H, m, =CHCH_2CH_2) ppm; δ_C (75 MHz, $CDCl_3$) 136.7 (C, Ph), 130.8 (PhCH=), 128.0 (2 x CH, Ph), 127.7 (PhCH=*C*H), 126.6 (CH, Ph), 125.4 (2 x CH, Ph), 68.7 (CH_2OMs), 36.8 (CH_3), 28.2 (2 x CH_2) ppm; MS (ES^+) *m/z* 241 [MH^+]; HRMS (ES^+) calcd. for $C_{12}H_{16}NaO_3S$ [MNa^+]: 263.0718; found 263.0705.

General method F: Mesylate displacement with sodium iodide.



Sodium iodide (2.0 M equiv) was added to a stirred solution of the mesylate (1.0 M equiv) in acetone (0.2 M). The resulting mixture was heated at reflux temperature for 3-4 hours then cooled to room temperature, whereupon the solvent was removed *in vacuo*. The crude mixture was taken up in Et_2O, filtered and washed several times with Et_2O. The combined organic washings were concentrated *in vacuo* to give the crude product. Purification by column chromatography afforded the title compounds.

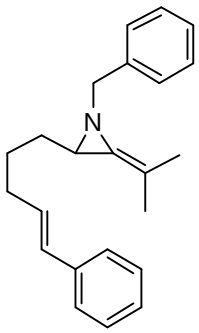
1-((*E*)-5-Iodopent-1-enyl)benzene 232



Sodium iodide (3.27 g, 21.8 mmol) and (*E*)-5-phenylpent-4-enyl methanesulfonate **231** (2.62 g, 10.9 mmol) were reacted together in acetone (55 mL) for 4 hours, in accordance with general

method F. After work-up, purification on silica (2% EtOAc in petroleum ether) afforded 1-((*E*)-5-iodopent-1-enyl)benzene **232** (2.84 g, 10.4 mmol, 96%) as a slightly orange oil, as an inseparable 99:1 (*E*:*Z*) mixture of geometrical isomers. R_f = 0.27 (4% EtOAc in petroleum ether); ν_{max} (neat) 3023, 2926, 2828, 1597, 1491, 1446, 1214, 1165, 962, 739, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36-7.17 (5H, m, 5 x CH, Ph), 6.45 (1H, d, *J* = 15.8 Hz, PhCH=), 6.14 (1H, dt, *J* = 15.8, 7.0 Hz, PhCH=C*H*), 3.24-3.20 (2H, m, CH_2I), 2.36-2.29 (2H, m, =CHCH_2), 2.03-1.94 (2H, m, =CHCH_2CH_2) ppm; δ_C (75 MHz, $CDCl_3$) 137.4 (C, Ph), 131.3 (PhCH=), 128.6 (2 x CH, Ph), 128.3 (PhCH=*C*H), 127.2 (CH, Ph), 126.0 (2 x CH, Ph), 33.6 (=CH*C*H_2), 32.9 (=CHCH_2*C*H_2), 6.4 (CH_2I) ppm; MS (ES^+) *m/z* 272 [MH^+].

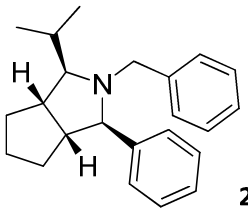
1-Benzyl-2-((*E*)-5-phenylpent-4-enyl)-3-(propan-2-ylidene)aziridine 204



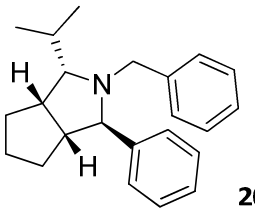
1-Benzyl-2-(propan-2-ylidene)aziridine **177** (198 mg, 1.14 mmol) was reacted with TMEDA (0.21 mL, 1.37 mmol) and *s*-BuLi (1.4 M in hexanes, 1.55 mL, 2.17 mmol) in THF (10 mL) in accordance with general method B, then a solution of 1-((*E*)-5-iodopent-1-enyl)benzene **232** (373 mg, 1.37 mmol) in THF (1 mL) was added. After work-up, purification on silica (0.5% Et_3N and 2% EtOAc in petroleum ether) afforded 1-benzyl-2-((*E*)-5-phenylpent-4-enyl)-3-(propan-2-ylidene)aziridine **204** (197 mg, 0.62 mmol, 54%) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 7.37-7.24 (9H, m, 9 x CH, Ph), 7.20-7.15 (1H, m, CH, Ph), 6.28 (1H, d, *J* = 15.8 Hz, PhCH=), 6.11 (1H, dt, *J* = 15.8, 6.8 Hz, PhCH=C*H*), 4.17 (1H, d, *J* = 13.3 Hz, PhC*H*H), 3.18 (1H, d, *J* = 13.3 Hz, 1 x PhCH*H*), 2.14-2.10 (2H, m, =CHCH_2), 2.02 (1H, t, *J* = 5.8 Hz, aziridine CH), 1.77 (3H, s, CH_3), 1.74 (3H, s, CH_3), 1.66-1.38 (4H, m, 2 x CH_2) ppm; δ_C (100 MHz, $CDCl_3$) 139.1 (C, Ph),

137.9 (C, Ph), 130.7 (PhCH=*C*H), 130.0 (=C-N), 129.9 (PhCH=), 128.5 (2 x CH, Ph), 128.4 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.1 (CH, Ph), 126.8 (CH, Ph), 125.9 (2 x CH, Ph), 104.0 (=*C*$(CH_3)_2$), 62.1 ($PhCH_2$), 44.1 (aziridine CH), 32.7 (CH*C*H_2), 31.9 (=CH*C*H_2), 27.2 (=CHCH_2*C*H_2), 20.7 (CH_3), 19.1 (CH_3) ppm.

(1*R*,3*R*,3a*R*,6a*S*)- and (1*S*,3*R*,3a*R*,6a*S*)-2-Benzyl-octahydro-1-isopropyl-3-phenylcyclopenta[c]pyrrole 205



205a



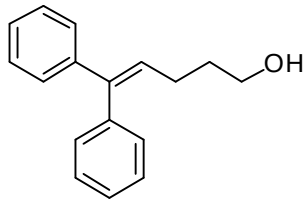
205b

To a stirred solution of 1-benzyl-2-((*E*)-5-phenylpent-4-enyl)-3-(propan-2-ylidene)aziridine **204** (178 mg, 0.56 mmol) in CH_2Cl_2 (11 mL) at -30 °C was added $BF_3{\cdot}OEt_2$ (0.11 mL, 0.84 mmol). The resulting mixture was allowed to warm slowly to room temperature for 15 hours, and then quenched by the addition of saturated $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product, which was taken up in THF (4 mL) and added to a stirred solution of $NaBH_4$ (65 mg, 1.68 mmol) in glacial AcOH (10 mL). The resulting mixture was stirred at room temperature for 15 hours, and then basified by the addition of 2M NaOH solution. The mixture was extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (0.5-1.5% Et_2O in petroleum ether) afforded successively (1*R*,3*R*,3a*R*,6a*S*)- 2-benzyl-octahydro-1-isopropyl-3-phenylcyclopenta[c]pyrrole **205a** (30.7 mg, 0.10 mmol, 17%) as a

colourless oil and (1*S*,3*R*,3a*R*,6a*S*)-2-benzyl-octahydro-1-isopropyl-3-phenylcyclopenta[c]pyrrole **205b** (55.4 mg, 0.17 mmol, 31%) as a yellow oil. Compound **205a**: R_f = 0.18 (1.5% EtOAc in petroleum ether); ν_{max} (neat) 2950, 1718, 1453, 1246, 1166, 699 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 7.42 (2H, d, *J* = 7.1, Hz, 2 x CH, Ph), 7.35 (2H, t, *J* = 7.6 Hz, 2 x CH, Ph), 7.25-7.22 (3H, m, 3 x CH, Ph), 7.18-7.15 (1H, m, CH, Ph), 7.03 (2H, d, *J* = 7.1 Hz, 2 x CH, Ph), 3.62 (1H, d, *J* = 14.5 Hz, PhC*H*H), 3.29 (1H, d, *J* = 14.5 Hz, 1 x PhCH*H*), 3.04 (1H, d, *J* = 8.7 Hz, PhCH), 2.31-2.26 (1H, m, CH), 2.23 (1H, dd, *J* = 3.5, 6.5 Hz, *i*-PrCH), 2.15 (1H, q, *J* = 8.4 Hz, CH), 1.96-1.89 (1H, m, C*H*$(CH_3)_2$), 1.58-1.25 (6H, m, 3 x CH_2), 0.88 (3H, d, *J* = 6.7 Hz, CH(C*H*$_3)_2$), 0.85 (3H, d, *J* = 7.0 Hz, CH(C*H*$_3)_2$) ppm; δ_C (150 MHz, DMSO-d_6) 144.3 (C, Ph), 137.5 (C, Ph), 129.5 (2 x CH, Ph), 128.9 (2 x CH, Ph), 128.2 (2 x CH, Ph), 128.1 (2 x CH, Ph), 127.5 (CH, Ph), 127.1 (CH, Ph), 74.8 (*i*-PrCH), 74.4 (PhCH), 54.0 ($PhCH_2$), 52.8 (CH), 41.3 (CH), 33.9 (CH_2), 29.5 (CH_2), 27.8 (*C*H$(CH_3)_2$), 25.0 (CH_2), 20.6 (CH(*C*H$_3)_2$), 15.6 (CH(*C*H$_3)_2$) ppm; MS (ES^+) *m/z* 320 [MH^+]; HRMS (ES^+) calcd. for $C_{23}H_{30}N$ [MH^+]: 320.2373; found 320.2373. Compound **205b**; R_f = 0.21 (3% EtOAc in petroleum ether); ν_{max} (neat) 2952, 1690, 1452, 697 cm^{-1}; δ_H(400 MHz, C_6H_6) 7.33 (2H, d, *J* = 7.5 Hz, 2 x CH, Ph), 7.20 (2H, t, *J* = 7.5 Hz, 2 x CH, Ph), 7.15-7.04 (4H, m, 4 x CH, Ph), 6.98 (2H, d, *J* = 7.5 Hz, 2 x CH, Ph), 3.92 (1H, d, *J* = 3.9 Hz, PhCH), 3.76 (1H, d, *J* = 14.5 Hz PhC*H*H), 3.19-3.13 (2H, m, 1 x PhCH*H*, *i*-PrCH), 2.57-2.51 (1H, m, CH), 2.47-2.39 (1H, m, CH), 1.90-1.77 (3H, m, C*H*$(CH_3)_2$, cp ring C*H*H, cp ring C*H*H), 1.68-1.60 (1H, m, cp ring C*H*H), 1.52-1.43 (1H, m, cp ring CH*H*), 1.40-1.24 (2H, m, cp ring CH*H*, cp ring CH*H*), 1.06 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3)_2$), 0.99 (3H, d, *J* = 7.0 Hz, CH(C*H*$_3)_2$) ppm; δ_C (100

MHz, C_6D_6) 141.9 (C, Ph), 139.8 (C, Ph), 128.0 (2 x CH, Ph), 127.0 (2 x CH, Ph), 126.9 (2 x CH, Ph), 126.6 (2 x CH, Ph), 125.4 (CH, Ph), 125.3 (CH, Ph), 70.8 (CH), 66.7 (CH), 49.6 ($PhCH_2$), 48.8 (CH), 46.2 (CH), 33.3 (CH_2), 28.4 (CH_2), 27.1 (CH_2), 27.1 ($CH(CH_3)_2$), 19.2 ($CH(CH_3)_2$), 17.4 ($CH(CH_3)_2$), ppm; MS (ES^+) *m/z* 320 [MH^+]; HRMS (ES^+) calcd. for $C_{23}H_{30}N$ [MH^+]: 320.2373; found 320.2370.

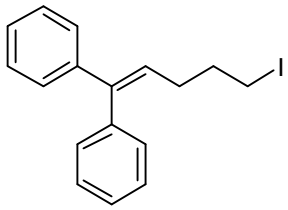
5,5-Diphenylpent-4-en-1-ol 237[127]



To a solution of phenylmagnesium bromide (freshly prepared from magnesium turnings (770 mg, 31.0 mmol) and bromobenzene (3.30 mL, 31.0 mmol) in Et_2O (30 mL)) was added a solution of δ-valerolactone (1.00 mL, 10.3 mmol) in Et_2O (5 mL). The resulting mixture was heated at reflux temperature for 2 hours, and then cooled in an ice bath to 0 °C whereupon the reaction was quenched by the cautious addition of saturated, aqueous NH_4Cl solution (30 mL). The mixture was extracted with Et_2O (3 x 60 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a yellow oil, which solidified on standing. The crude diol was dissolved in EtOH (100 mL) and treated with 2M HCl. The mixture was heated at reflux temperature for 1 hour, and then cooled to room temperature whereupon the solvent was removed *in vacuo*. The aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo* to give the crude product. Purification on silica (20% EtOAc in petroleum ether) afforded 5,5-diphenylpent-4-en-1-ol **237** (731 mg, 3.07 mmol, 30%). δ_H (400 MHz, $CDCl_3$) 7.38-7.16 (10H, m, 10 x CH, Ar), 6.09 (1H, t, *J* = 7.5 Hz, =CH),

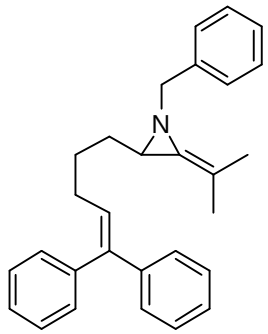
3.61 (2H, t, *J* = 6.5 Hz, CH_2OH), 2.22-2.17 (2H, m, =CHC*H*$_2$), 1.73- 1.66 (2H, m, =CHCH$_2$C*H*$_2$), 1.34 (1H, br s, OH) ppm; δ_C (100 MHz, $CDCl_3$) 142.6 (C, Ar), 142.3 (C, Ar), 140.1 (Ph_2C=), 129.9 (2 x CH, Ar), 129.0 (=CH), 128.3 (2 x CH, Ar), 128.2 (2 x CH, Ar), 127.2 (2 x CH, Ar), 127.0 (CH, Ar), 127.0 (CH, Ar), 62.4 (CH_2OH), 32.9 (=CHCH$_2$*C*H$_2$), 26.1 (=CH*C*H$_2$) ppm.

5-Iodo-1,1-diphenylpent-1ene 238[128]



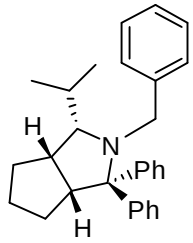
To a stirred solution of triphenylphosphine (3.43 g, 13.1 mmol) and imidazole (1.20 g, 17.4 mmol) in THF (20 mL) was added iodine (3.32 g, 13.1 mmol). After 5 minutes stirring, a solution of 5,5-diphenylpent-4-en-1-ol **237** in THF (5 mL) was added dropwise. The resulting mixture was stirred at room temperature for 15 hours. Water (20 mL) was added and the mixture extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (1% EtOAc in petroleum ether) afforded 5-iodo-1,1-diphenylpent-1ene **238** (2.46 g, 7.06 mmol, 65%) as a pale, yellow oil. δ_H (400 MHz, $CDCl_3$) 7.38-7.15 (10H, m, 10 x CH, Ph), 6.02 (1H, t, *J* = 7.5 Hz, =CH), 3.14 (2H, t, *J* = 7.1 Hz, CH_2I), 2.24-2.18 (2H, m, =CHC*H*$_2$), 2.00-1.93 (2H, m, =CHCH$_2$C*H*$_2$) ppm; δ_C (100 MHz, $CDCl_3$) 143.1 (C, Ph), 142.5 (C, Ph), 139.9 (Ph_2C=), 129.9 (2 x CH, Ph), 128.3 (2 x CH, Ph), 128.2 (2 x CH, Ph), 127.4 (=CH), 127.3 (2 x CH, Ph), 127.1 (CH, Ph), 127.1 (CH, Ph), 34.0 (=CHCH$_2$*C*H$_2$), 30.8 (=CH*C*H$_2$), 6.0 (CH_2I) ppm.

1-Benzyl-2-(5,5-diphenylpent-4-enyl)-3-(propan-2-ylidene)aziridine 239



1-Benzyl-2-(propan-2-ylidene)aziridine **177** (201 mg, 1.16 mmol) was reacted with TMEDA (0.21 mL, 1.39 mmol) and *s*-BuLi (1.58 mL, 2.21 mmol) in THF (10 mL) in accordance with general method B, then a solution of 5-iodo-1,1-diphenylpent-1ene **238** (486 mg, 1.39 mmol) in THF (1 mL) was added. After work-up, purification on silica (1% Et_3N in petroleum ether) afforded 1-benzyl-2-(5,5-diphenylpent-4-enyl)-3-(propan-2-ylidene)aziridine **239** (188 mg, 0.48 mmol, 41%) as a yellow oil. R_f = 0.30 (10% EtOAc in petroleum ether); ν_{max} (neat) 2919, 1796, 1596, 1493, 1442, 1129, 1028, 760, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35-7.10 (15H, m, 15 x CH, Ph), 5.97 (1H, t, *J* = 7.5 Hz, =CH), 4.10 (1H, d, *J* = 13.4 Hz, PhC*H*H), 3.15 (1H, d, *J* = 13.4 Hz, PhCH*H*), 2.04 (2H, q, *J* = 7.4 Hz, =CHCH_2), 1.93 (1H, t, *J* = 5.8 Hz, aziridine CH), 1.73 (3H, s, CH_3), 1.71 (3H, s, CH_3), 1.58-1.35 (4H, m, 2 x CH_2) ppm; δ_C (100 MHz, $CDCl_3$) 142.8 (C, Ph), 141.7 (C, Ph), 140.2 (C, Ph), 139.1 (Ph_2C=), 130.0 (=C-N), 129.9 (2 x CH, Ar), 129.8 (=CH), 128.5 (2 x CH, Ph), 128.3 (2 x CH, Ph), 128.2 (2 x CH, Ph), 128.1 (2 x CH, Ph), 127.2 (2 x CH, Ph), 127.1 (CH, Ph), 126.9 (CH, Ph), 126.8 (CH, Ph), 104.0 (=*C*$(CH_3)_2$), 62.0 ($PhCH_2$), 44.0 (aziridine CH), 31.9 (CH*C*H_2), 29.4 (=CH*C*H_2), 27.8 (=CHCH_2*C*H_2), 20.6 (CH_3), 19.1 (CH_3) ppm; MS (ES^+) *m/z* 394 [MH^+]; HRMS (ES^+) calcd. for $C_{29}H_{32}N$ [MH^+]: 394.2529; found 394.2539.

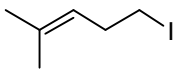
(3*R*,3a*S*,6a*R*)-2-Benzyl-octahydro-3-isopropyl-1,1-diphenylcyclopenta[*c*]pyrrole 244



To a stirred solution of 1-benzyl-2-(5,5-diphenylpent-4-enyl)-3-(propan-2-ylidene)aziridine **239** (169 mg, 0.43 mmol) in CH_2Cl_2 (8.5 mL) at -30 °C was added $BF_3{\cdot}OEt_2$ (0.08 mL, 0.65 mmol). The resulting mixture was allowed to warm slowly to room temperature for 15 hours, and then quenched by the addition of saturated $NaHCO_3$ solution (10 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product, which was taken up in THF (4 mL) and added to a stirred solution of $NaBH_4$ (49 mg, 1.28 mmol) in glacial AcOH (10 mL). The resulting mixture was stirred at room temperature for 15 hours, and then basified by the addition of 2M NaOH solution. The mixture was extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (2% Et_2O in petroleum ether) afforded (3*R*,3a*S*,6a*R*)-2-benzyl-octahydro-3-isopropyl-1,1-diphenylcyclopenta[*c*]pyrrole **244** (39.0 mg, 0.10 mmol, 23%) as a white solid. mp 119-122 °C (from Et_2O/petroleum ether); R_f = 0.36 (1% Et_2O in petroleum ether); ν_{max} (film) 2956, 1601, 1493, 1443, 1262, 1028, 909, 734 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.34-7.12 (15H, m, 15 x CH, Ph), 4.29 (1H, d, *J* = 16.0 Hz, 1 x PhC*H*H), 3.68 (1H, d, *J* = 16.0 Hz, 1 x PhCH*H*), 3.28-3.27 (1H, m, *i*-PrCH), 3.22-3.17 (1H, m, CH), 2.75-2.71 (1H, m, CH), 2.01-1.96 (1H, m, cp ring C*H*H), 1.74-1.69 (1H, m, cp ring C*H*H), 1.58-1.36 (4H, m, C*H*$(CH_3)_2$ and cp ring CH*H*, cp ring CH*H*, cp ring C*H*H), 1.12-1.08 (1H, m, cp ring CH*H*), 0.57 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3)_2$), 0.11

(3H, d, J = 6.8 Hz, CH(CH_3)$_2$) ppm; δ_C (150 MHz, $CDCl_3$) 147.1 (C, Ph), 146.8 (C, Ph), 141.0 (C, Ph), 129.0 (2 x CH, Ph), 128.6 (2 x CH, Ph), 128.2 (2 x CH, Ph), 127.5 (2 x CH, Ph), 127.3 (2 x CH, Ph), 127.1 (2 x CH, Ph), 126.2 (CH, Ph), 126.2 (CH, Ph), 125.7 (CH, Ph), 76.1 (*C*Ph$_2$), 73.0 (CH), 55.4 (CH), 50.0 (PhCH$_2$), 41.6 (CH), 34.0 (CH$_2$), 31.3 (CH$_2$), 28.2 (*C*H(CH$_3$)$_2$), 26.2 (CH$_2$), 20.5 (CH(*C*H$_3$)$_2$), 17.0 (CH(*C*H$_3$)$_2$), ppm; MS (ES$^+$) *m/z* 396 [MH$^+$]; HRMS (ES$^+$) calcd. for $C_{29}H_{34}NO$ [MH$^+$]: 396.2686; found 396.2683.

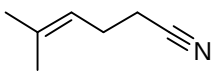
5-Iodo-2-methylpent-2-ene 246[129]



To a solution of methylmagnesium iodide (freshly prepared from magnesium turnings (2.56 g, 0.10 mol) and iodomethane (6.47 mL, 0.10 mol) in Et_2O (48 mL)) was added dropwise to a stirred solution of cyclopropyl methyl ketone (10.0 mL, 0.10 mol) in Et_2O (12 mL). The Grignard adduct thus formed was added slowly to a stirred solution of concentrated H_2SO_4 (18 mL) and water (36 mL) at a rate to maintain the temperature below 10°C. After the addition was complete, stirring was continued for 30 minutes. The mixture was extracted three times with Et_2O (3 x 60 mL). The combined organic extracts were decolourised with 5% aqueous $NaHSO_3$ solution (100 ml), neutralised with 5% aqueous $NaHCO_3$ solution (100 mL), washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by bulb-to-bulb distillation (50 °C, 0.4 MmHg) afforded 5-iodo-2-methylpent-2-ene **246** (16.1 g, 76.6 mmol, 77%) as a dark, orange oil. δ_H (400 MHz, $CDCl_3$) 5.09 (1H, t, J = 7.1 Hz, =CH), 3.11 (2H, t, J = 7.4 Hz, CH_2I), 2.57 (2H, q, J = 7.3 Hz, =CHCH_2), 1.70 (3H, s, CH_3), 1.62 (3H, s, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 134.5

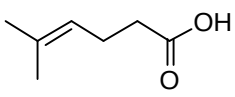
($(CH_3)_2C$=), 123.1 (=CH), 32.6 (=CHCH_2), 25.7 (CH_3), 18.0 (CH_3), 6.1 (CH_2I) ppm.

5-Methylhex-4-enenitrile 247[130]



To a stirred solution of 5-iodo-2-methylpent-2-ene **246** (6.00 g, 28.6 mmol) in DMSO (20 mL) was added sodium cyanide (2.16 g, 42.8 mmol). The resulting mixture was heated at 80°C for 15 hours and then cooled to room temperature whereupon the mixture was diluted with water. The mixture was extracted three times with petroleum ether (3 x 40 mL). The combined organic extracts were washed with water (60 mL) and then brine (60 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 5-methylhex-4-enenitrile **247** (2.27 g, 20.8 mmol, 73%) as a colourless oil. The crude oil was characterised and used without further purification. δ_H (400 MHz, $CDCl_3$) 5.16-5.12 (1H, m, =CH), 2.35-2.34 (4H, m, 2 x CH_2), 1.73 (3H, s, CH_3), 1.65 (3H, s, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 135.6 ($(CH_3)_2C$=), 120.2 (=CH), 119.7 (C≡N), 25.7 (CH_3), 24.1 (CH_2C≡N), 17.8 (CH_3), 17.7 (=CHCH_2) ppm.

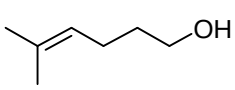
5-Methylhex-4-enoic acid 248[130]



To a stirred solution of 5-methylhex-4-enenitrile **247** (2.18 g, 20.0 mmol) in ethylene glycol (16 mL) and water (2 mL) was added KOH (3.69 g, 65.8 mmol). The resulting mixture was heated at 140 °C for 15 hours, cooled to room temperature and then diluted with water. The mixture was acidified to pH 1 with concentrated HCl and then extracted with Et_2O (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by bulb-to-bulb distillation (90 °C, 0.4 MmHg) afforded 5-methylhex-4-enoic acid **248** (2.56 g,

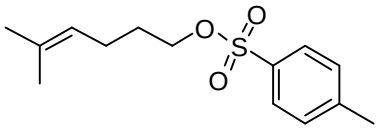
20.0 mmol, 100 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 8.61 (1H, br s, CO_2H), 5.11-5.07 (1H, m, =CH), 2.38-2.27 (4H, m, 2 x CH_2), 1.68 (3H, s, CH_3), 1.61 (3H, s, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 179.6 (C=O), 133.4 ($(CH_3)_2C$=), 122.1 (=CH), 34.3 (CH_2CO_2H), 25.7 (CH_3), 23.3 (=CHCH_2), 17.6 (CH_3) ppm.

5-Methylhex-4-en-1-ol 249[130]



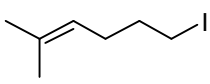
A solution of 5-methylhex-4-enoic acid **248** (2.55 g, 19.9 mmol) in Et_2O (10 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (906 mg, 23.9 mmol) in Et_2O (60 mL) at 0 °C. The resulting mixture was allowed to gradually return to room temperature for 15 hours. The mixture was cooled to 0°C and then cautiously hydrolysed by the addition of water. The mixture was poured into a saturated, aqueous potassium sodium tartrate solution (150 mL) and stirred at room temperature for 30 minutes. The mixture was extracted with Et_2O (3 x 150 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 5-methylhex-4-en-1-ol **249** (1.94 g, 17.0 mmol, 85%) as a colourless oil. The crude oil was characterised and used without further purification. δ_H (400 MHz, $CDCl_3$) 5.16-5.11 (1H, m, =CH), 3.66-3.62 (2H, m, CH_2OH), 2.09-2.04 (2H, m, =CHCH_2), 1.69 (3H, s, CH_3), 1.64-1.57 (6H, m, =CHCH_2CH_2, CH_3 and OH) ppm; δ_C (100 MHz, $CDCl_3$) 132.2 ($(CH_3)_2C$=), 123.9 (=CH), 62.7 (CH_2OH), 32.8 (=CHCH_2CH_2), 25.7 (CH_3), 24.4 (=CHCH_2), 17.6 (CH_3) ppm.

5-Methylhex-4-enyl 4-methylbenzenesulfonate 250[130]



p-Toluenesulfonyl chloride (3.94g, 20.3 mmol) was added to a stirred solution of 5-methylhex-4-en-1-ol **249** (1.78 g, 15.6 mmol) in pyridine (12 mL) at 0 °C. The resulting mixture was stirred at room temperature for 3 hours, then diluted with water and extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed successively with 0.2M HCl (50 mL), saturated aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 5-methylhex-4-enyl 4-methylbenzenesulfonate **250** (3.67 g, 13.7 mmol, 88%) as a slightly pink oil. The crude oil was characterised and used without further purification. δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* = 8.1 Hz, 2 x CH, Ph), 7.34 (2H, d, *J* = 8.1 Hz, 2 x CH, Ph), 4.97 (1H, t, *J* = 7.2 Hz, =CH), 4.02 (2H, t, *J* = 6.4 Hz, CH_2OTs), 2.45 (3H, s, CCH_3, Ph), 2.00 (2H, q, *J* = 7.2 Hz, $=CHCH_2$), 1.70-1.63 (5H, m, $=CHCH_2CH_2$ and CH_3), 1.54 (3H, s, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 144.6 (SO_2C, Ph), 133.3 (CCH_3, Ph), 133.2 ($(CH_3)_2C=$), 129.8 (2 x CH, Ph), 127.9 (2 x CH, Ph), 122.4 (=CH), 70.1 (CH_2OTs), 28.9 ($=CHCH_2CH_2$), 25.7 (CH_3), 23.8 ($=CHCH_2$), 21.6 (CCH_3, Ph), 17.7 (CH_3) ppm.

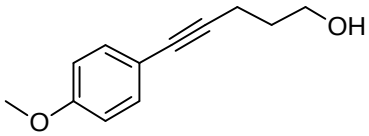
6-Iodo-2-methylhex-2-ene 251[130]



Sodium iodide (5.95 g, 39.7 mmol) was added to a stirred solution of 5-methylhex-4-enyl 4-methylbenzenesulfonate **250** (3.55 g, 13.2 mmol) in acetone (20 mL). The resulting mixture was heated at 50 °C for 15 hours and then cooled to room temperature. The mixture was diluted with water and then extracted with EtOAc (3 x 30 mL). The combined organic extracts were decolourised with 5% aqueous $NaHSO_3$ solution (50 mL), washed

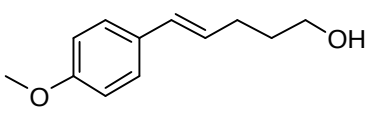
successively with 5% aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (100% petroleum ether) afforded 6-iodo-2-methylhex-2-ene **251** (1.30 g, 5.80 mmol, 44%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.06 (1H, t, *J* = 7.2 Hz, =CH), 3.18 (2H, t, *J* = 6.9 Hz, CH_2I), 2.09 (2H, q, *J* = 7.1 Hz, =CHC*H*$_2$), 1.86 (2H, p, *J* = 7.0 Hz, =CHCH$_2$C*H*$_2$), 1.69 (3H, s, CH_3), 1.64 (3H, s, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 133.2 ((CH$_3$)$_2$*C*=), 122.4 (=CH), 33.7 (=CHCH$_2$*C*H$_2$), 28.8 (=CH*C*H$_2$), 25.8 (CH_3), 17.9 (CH_3), 6.9 (CH_2I) ppm.

5-(4-Methoxyphenyl)pent-4-yn-1-ol 254[133]



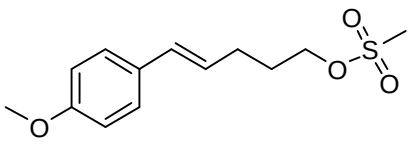
Tetrakis(triphenylphosphine)palladium(0) (485 mg, 0.42 mmol), 4-pentynol (2.00 mL, 21.0 mmol), 4-iodoanisole (10.0 g, 41.9 mmol), diisopropylamine (17.6 mL, 0.13 mol) and CuI (40.0 mg, 0.21 mmol) were reacted together in THF (42 mL), in accordance with general method C. After work-up, purification on silica gel (35% EtOAc in petroleum ether) afforded 5-(4-methoxyphenyl)pent-4-yn-1-ol **254** (2.98 g, 15.7 mmol, 75%) as an orange semi-solid. δ_H (300 MHz, $CDCl_3$) 7.33 (2H, d, *J* = 8.9 Hz, 2 x CH, Ph), 6.81 (2H, d, *J* = 8.9 Hz, 2 x CH, Ph), 3.82 (2H, t, *J* = 6.1 Hz, CH_2OH), 3.80 (3H, s, OCH_3), 2.52 (2H, t, *J* = 6.9 Hz, ≡CC*H*$_2$), 1.85 (2H, p, *J* = 6.5 Hz, ≡CCH$_2$C*H*$_2$), 1.57 (1H, br s, OH) ppm; δ_C (150 MHz, $CDCl_3$) 159.1 (*C*OCH_3, Ph), 132.9 (2 x CH, Ph), 115.9 (C, Ph), 113.8 (2 x CH, Ph), 87.7 (C≡), 80.9 (C≡), 61.9 (CH_2OH), 55.3 (OCH_3), 31.5 (≡CCH$_2$*C*H$_2$), 16.0 (≡C*C*H$_2$) ppm.

(*E*)-5-(4-Methoxyphenyl)pent-4-en-1-ol[135]



5-(4-Methoxyphenyl)pent-4-yn-1-ol **254** (2.97 g, 15.6 mmol) in THF (5 mL) was reacted with $LiAlH_4$ (2.07 g, 54.6 mmol) in THF (25 mL), in accordance with general method D. After work-up, purification on silica gel (10-40% EtOAc in petroleum ether) afforded (*E*)-5-(4-methoxyphenyl)pent-4-en-1-ol **255** (1.96 g, 10.3 mmol, 66%) as a white solid. δ_H (400 MHz, $CDCl_3$) 7.27 (2H, d, *J* = 8.8 Hz, 2 x CH, Ph), 6.84 (2H, d, *J* = 8.8 Hz, 2 x CH, Ph), 6.36 (1H, d, *J* = 15.8 Hz, PhCH=), 6.08 (1H, dt, *J* = 15.8, 7.0 Hz, PhCH=C*H*), 3.80 (3H, s, OCH_3), 3.72-3.69 (2H, m, CH_2OH), 2.31-2.26 (2H, m, CH_2), 1.78-1.71 (2H, m, =CHCH_2), 1.35 (1H, br s, OH) ppm; δ_C(100 MHz, $CDCl_3$) 158.8 (*C*OCH_3, Ph), 130.5 (C, Ph), 129.8 (PhCH=), 127.9 (PhCH=*C*H), 127.1 (2 x CH, Ph), 114.0 (2 x CH, Ph), 62.5 (*C*H_2OH), 55.3 (OCH_3), 32.4 (CH_2), 29.3 (=CH*C*H_2) ppm.

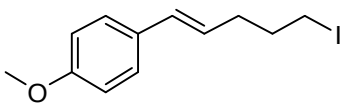
(*E*)-5-(4-Methoxyphenyl)pent-4-enyl methanesulfonate 256[136]



(*E*)-5-(4-Methoxyphenyl)pent-4-en-1-ol **255** (1.96 g, 10.3 mmol), Et_3N (2.89 mL, 20.6 mmol) and methanesulfonyl chloride (1.20 mL, 15.5 mmol) were reacted together in CH_2Cl_2 (35 mL), in accordance with general method E. After work-up, (*E*)-5-(4-methoxyphenyl)pent-4-enyl methanesulfonate **256** (2.54 g, 9.40 mmol, 91%), as a crude, white solid was characterised and used without further purification. δ_H (400 MHz, $CDCl_3$) 7.27 (2H, d, *J* = 8.8 Hz, 2 x CH, Ph), 6.84 (2H, d, *J* = 8.8 Hz, 2 x CH, Ph), 6.38 (1H, d, *J* = 15.8 Hz, PhCH=), 6.02 (1H, dt, *J* = 15.8, 7.0 Hz, PhCH=C*H*), 4.27 (2H, t, *J* = 6.4 Hz, CH_2OMs), 3.80 (3H, s, CH_3), 3.00 (3H, s, CH_3), 2.36-2.30 (2H, m, =CHCH_2), 1.96-1.89 (2H,

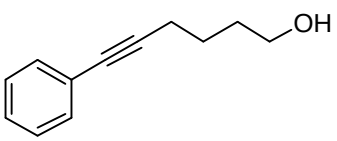
m, =CHCH$_2$C*H*$_2$) ppm; δ_C (100 MHz, $CDCl_3$) 159.0 (*C*OCH$_3$, Ph), 130.8 (PhCH=), 130.1 (C, Ph), 127.2 (2 x CH, Ph), 126.1 (PhCH=*C*H), 114.0 (2 x CH, Ph), 69.4 (CH_2OMs), 55.3 (OCH_3), 37.4 (SO_2CH_3), 28.9 (=CHCH$_2$C*H*$_2$), 28.8 (CH_2) ppm.

1-((*E*)-5-Iodopent-1-enyl)-4-methoxybenzene 257[131]



Sodium iodide (2.72 g, 18.1 mmol) and (*E*)-5-(4-methoxyphenyl)pent-4-enyl methanesulfonate **256** (2.45 g, 9.06 mmol) were reacted together in acetone (45 mL) for 3 hours, in accordance with general method F. After work-up, purification on silica (4% EtOAc in petroleum ether) afforded 1-((*E*)-5-iodopent-1-enyl)-4-methoxybenzene **257** (2.31 g, 7.65 mmol, 84%) as a colourless oil, which solidified on standing. δ_H (400 MHz, $CDCl_3$) 7.27 (2H, d, *J* = 8.8 Hz, 2 x CH, Ph), 6.83 (2H, d, *J* = 8.8 Hz, 2 x CH, Ph), 6.39 (1H, d, *J* = 15.8 Hz, PhCH=), 5.99 (1H, dt, *J* = 15.8, 7.0 Hz, PhCH=C*H*), 3.79 (3H, s, OCH_3), 3.22 (2H, t, *J* = 6.9 Hz, CH_2I), 2.32-2.27 (2H, m, =CCH_2), 1.97 (2H, p, *J* = 7.0 Hz, =CCH$_2$C*H*$_2$) ppm; δ_C (100 MHz, $CDCl_3$) 158.9 (*C*OCH$_3$, Ph), 130.7 (PhCH=), 130.3 (C, Ph), 127.1 (2 x CH, Ph), 126.1 (PhCH=*C*H), 114.0 (2 x CH, Ph), 55.3 (OCH_3), 33.5 (=C*C*H$_2$), 33.0 (=CCH$_2$*C*H$_2$), 6.5 (CH_2I) ppm.

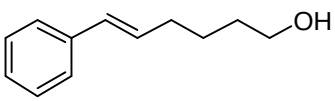
6-Phenylhex-5-yn-1-ol 258[134]



Tetrakis(triphenylphosphine)palladium(0) (413 mg, 0.36 mmol), 5-hexyn-1-ol (2.00 mL, 17.7 mmol), iodobenzene (4.00 mL, 35.0 mmol), diisopropylamine (14.9 mL, 0.11 mol) and CuI (34.0 mg, 0.18 mmol) were reacted together in THF (35 mL), in accordance with general method C. After work-up, purification on silica gel (30% EtOAc in

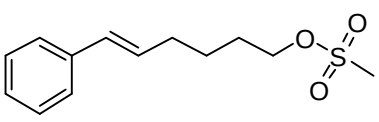
petroleum ether) afforded 6-phenylhex-5-yn-1-ol **258** (997 mg, 5.72 mmol, 32%) as a dark, orange oil. δ_H (400 MHz, $CDCl_3$) 7.41-7.37 (2H, m, 2 x CH, Ar), 7.30-7.24 (3H, m, 3 x CH, Ph), 3.73-3.70 (2H, m, CH_2OH), 2.46 (2H, t, *J* = 6.7 Hz, $\equiv CCH_2$), 1.79-1.66 (4H, m, 2 x CH_2), 1.34 (1H, br s, OH) ppm; δ_C (100 MHz, $CDCl_3$) 131.6 (2 x CH, Ph), 128.2 (2 x CH, Ph), 127.6 (CH, Ph), 123.9 (C, Ph), 89.9 (C≡), 81.0 (C≡), 62.5 (CH_2OH), 31.9 (CH_2), 25.0 (CH_2), 19.2 (CH_2) ppm.

(*E*)-6-Phenylhex-5-en-1-ol 259[136]



6-Phenylhex-5-yn-1-ol **258** (966 mg, 5.54 mmol) in THF (1 mL) was reacted with $LiAlH_4$ (736 mg, 19.4 mmol) in THF (10 mL), in accordance with general method D. After work-up, purification on silica (30% EtOAc in petroleum ether) afforded (*E*)-6-phenylhex-5-en-1-ol **259** (851 mg, 4.83 mmol, 87%) as an orange oil, as an inseparable 98:2 (*E*:*Z*) mixture of geometrical isomers. δ_H (400 MHz, $CDCl_3$) 7.35-7.25 (4H, m, 4 x CH, Ar), 7.21-7.16 (1H, m, CH, Ph), 6.39 (1H, d, *J* = 15.8 Hz, PhCH=), 6.21 (1H, dt, *J* = 15.8, 6.9 Hz, PhCH=C*H*), 3.67 (2H, t, *J* = 6.3 Hz, CH_2OH), 2.27-2.22 (2H, m, =CHCH_2), 1.67-1.51 (4H, m, 2 x CH_2), 1.34 (1H, br s, OH), ppm; δ_C(100 MHz, $CDCl_3$) 137.8 (C, Ph), 130.6 (PhCH=*C*H), 130.2 (PhCH=), 128.5 (2 x CH, Ph), 126.9 (CH, Ph), 126.0 (2 x CH, Ph), 62.9 (*C*H_2OH), 32.7 (=CH*C*H_2), 32.3 (CH_2), 25.5 (CH_2) ppm.

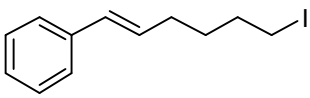
(*E*)-6-Phenylhex-5-enyl methane sulfonate 260[137]



(*E*)-6-Phenylhex-5-en-1-ol **259** (845 mg, 4.79 mmol), Et_3N (1.35 mL, 9.64 mmol) and methanesulfonyl chloride (0.56 mL, 7.21 mmol) were reacted together in CH_2Cl_2 (16 mL), in accordance with general method E. After work-up, (*E*)-6-phenylhex-

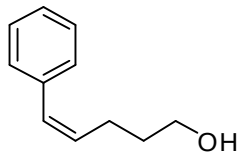
5-enyl methane sulfonate **260** (1.15 g, 4.52 mmol, 94%), as a crude, orange oil, was characterised and used without further purification. δ_H (400 MHz, $CDCl_3$) 7.34-7.25 (4H, m, 4 x CH, Ar), 7.21-7.18 (1H, m, CH, Ph), 6.40 (1H, d, *J* = 15.8 Hz, PhCH=), 6.18 (1H, dt, *J* = 15.8, 7.1 Hz, PhCH=C*H*), 4.25 (2H, t, *J* = 6.5 Hz, CH_2OMs) 2.99 (3H, s, CH_3), 2.26 (2H, q, *J* = 7.1 Hz, =CHCH_2), 1.85-1.77 (2H, m, CH_2), 1.64-1.56 (2H, m, CH_2) ppm; δ_C (100 MHz, $CDCl_3$) 137.5 (C, Ph), 130.7 (PhCH=), 129.7 (PhCH=*C*H), 128.6 (2 x CH, Ph), 127.1 (CH, Ph), 126.0 (2 x CH, Ph), 69.9 (CH_2OMs), 37.4 (CH_3), 32.3 (=CHCH_2CH_2), 28.6 (CH_2), 25.2 (CH_2) ppm.

1-((*E*)-6-Iodohex-1-enyl)benzene 261[132]



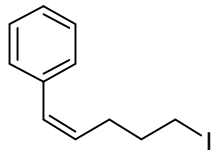
Sodium iodide (1.30 g, 8.67 mmol) and (*E*)-6-phenylhex-5-enyl methane sulfonate **260** (1.11 g, 4.36 mmol) were reacted together in acetone (22 mL) for 3 hours, in accordance with general method F. After work-up, purification on silica (100% petroleum ether) afforded 1-((*E*)-6-iodohex-1-enyl)benzene **261** (816 mg, 2.85 mmol, 65%) as an orange oil, as an inseparable mixture of geometrical isomers (*E*:*Z*, 98:2). δ_H (400 MHz, $CDCl_3$) 7.35-7.25 (4H, m, 4 x CH, Ph), 7.21-7.18 (1H, m, CH, Ph), 6.39 (1H, d, *J* = 15.8 Hz, PhCH=), 6.19 (1H, dt, *J* = 15.8, 7.0 Hz, PhCH=C*H*), 3.21 (2H, t, *J* = 7.0 Hz, CH_2I), 2.27-2.21 (2H, m, =CHCH_2), 1.92-1.85 (2H, m, CH_2), 1.63-1.55 (2H, m, CH_2) ppm; δ_C (100 MHz, $CDCl_3$) 137.4 (C, Ph), 130.5 (PhCH=), 130.0 (PhCH=*C*H), 128.5 (2 x CH, Ph), 127.0 (CH, Ph), 126.0 (2 x CH, Ph), 33.0 (=CH*C*H_2), 31.9 (CH_2), 30.2 (CH_2), 6.8 (CH_2I) ppm.

(*Z*)-5-Phenylpent-4-en-1-ol 263[138]



To a stirred solution of $(Ph_3P)_2NiCl_2$ (1.30 g, 2.00 mmol) in toluene (150 mL) was added a 3.0 M solution of phenylmagnesium bromide in Et_2O (0.67 mL, 2.00 mmol). The resulting mixture was stirred at room temperature for 30 minutes. At the end of this period, additional phenylmagnesium bromide (6.70 mL, 66.0 mmol) was added, followed by 3,4-dihydro-2*H*-pyran (6.20 mL, 66.0 mmol). The resulting mixture was refluxed for 72 hours. The cooled reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (100 mL), and the mixture extracted with Et_2O (2 x 200 mL). The combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (20% EtOAc in petroleum ether) afforded 5-phenylpent-4-en-1-ol **263** (1.51 g, 9.31 mmol, 42%) as an orange oil, as an inseparable mixture of geometrical isomers (*E*:*Z*, 87:13). δ_H (400 MHz, $CDCl_3$) 7.36-7.17 (5H, m, 5 x CH, Ph), 6.45 (1H, d, *J* = 11.6 Hz, PhCH=), 5.66 (1H, dt, *J* = 11.6, 7.4 Hz, PhCH=C*H*), 3.65 (2H, t, *J* = 6.5 Hz, CH_2OH), 2.42 (2H, dq, *J* = 1.5, 7.4 Hz, =CHCH_2), 1.71 (2H, p, *J* = 7.0 Hz, =CHCH_2CH_2), 1.43 (1H, br s, OH) ppm; δ_C (100 MHz, $CDCl_3$) 137.5 (C, Ph), 132.1 (PhCH=), 129.5 (Ph*C*H=CH), 128.8 (2 x CH, Ph), 128.2 (2 x CH, Ph), 126.6 (CH, Ph), 62.5 (CH_2OH), 32.9 (=CHCH_2CH_2), 24.9 (=CH*C*H_2) ppm.

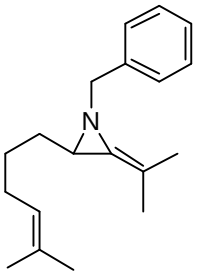
1-((*Z*)-5-Iodopent-1-enyl)benzene 264[139]



To a stirred solution of triphenylphosphine (2.72 g, 10.4 mmol) and imidazole (0.95 g, 13.9 mmol) in THF (15 mL) was added iodine (2.64 g, 10.4 mmol). After 5 minutes stirring, a solution of (*Z*)-5-phenylpent-4-en-1-ol **263** (1.40 g, 8.63 mmol) in THF (5 mL) was added.

The resulting mixture was stirred at room temperature for 15 hours. The mixture was partitioned between water and Et_2O. The aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (100% petroleum ether) afforded 1-((*Z*)-5-iodopent-1-enyl)benzene **264** (1.53 g, 5.62 mmol, 64%) as a yellow oil, as an inseparable mixture of geometrical isomers (*E*:*Z*, 12:88). δ_H (400 MHz, $CDCl_3$) 7.35-7.17 (5H, m, 5 x CH, Ph), 6.47 (1H, d, *J* = 11.6 Hz, PhCH=), 5.60 (1H, dt, *J* = 11.6, 7.3 Hz, PhCH=C*H*), 3.18 (2H, t, *J* = 7.0 Hz, CH_2I), 2.43 (2H, dq, *J* = 1.6, 7.3 Hz, =CHC*H*$_2$), 1.97 (2H, p, *J* = 7.2 Hz, =CHCH$_2$C*H*$_2$) ppm; δ_C (100 MHz, $CDCl_3$) 137.3 (C, Ph), 130.4 (PhCH=), 130.3 (PhCH=*C*H), 128.8 (2 x CH, Ph), 128.3 (2 x CH, Ph), 126.8 (CH, Ph), 33.8 (=CH*C*H$_2$), 29.6 (=CHCH$_2$*C*H$_2$), 6.0 (CH_2I) ppm.

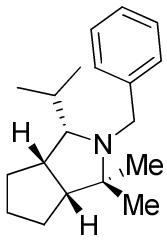
1-Benzyl-2-(5-methylhex-4-enyl)-3-(propan-2-ylidene)aziridine 265



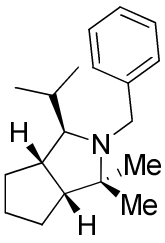
1-Benzyl-2-(propan-2-ylidene)aziridine **177** (200 mg, 1.15 mmol) was reacted with TMEDA (0.21 mL, 1.39 mmol) and *s*-BuLi (1.57 mL, 2.19 mmol) in THF (10 mL) in accordance with general method B, then a solution of 6-iodo-2-methylhex-2-ene **251** (310 mg, 1.39 mmol) in THF (2 mL) was added. After work-up, purification on silica (0.5% Et_3N and 2% EtOAc in petroleum ether) afforded 1-benzyl-2-(5-methylhex-4-enyl)-3-(propan-2-ylidene)aziridine **265** (72.0 mg, 0.27 mmol, 23%) as a yellow oil. R_f = 0.22 (5% EtOAc in petroleum ether); ν_{max} (film) 2925, 1797, 1452, 1130, 732, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37-7.30 (4H, m, 4 x CH, Ph), 7.28-7.24 (1H, m, CH, Ph), 5.03 (1H, tt, *J* = 1.3, 7.1 Hz, =CH), 4.13 (1H, d, *J* = 13.4 Hz, PhC*H*H), 3.22 (1H, d, *J* = 13.4 Hz, PhCH*H*), 1.99 (1H, t, *J* = 6.0 Hz,

aziridine CH), 1.91 (2H, q, J = 7.3 Hz, =CHCH_2), 1.76 (3H, s, CH_3), 1.72 (3H, s, CH_3), 1.66 (3H, s, CH_3), 1.55 (5H, m, CHCH_2 and CH_3), 1.36-1.24 (2H, m, =CHCH$_2$CH_2) ppm; δ_C (100 MHz, $CDCl_3$) 139.2 (C, Ph), 131.5 ((CH$_3$)$_2$$C$=), 130.1 (=C-N), 128.4 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.0 (C, Ph), 124.4 (=CH), 104.0 (C(CH$_3$)$_2$), 62.0 (PhCH$_2$), 44.3 (aziridine CH), 32.0 (CHCH$_2$), 27.8 (=CHCH$_2$), 27.7 (=CHCH$_2$$CH_2$), 25.7 ($CH_3$), 20.6 ($CH_3$), 19.1 ($CH_3$), 17.7 ($CH_3$) ppm; MS (ES$^+$) *m/z* 270 [MH$^+$]; HRMS (ES$^+$) calcd. for $C_{19}H_{28}N$ [MH$^+$]: 270.2216; found 270.2218.

(3*S*,3a*S*,6a*R*)- and (3*R*,3a*S*,6a*R*)-2-Benzyl-octahydro-3-isopropyl-1,1-dimethylcyclopenta[*c*]pyrrole 266



266a



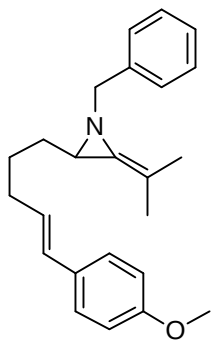
266b

To a stirred solution of 1-benzyl-2-(5-methylhex-4-enyl)-3-(propan-2-ylidene)aziridine **265** (65.0 mg, 0.24 mmol) in 1,2-dichloroethane (5 mL) at -30 °C was added BF_3·OEt_2 (0.05 mL, 0.36 mmol). The resulting mixture was heated at reflux temperature for 15 hours, cooled and then quenched by the addition of saturated $NaHCO_3$ solution (10 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product, which was taken up in THF (2 mL) and added to a stirred solution of $NaBH_4$ (28 mg, 0.73 mmol) in glacial AcOH (5 mL). The resulting mixture was stirred at room temperature for 15 hours, and then basified by the addition of 2M NaOH solution. The mixture

was extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (0.5% Et_2O in petroleum ether) afforded an inseparable 53:47 diastereomeric mixture of (3*S*,3a*S*,6a*R*)-2-benzyl-octahydro-3-isopropyl-1,1-dimethylcyclopenta[*c*]pyrrole **266a** and (3*R*,3a*S*,6a*R*)-2-benzyl-octahydro-3-isopropyl-1,1-dimethylcyclopenta[*c*]pyrrole **266b** (6.80 mg, 0.03 mmol, 10%) as a colourless oil. Compound **266a**: R_f = 0.19 (2% EtOAc in petroleum ether); ν_{max} (film) 2958, 1494, 1453, 1356, 1245, 1190, 1113, 1028, 738, 699 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.38 (2H, d, *J* = 7.6 Hz, 2 x CH, Ph), 7.25 (2H, t, *J* = 7.7 Hz, 2 x CH, Ph), 7.15 (1H, t, *J* = 7.3 Hz, CH, Ph), 3.76 (1H, d, *J* = 16.1 Hz, 1 x PhC*H*H), 3.37 (1H, d, *J* = 16.1 Hz, 1 x PhCH*H*), 2.67 (1H, t, *J* = 6.5 Hz, *i*-PrCH), 2.44-2.39 (1H, m, CH), 2.08-2.04 (1H, m, CH), 1.78-1.72 (1H, m, C*H*$(CH_3)_2$), 1.72-1.66 (1H, m, cp ring C*H*H), 1.65-1.59 (3H, m, cp ring C*H*H, cp ring CH_2), 1.55-1.49 (1H, m, cp ring CH*H*), 1.31-1.20 (1H, m, cp ring CH*H*), 0.97 (3H, s, CH_3), 0.96 (3H, s, CH_3), 0.89 (3H, d, *J* = 6.9 Hz, CH(C*H*$_3)_2$), 0.64 (3H, d, *J* = 6.9 Hz, CH(C*H*$_3)_2$) ppm; δ_C (150 MHz, $CDCl_3$) 144.0 (C, Ph), 127.8 (2 x CH, Ph), 127.7 (2 x CH, Ph), 125.8 (CH, Ph), 70.0 (CH), 62.0 (*C*$(CH_3)_2$), 52.8 (CH), 51.1 ($PhCH_2$), 43.9 (CH), 29.5 (CH_2), 29.1 (CH_2), 28.9 (*C*H$(CH_3)_2$), 27.5 (CH_2), 25.4 (CH_3), 21.0 (CH_3), 21.0 (CH(*C*$H_3)_2$), 19.3 (CH(*C*$H_3)_2$) ppm; MS (ES^+) *m/z* 272 [MH^+]; HRMS (ES^+) calcd. for $C_{19}H_{30}N$ [MH^+]: 272.2373; found 272.2374. Compound **266b**: R_f = 0.16 (2% EtOAc in petroleum ether); ν_{max} (film) 2956, 1494, 1454, 1387, 1259, 1177, 1115, 1028, 737, 698 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.35 (2H, d, *J* = 7.6 Hz, 2 x CH, Ph), 7.26-7.23 (2H, m, 2 x CH, Ph), 7.17-7.14 (1H, m, CH, Ph), 3.88 (1H, d, *J* = 15.4 Hz, 1 x PhC*H*H), 3.29 (1H, d, *J* = 15.4 Hz, 1 x PhCH*H*), 2.46-2.44 (1H, m,

CH), 2.28-2.23 (1H, m, CH), 2.22-2.16 (1H, m, CH), 1.77-1.49 (6H, m, C*H*$(CH_3)_2$ and 2 x cp ring CH_2, cp ring C*H*H), 1.36-1.29 (1H, m, cp ring CH*H*), 1.03 (3H, s, CH_3), 0.88 (3H, s, CH_3), 0.78 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3)_2$), 0.57 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3)_2$) ppm; δ_C (150 MHz, $CDCl_3$) 143.4 (C, Ph), 128.0 (2 x CH, Ph), 127.7 (2 x CH, Ph), 125.9 (CH, Ph), 76.8 (CH), 63.4 (*C*$(CH_3)_2$), 54.9 (CH), 52.4 ($PhCH_2$), 42.2 (CH), 33.8 (CH_2), 30.2 (CH_3), 28.5 (*C*H$(CH_3)_2$), 28.2 (CH_2), 26.7 (CH_2), 20.7 (CH(*C*$H_3)_2$), 16.8 (CH_3), 14.9 (CH(*C*$H_3)_2$) ppm; MS (ES^+) *m/z* 272 [MH^+]; HRMS (ES^+) calcd. for $C_{19}H_{30}N$ [MH^+]: 272.2373; found 272.2370.

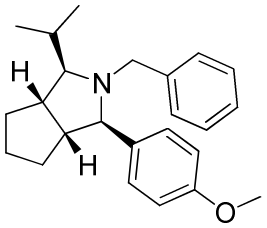
1-Benzyl-2-((*E*)-5-(4-methoxyphenyl)pent-4-enyl)-3-(propan-2-ylidene)aziridine 267



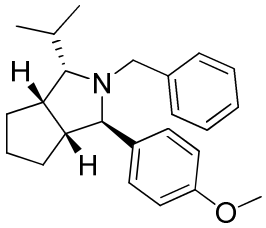
1-Benzyl-2-(propan-2-ylidene)aziridine **177** (149 mg, 0.86 mmol) was reacted with TMEDA (0.16 mL, 1.03 mmol) and *s*-BuLi (1.17 mL, 1.64 mmol) in THF (8 mL) in accordance with general method B, then a solution of 1-((*E*)-5-iodopent-1-enyl)-4-methoxybenzene **257** (312 mg, 1.03 mmol) in THF (1 mL) was added. After work-up, purification on silica (0.5% Et_3N and 2% EtOAc in petroleum ether) afforded 1-benzyl-2-((*E*)-5-(4-methoxyphenyl)pent-4-enyl)-3-(propan-2-ylidene)aziridine **267** (170 mg, 0.49 mmol, 57%) as a pale, yellow oil. R_f = 0.33 (10% EtOAc in petroleum ether); ν_{max} (neat) 2924, 1797, 1607, 1509, 1453, 1244, 1174, 1034, 964, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36-7.21 (7H, m, 7 x CH, Ph), 6.82 (2H, d, *J* = 8.6 Hz, 2 x CH, Ph), 6.23 (1H, d, *J* = 15.8 Hz, PhCH=), 5.96 (1H, dt, *J* = 15.8, 6.9 Hz, PhCH=C*H*), 4.16 (1H, d, *J* = 13.3 Hz, PhC*H*H), 3.77 (3H, s, OCH_3), 3.18 (1H, d, *J* = 13.3, 1 x PhCH*H*), 2.10 (2H, q, *J* = 7.1 Hz, =CH*C*H_2), 2.02 (1H, t, *J* = 5.7 Hz, aziridine CH), 1.76 (3H, s, CH_3), 1.73

(3H, s, CH_3), 1.65-1.35 (4H, m, 2 x CH_2) ppm; δ_C (100 MHz, $CDCl_3$) 158.7 (*C*OCH_3, Ph), 139.2 (C, Ph), 130.7 (C, Ph), 130.0 (=C-N), 129.3 (PhCH=), 128.5 (2 x CH, Ph), 128.5 (PhCH=*C*H), 128.3 (2 x CH, Ph), 127.1 (CH, Ph), 127.0 (2 x CH, Ph), 113.9 (2 x CH, Ph), 104.0 (*C*$(CH_3)_2$), 62.1 ($PhCH_2$), 55.3 (OCH_3), 44.1 (aziridine CH), 32.7 (CH*C*H_2), 31.9 (=CH*C*H_2), 27.3 (=CHCH_2*C*H_2), 20.6 (CH_3), 19.1 (CH_3) ppm; MS (ES^+) *m/z* 348 [MH^+]; HRMS (ES^+) calcd. for $C_{24}H_{30}NO$ [MH^+]: 348.2322; found 348.2324.

(1*R*,3*R*,3a*R*,6a*S*)- and (1*S*,3*R*,3a*R*,6a*S*)-2-Benzyl-octahydro-1-isopropyl-3-(4-methoxyphenyl)cyclopenta[*c*]pyrrole 268



268a



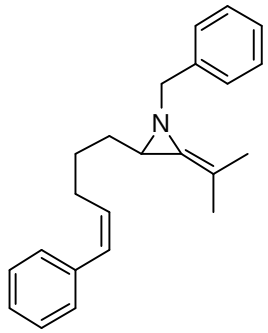
268b

To a stirred solution of 1-benzyl-2-((*E*)-5-(4-methoxyphenyl)pent-4-enyl)-3-(propan-2-ylidene)aziridine **267** (167 mg, 0.48 mmol) in CH_2Cl_2 (10 mL) at -30 °C was added $BF_3{\cdot}OEt_2$ (0.09 mL, 0.72 mmol). The resulting mixture was allowed to warm slowly to room temperature for 15 hours, and then quenched by the addition of saturated $NaHCO_3$ solution (15 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product, which was taken up in THF (4 mL) and added to a stirred solution of $NaBH_4$ (56 mg, 1.44 mmol) in glacial AcOH (10 mL). The resulting mixture was stirred at room temperature for 15 hours, and then basified by the addition of 2M NaOH solution. The mixture was extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, filtered

and concentrated *in vacuo* to give the crude product. Purification on silica (2% Et_2O in petroleum ether) afforded successively (1*R*,3*R*,3a*R*,6a*S*)- 2-benzyl-octahydro-1-isopropyl-3-(4-methoxyphenyl)cyclopenta[*c*]pyrrole **268a** (20.6 mg, 0.06 mmol, 12%) as a colourless oil and (1*S*,3*R*,3a*R*,6a*S*)-2-benzyl-octahydro-1-isopropyl-3-(4-methoxyphenyl)cyclopenta[*c*]pyrrole **268b** (33.2 mg, 0.10 mmol, 20%) as colourless oil, which solidified on standing. Recrystallisation from the minimum amount of hot MeOH provided crystals suitable for X-ray analysis (*see Appendix*). Compound **268a**: R_f = 0.35 (5% EtOAc in petroleum ether);ν_{max} (film) 2952, 1611, 1511, 1453, 1247, 1038, 826 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27 (2H, d, *J* = 8.6 Hz, 2 x CH, Ph), 7.17-7.06 (3H, m, 3 x CH, Ph), 6.98-6.96 (2H, m, 2 x CH, Ph), 6.80 (2H, d, *J* = 8.6 Hz, 2 x CH, Ph), 3.73 (3H, s, OCH_3), 3.60 (1H, d, *J* = 14.4 Hz, 1 x PhC*H*H), 3.27 (1H, d, *J* = 14.4 Hz, 1 x PhCH*H*), 2.91 (1H, d, *J* = 8.5 Hz, PhCH), 2.26-2.10 (3H, m, *i*-PrCH, 2 x CH), 1.94-1.86 (1H, m, C*H*$(CH_3)_2$), 1.54-1.22 (6H, m, 3 x cp ring CH_2), 0.84 (3H, d, *J* = 6.7 Hz, CH(C*H*$_3)_2$), 0.82 (3H, d, *J* = 7.0 Hz, CH(C*H*$_3)_2$) ppm; δ_C (75 MHz, $CDCl_3$) 158.0 (C, Ph), 137.0 (C, Ph), 135.8 (C, Ph), 128.9 (2 x CH, Ph), 128.4 (2 x CH, Ph), 127.0 (2 x CH, Ph), 125.8 (CH, Ph), 113.1 (2 x CH, Ph), 74.0 (CH), 73.2 (CH), 54.6 (OCH_3), 53.1 ($PhCH_2$), 52.1 (CH), 40.6 (CH), 33.3 (CH_2), 28.9 (CH_2), 27.2 (*C*H$(CH_3)_2$), 24.4 (CH_2), 19.7 (CH(*C*H$_3)_2$), 14.6 (CH(*C*H$_3)_2$) ppm; MS (ES^+) *m/z* 350 [MH^+]; HRMS (ES^+) calcd. for $C_{24}H_{32}NO$ [MH^+]: 350.2478; found 350.2479. Compound **268b**: R_f = 0.29 (5% EtOAc in petroleum ether); ν_{max} (film) 2953, 1608, 1510, 1453, 1250, 1038, 822 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.19-7.18 (4H, m, 4 x CH, Ph), 7.14-7.09 (1H, m, CH, Ph), 6.79 (2H, d, *J* = 8.6 Hz, 2 x CH, Ph), 6.69 (2H, d, *J* = 8.6 Hz, 2 x CH, Ph), 3.74-3.69 (5H, m, PhC*H*H, OCH_3, PhCH),

3.03 (1H, t, *J* = 5.8 Hz, CH), 2.98 (1H, d, *J* = 14.5 Hz, PhCH*H*), 2.60-2.50 (2H, m, *i*-PrCH, CH), 1.97-1.86 (2H, m, C*H*(CH_3)$_2$, cp ring C*H*H), 1.83-1.64 (3H, m, cp ring CH_2, cp ring C*H*H), 1.45-1.31 (2H, m, 2 x cp ring CH*H*), 1.03 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3$)$_2$), 0.93 (3H, d, *J* = 7.0 Hz, CH(C*H*$_3$)$_2$) ppm; δ_C (75 MHz, $CDCl_3$) 157.1 (C, Ph), 140.0 (C, Ph), 133.8 (C, Ph), 129.1 (2 x CH, Ph), 127.0 (4 x CH, Ph), 125.1 (CH, Ph), 111.9 (2 x CH, Ph), 69.6 (CH), 66.3 (CH), 54.2 (OCH_3), 49.4 ($PhCH_2$), 48.5 (CH), 46.2 (CH), 33.6 (CH_2), 28.6 (CH_2), 27.2 (CH_2), 27.1 (*C*H(CH_3)$_2$), 19.4 (CH(*C*H_3)$_2$), 17.5 (CH(*C*H_3)$_2$) ppm; MS (ES^+) *m/z* 350 [MH^+]; HRMS (ES^+) calcd. for $C_{24}H_{32}NO$ [MH^+]: 350.2478; found 350.2479.

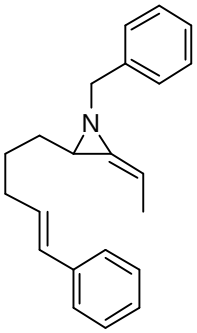
1-Benzyl-2-((*Z*)-5-phenylpent-4-enyl)-3-(propan-2-ylidene)aziridine 269



1-Benzyl-2-(propan-2-ylidene)aziridine **177** (148 mg, 0.85 mmol) was reacted with TMEDA (0.16 mL, 1.03 mmol) and *s*-BuLi (1.16 mL, 1.63 mmol) in THF (8 mL) in accordance with general method B, then a solution of 1-((*Z*)-5-iodopent-1-enyl)benzene **264** (280 mg, 1.03 mmol) in THF (1 mL) was added. After work-up, purification on silica (0.5% Et_3N and 2% EtOAc in petroleum ether) afforded 1-benzyl-2-((*Z*)-5-phenylpent-4-enyl)-3-(propan-2-ylidene)aziridine **269** (154 mg, 0.49 mmol, 57%) as a pale, yellow oil, as an inseparable 9:91 (*E*:*Z*) mixture of geometrical isomers. R_f = 0.19 (6% EtOAc in petroleum ether); ν_{max} (neat) 2923, 1798, 1601, 1494, 1447, 1128, 731, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35-7.18 (10H, m, 10 x CH, Ph), 6.37 (1H, d, *J* = 11.7 Hz, PhCH=), 5.55 (1H, dt, *J* = 11.7, 6.7 Hz, PhCH=C*H*), 4.13 (1H, d, *J* = 13.3 Hz, PhC*H*H), 3.17 (1H, d, *J* = 13.3 Hz, 1 x PhCH*H*), 2.8-2.22 (2H, m, =CHC*H*$_2$), 1.97 (1H, t, *J* = 5.8 Hz, aziridine CH), 1.74 (3H, s, CH_3), 1.72 (3H, s,

CH_3), 1.63-1.47 (2H, m, CHCH_2), 1.44-1.36 (2H, m, =CHCH$_2$CH_2) ppm; δ_C (100 MHz, $CDCl_3$) 139.1 (C, Ph), 137.7 (C, Ph), 132.7 (PhCH=*C*H), 129.9 (=C-N), 129.0 (PhCH=), 128.8 (2 x CH, Ph), 128.5 (2 x CH, Ph), 128.3 (2 x CH, Ph), 128.1 (2 x CH, Ph), 127.1 (CH, Ph), 126.5 (CH, Ph), 104.0 (*C*(CH$_3$)$_2$), 62.0 (PhCH$_2$), 44.0 (aziridine CH), 31.9 (CH*C*H$_2$), 28.3 (=CH*C*H$_2$), 27.8 (=CHCH$_2$*C*H$_2$), 20.6 (CH_3), 19.1 (CH_3) ppm; MS (ES^+) *m/z* 318 [MH^+]; HRMS (ES^+) calcd. for $C_{23}H_{28}N$ [MH^+]: 318.2216; found 318.2218.

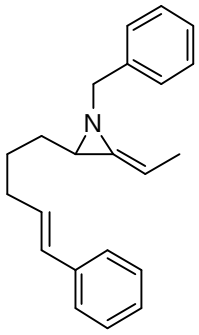
(2*E*)-1-Benzyl-2-ethylidene-3-((*E*)-5-phenylpent-4-enyl)aziridine 275



(*E*)-1-Benzyl-2-ethylideneaziridine **182** (150 mg, 0.94 mmol) was reacted with TMEDA (0.17 mL, 1.13 mmol) and *s*-BuLi (1.28 mL, 1.79 mmol) in THF (8.5 mL) in accordance with general method B, then a solution of 1-((*E*)-5-iodopent-1-enyl)benzene **232** (308 mg, 1.13 mmol) in THF (1 mL) was added. After work-up, purification on silica (0.5% Et_3N and 2% Et_2O in petroleum ether) afforded (2*E*)-1-Benzyl-2-ethylidene-3-((*E*)-5-phenylpent-4-enyl)aziridine **275** (111 mg, 0.37 mmol, 39%) as a yellow oil. R_f = 0.18 (5% EtOAc in petroleum ether); ν_{max} (film) 2924, 1779, 1598, 1453, 1150, 964 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36-7.24 (9H, m, 9 x CH, Ph), 7.20-7.16 (1H, m, CH, Ph), 6.32 (1H, d, *J* = 15.8 Hz, PhCH=), 6.15 (1H, dt, *J* = 15.8, 6.9 Hz, PhCH=*C*H), 5.13 (1H, dq, *J* = 1.2, 6.7 Hz, =CH), 3.83 (1H, d, *J* = 13.2 Hz, PhC*H*H), 3.46 (1H, d, *J* = 13.2 Hz, PhCH*H*), 2.21-2.15 (2H, m, =CHCH_2) ,2.04 (1H, t, *J* = 5.9 Hz, aziridine CH), 1.75 (3H, d, *J* = 6.6 Hz, CH_3), 1.70-1.57 (2H, m, CHCH_2), 1.56-1.44 (2H, m, =CHCH$_2$CH_2) ppm; δ_C (100 MHz, $CDCl_3$) 139.0 (C, Ph), 137.8 (C, Ph), 135.8 (=C-N), 130.6 (PhCH=*C*H), 130.1 (PhCH=), 128.5 (2 x CH, Ph), 128.4

(2 x CH, Ph), 128.4 (2 x CH, Ph), 127.2 (CH, Ph), 126.8 (CH, Ph), 126.0 (2 x CH, Ph), 94.8 (=CH), 62.9 ($PhCH_2$), 43.1 (aziridine CH), 32.7 ($CHCH_2$), 31.7 ($=CHCH_2$), 27.2 ($=CHCH_2CH_2$), 14.5 (CH_3) ppm; MS (ES^+) *m/z* 304 [MH^+]; HRMS (ES^+) calcd. for $C_{22}H_{26}N$ [MH^+]: 304.2060; found 304.2060.

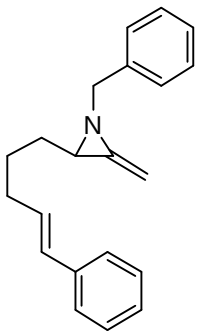
(2*Z*)-1-Benzyl-2-ethylidene-3-((*E*)-5-phenylpent-4-enyl)aziridine 276



(*Z*)-1-Benzyl-2-ethylideneaziridine **187** (208 mg, 1.31 mmol) was reacted with TMEDA (0.24 mL, 1.56 mmol) and *s*-BuLi (1.77 mL, 2.48 mmol) in THF (10 mL) in accordance with general method B, then a solution of 1-((*E*)-5-iodopent-1-enyl)benzene **232** (427 mg, 1.56 mmol) in THF (2 mL) was added. After work-up, purification on silica (0.5% Et_3N and 0-1% EtOAc in petroleum ether) afforded (2*Z*)-1-benzyl-2-ethylidene-3-((*E*)-5-phenylpent-4-enyl)aziridine **276** (70 mg, 0.23 mmol, 18%) as a yellow oil. R_f = 0.24 (5% EtOAc in petroleum ether); ν_{max} (film) 2930, 1779, 1495, 1454, 1130, 964 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.16 (10H, m, 10 x CH, Ph), 6.29 (1H, d, *J* = 15.8 Hz, PhCH=), 6.11 (1H, dt, *J* = 15.8, 6.9 Hz, PhCH=*C*H), 5.11 (1H, q, *J* = 6.7 Hz, =CH), 4.20 (1H, d, *J* = 13.3 Hz, PhC*H*H), 3.28 (1H, d, *J* = 13.3 Hz, PhCH*H*), 2.12 (2H, q, *J* = 7.2 Hz, $=CHCH_2$), 2.01 (1H, t, *J* = 6.0 Hz, aziridine CH), 1.72 (3H, d, *J* = 6.7 Hz, CH_3), 1.60-1.54 (2H, m, $CHCH_2$), 1.47-1.37 (2H, m, $=CHCH_2CH_2$) ppm; δ_C (100 MHz, $CDCl_3$) 138.8 (C, Ph), 137.8 (C, Ph), 135.6 (=C-N), 130.6 (PhCH=*C*H), 130.0 (PhCH=), 128.6 (2 x CH, Ph), 128.5 (2 x CH, Ph), 128.4 (2 x CH, Ph), 127.3 (CH, Ph), 126.8 (CH, Ph), 125.9 (2 x CH, Ph), 94.8 (=CH), 61.8 ($PhCH_2$), 43.3 (aziridine CH), 32.5 ($CHCH_2$), 31.7 ($=CHCH_2$), 26.9

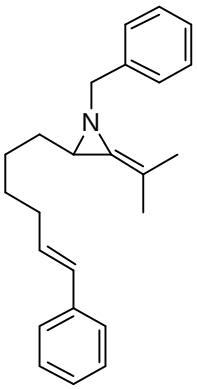
(=CHCH$_2$*C*H$_2$), 13.3 (CH$_3$) ppm; MS (ES$^+$) *m/z* 304 [MH$^+$]; HRMS (ES$^+$) calcd. for $C_{22}H_{26}N$ [MH$^+$]: 304.2060; found 304.2061.

1-Benzyl-2-methylene-3-((*E*)-5-phenylpent-4-enyl)aziridine 277



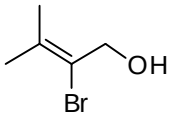
1-Benzyl-2-methyleneaziridine **172** (173 mg, 1.19 mmol) was reacted with TMEDA (0.22 mL, 1.43 mmol) and *s*-BuLi (1.62 mL, 2.26 mmol) in THF (10 mL) in accordance with general method B, then a solution of 1-((*E*)-5-iodopent-1-enyl)benzene **232** (308 mg, 1.13 mmol) in THF (2 mL) was added. After work-up, the unreacted methyleneaziridine was removed by bulb-to-bulb distillation (80 °C, 0.4 mmHg), and the residue passed through a short plug of basic alumina (Et$_2$O) to afford 1-benzyl-2-methylene-3-((*E*)-5-phenylpent-4-enyl)aziridine **277** (193 mg, 0.67 mmol, 59%) as a yellow oil. R_f = 0.22 (4% EtOAc in petroleum ether); ν_{max} (film) 2930, 1769, 1494, 1452, 1156, 964, 741 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37-7.16 (10H, m, 10 x CH, Ph), 6.32 (1H, d, *J* = 15.8 Hz, PhCH=), 6.14 (1H, dt, *J* = 15.8, 6.8 Hz, PhCH=*C*H), 4.69 (2H, d, *J* = 10.7 Hz, =CH$_2$), 3.93 (1H, d, *J* = 13.2 Hz, PhC*H*H), 3.51 (1H, d, *J* = 13.2, PhCH*H*), 2.17 (2H, q, *J* = 7.1 Hz, =CHC*H*$_2$), 2.04 (1H, t, *J* = 5.9 Hz, aziridine CH), 1.68-1.44 (4H, m, 2 x CH$_2$) ppm; δ_C (100 MHz, $CDCl_3$) 142.6 (=C-N), 138.5 (C, Ph), 137.8 (C, Ph), 130.5 (PhCH=*C*H), 130.1 (PhCH=), 128.5 (2 x CH, Ph), 128.4 (4 x CH, Ph), 127.3 (CH, Ph), 126.9 (CH, Ph), 125.9 (2 x CH, Ph), 83.2 (=CH$_2$), 62.4 (PhCH$_2$), 42.7 (aziridine CH), 32.5 (CH*C*H$_2$), 31.4 (=CH*C*H$_2$), 26.8 (=CHCH$_2$*C*H$_2$) ppm; MS (ES$^+$) *m/z* 290 [MH$^+$]; HRMS (ES$^+$) calcd. for $C_{21}H_{24}N$ [MH$^+$]: 290.1903; found 290.1902.

1-Benzyl-2-((*E*)-6-phenylhex-5-enyl)-3-(propan-2-ylidene)aziridine 278



1-Benzyl-2-(propan-2-ylidene)aziridine **177** (265 mg, 1.53 mmol) was reacted with TMEDA (0.28 mL, 1.84 mmol) and *s*-BuLi (2.08 mL, 2.91 mmol) in THF (12 mL) in accordance with general method B, then a solution of 1-((*E*)-6-iodohex-1-enyl)benzene **261** (482 mg, 1.68 mmol) in THF (3 mL) was added. After work-up, purification on silica (0.5% Et_3N in petroleum ether) afforded 1-benzyl-2-((*E*)-6-phenylhex-5-enyl)-3-(propan-2-ylidene)aziridine **278** (186 mg, 0.56 mmol, 37%) as a yellow oil. R_f = 0.36 (10% EtOAc in petroleum ether); ν_{max} (film) 2927, 1797, 1710, 1599, 1495, 1130, 964, 738, 695 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36-7.16 (10H, m, 10 x CH, Ph), 6.32 (1H, d, *J* = 15.8 Hz, PhCH=), 6.14 (1H, dt, *J* = 15.8, 6.9 Hz, PhCH=C*H*), 4.17 (1H, d, *J* = 13.3 Hz, 1 x PhC*H*H), 3.16 (1H, d, *J* = 13.3 Hz, 1 x PhCH*H*), 2.13-2.08 (2H, m, CH_2), 2.00 (1H, t, *J* = 6.0 Hz, aziridine CH), 1.76 (3H, s, CH_3), 1.73 (3H, s, CH_3), 1.62-1.23 (6H, m, 3 x CH_2) ppm; δ_C (100 MHz, $CDCl_3$) 139.2 (C, Ph), 137.9 (C, Ph), 130.9 (PhCH=*C*H), 130.1 (=C-N), 129.8 (PhCH=), 128.5 (2 x CH, Ph), 128.5 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.1 (CH, Ph), 126.8 (CH, Ph), 125.9 (2 x CH, Ph), 103.9 (*C*$(CH_3)_2$), 62.1 (PhCH_2), 44.2 (aziridine CH), 32.9 (CH_2), 32.2 (CH_2), 29.0 (CH_2), 27.1 (CH_2), 20.6 (CH_3), 19.1 (CH_3) ppm; MS (ES^+) *m/z* 332 [MH^+]; HRMS (ES^+) calcd. for $C_{24}H_{30}N$ [MH^+]: 332.2373; found 332.2373.

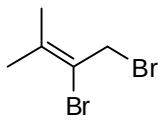
2-Bromo-3-methylbut-2-en-1-ol 282[100b]



A solution of Br_2 (0.64 mL, 12.3 mmol) in CH_2Cl_2 (2 mL) was added to a stirred solution of 3-methyl-but-2-enol (1.20 mL, 11.7 mmol) in CH_2Cl_2 (10 mL) at 0 °C and the resulting mixture was stirred at this

temperature for 1 hour and then allowed to warm slowly to room temperature over a 3 hour period. Diazabicyclo[5.4.0]undec-7-ene (2.68 mL, 17.5 mmol) was added with vigorous stirring and the resulting mixture heated at reflux temperature for 15 hours. The cooled mixture was quenched by the dropwise addition of $Na_2S_2O_3$ (15 mL) and then partitioned between 1M HCl (20 mL) and Et_2O (30 mL). The aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with saturated, aqueous $NaHCO_3$ solution (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 2-bromo-3-methylbut-2-en-1-ol **282** (1.53 g, 9.27 mmol, 79%) as a colourless oil. The crude oil was characterised and used without further purification. δ_H (400 MHz, $CDCl_3$) 4.38-4.37 (2H, m, CH_2), 2.26 (1H, br s, OH), 1.91 (3H, s CH_3), 1.87 (3H, s, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 134.7 ($C(CH_3)_2$), 121.0 (CBr), 64.6 (CH_2), 25.4 (CH_3), 20.5 (CH_3) ppm.

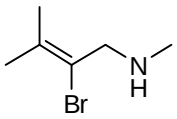
1,2-Dibromo-3-methylbut-2-ene 286[100b]



To a stirred solution of 2-bromo-3-methylbut-2-en-1-ol **282** (1.03 g, 5.61 mmol) and triphenylphosphine (7.69 g, 29.3 mmol) in CH_2Cl_2 (65 mL) at 0 °C was added *N*-bromosuccinimide (5.27 g, 29.3 mmol). The resulting mixture was stirred at room temperature for 5 hours and then diluted with CH_2Cl_2 (50 mL). The organic layer was washed water then brine (75 mL), dried over $MgSO_4$, filtered through a plug of Celite® and concentrated *in vacuo* to give the crude product. Purification on silica (100% petroleum ether) afforded 1,2-dibromo-3-methylbut-2-ene **286** (1.57 g, 6.89 mmol, 47%) as a pale, yellow oil. δ_H (400 MHz, $CDCl_3$) 4.38 (2H, s, CH_2), 1.92 (3H, s, CH_3), 1.87 (3H, s, CH_3)

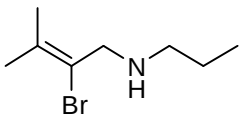
ppm; δ_C (100 MHz, $CDCl_3$) 138.7 ($C(CH_3)_2$), 115.8 (CBr), 36.4 (CH_2), 25.8 (CH_3), 20.5 (CH_3) ppm.

2-Bromo-*N*-3-dimethylbut-2-en-1-amine 289



To a 2.0 M solution of methylamine (6.67 mL, 13.3 mmol) and K_2CO_3 (203 mg, 1.47 mmol) in THF was added a solution of 1,2-dibromo-3-methylbut-2-ene **286** (304 mg, 1.33 mmol) in THF (3 mL). The resulting mixture was stirred at room temperature for 72 hours and then partitioned between 10% NaOH solution (10 mL) and Et_2O (15 mL). The aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organic extracts were washed with 10% NaOH solution (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by bulb-to-bulb distillation (50 °C, 0.4 mmHg) afforded 2-bromo-*N*,3-dimethylbut-2-en-1-amine **289** (133 mg, 0.75 mmol, 56%) as a colourless oil. R_f = 0.25 (10% MeOH in CH_2Cl_2); ν_{max} (film) 2921, 1665, 1459, 1398, 1033, cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.52 (2H, s, CH_2), 2.34 (3H, s, NHCH_3), 1.92 (3H, s, CH_3), 1.84 (3H, s, CH_3), 1.47 (1H, br s, NH) ppm; δ_C (100 MHz, $CDCl_3$) 133.5 ($C(CH_3)_2$), 121.2 (CBr), 55.2 (CH_2), 34.5 ($NHCH_3$), 25.5 (CH_3), 20.6 (CH_3) ppm; MS (ES^+) *m/z* 178 [MH^+, ^{79}Br], 180 [MH^+, ^{81}Br]; HRMS (ES^+) calcd. for $C_6H_{13}BrN$ [MH^+, ^{79}Br]: 178.0226; found 178.0227, [MH^+, ^{81}Br]: 180.0205; found 180.0206.

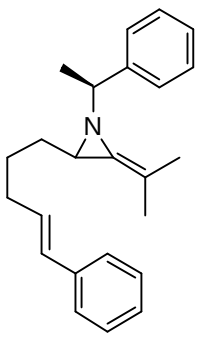
2-Bromo-3-methyl-*N*-propylbut-2-en-1-amine 290



To a stirred solution of propylamine (7.88 mL, 93.9 mmol) and K_2CO_3 (1.43 g, 10.3 mmol) in THF (18 mL) was added a solution of 1,2-dibromo-3-methylbut-2-ene **286** (2.14 mg, 9.39 mmol) in THF (4 mL). The resulting mixture was stirred at room temperature for 15 hours and then

partitioned between 10% NaOH solution (20 mL) and Et_2O (40 mL). The organic phase was washed with 10% NaOH solution (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (1% Et_3N in EtOAc) afforded 2-bromo-3-methyl-*N*-propylbut-2-en-1-amine **290** (1.64 g, 7.96 mmol, 85%) as a pale, yellow oil. R_f = 0.23 (4% MeOH in CH_2Cl_2); ν_{max} (neat) 2923, 1654, 1456, 1380, 1228, 1126, 1021, 729 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.55 (2H, s, =C(Br)CH_2), 2.47 (2H, t, *J* = 7.2 Hz, NHCH_2), 1.91 (3H, s, =CCH_3), 1.84 (3H, s, =CCH_3), 1.51 (3H, m, $NHCH_2CH_2$ and OH), 0.93 (3H, t, *J* = 7.4 Hz, $NHCH_2CH_2CH_3$) ppm; δ_C (100 MHz, $CDCl_3$) 133.0 ($C(CH_3)_2$), 121.8 (CBr), 53.4 (=C(Br)CH_2), 49.6 ($NHCH_2$), 25.4 (=CCH_3), 23.2 ($NHCH_2CH_2$), 20.6 (=CCH_3), 11.8 ($NH(CH_2)_2CH_3$) ppm; MS (ES^+) *m/z* 206 [MH^+, ^{79}Br], 208 [MH^+, ^{81}Br]; HRMS (ES^+) calcd. for $C_8H_{17}BrN$ [MH^+, ^{79}Br]: 206.0539; found 206.0540, [MH^+, ^{81}Br]: 208.0518; found 208.0519.

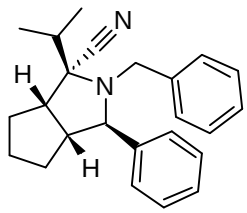
1-((*S*)-1-Phenylethyl)-2-((*E*)-5-phenylpent-4-enyl)-3-(propan-2-ylidene)aziridine (major) 296



1-((*S*)-1-Phenylethyl)-2-(propan-2-ylidene)aziridine **175** (202 mg, 1.08 mmol) was reacted with TMEDA (0.20 mL, 1.29 mmol) and *s*-BuLi (1.46 mL, 2.05 mmol) in THF (10 mL) in accordance with general method B, then a solution of 1-((*E*)-5-iodopent-1-enyl)benzene **232** (587 mg, 2.16 mmol) in THF (1 mL) was added. After work-up, purification on silica (0.25% Et_3N and 1% EtOAc in petroleum ether) afforded 1-((*S*)-1-phenylethyl)-2-((*E*)-5-phenylpent-4-enyl)-3-(propan-2-ylidene)aziridine(major) **296** (202 mg, 0.61 mmol, 56%) as a yellow

oil. R_f = 0.18 (5% EtOAc in petroleum ether); ν_{max} (neat) 2926, 1718, 1448, 1132, 964, 745, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40-7.16 (10H, m, 10 x CH, Ph), 6.40 (1H, d, *J* = 15.8 Hz, PhCH=), 6.24 (1H, dt, *J* = 15.8, 6.8 Hz, PhCH=C*H*), 2.91 (1H, q, *J* = 6.6 Hz, CH), 2.32-2.26 (2H, m, =CHCH_2), 2.04-1.93 (1H, m, aziridine CH), 1.78-1.51 (4H, m, 2 x CH_2), 1.66 (3H, s, CH_3), 1.46 (3H, d, *J* = 6.6 Hz, CH_3), 1.03 (3H, s, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 145.2 (=C-N), 137.8 (C, Ph), 130.7 (PhCH=), 130.1 (PhCH=C*H*), 129.6 (C, Ph), 128.5 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.1 (CH, Ph), 126.9 (CH, Ph), 126.0 (2 x CH, Ph), 104.1 (*C*$(CH_3)_2$), 68.3 (CH), 43.1 (aziridine CH), 33.1 (CH*C*H_2), 32.3 (=CH*C*H_2), 27.7 (=CHCH$_2$*C*H_2), 23.6 (CH_3), 21.1 (CH_3), 19.1 (CH_3) ppm; MS (ES^+) *m/z* 332 [MH^+]; HRMS (ES^+) calcd. for $C_{24}H_{30}N$ [MH^+]: 332.2373; found 332.2376.

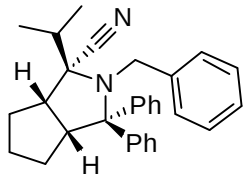
(1*R*,3*R*,3a*R*,6a*S*)-2-Benzyl-octahydro-1-isopropyl-3-phenylcyclopenta[*c*]pyrrole-1-carbonitrile 302



To a stirred solution of 1-benzyl-2-((*E*)-5-phenylpent-4-enyl)-3-(propan-2-ylidene)aziridine **204** (152 mg, 0.48 mmol) in CH_2Cl_2 (10 mL) at -30 °C was added $BF_3{\cdot}OEt_2$ (0.09 mL, 0.72 mmol). The resulting mixture was allowed to warm slowly to room temperature for 15 hours, and then quenched by the addition of saturated $NaHCO_3$ solution (15 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product, which was taken up in THF (5 mL) and cooled to 0 °C. In a separate flask, glacial AcOH (0.07 mL, 1.20 mmol) was added to a solution of TMSCN (0.09 mL, 0.72 mmol) in THF (1 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours, and then added

to the stirred iminium ion solution. The resulting combined mixture was allowed to warm to room temperature for 15 hours. Water (15 mL) was added followed by saturated, aqueous $NaHCO_3$ solution (25 mL). The mixture was extracted with Et_2O (3 x 30 mL). The combined organic washings were washed with saturated, aqueous $NaHCO_3$ solution (50 mL) and then brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (2% Et_2O in petroleum ether) afforded (1*R*,3*R*,3a*R*,6a*S*)-2-benzyl-octahydro-1-isopropyl-3-phenylcyclopenta[*c*]pyrrole-1-carbonitrile **302** (48 mg, 0.14 mmol, 29%) as a white solid. mp 109-110 °C (from Et_2O/petroleum ether); R_f = 0.25 (4% Et_2O in petroleum ether); ν_{max} (film) 2956, 1601, 1493, 1443, 1262, 1028, 909, 734 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.39 (2H, d, *J* = 7.3 Hz, 2 x CH, Ph), 7.29 (2H, t, *J* = 7.6 Hz, 2 x CH, Ph), 7.22 (1H, t, *J* = 7.3 Hz, CH, Ph), 7.15-7.08 (5H, m, 5 x CH, Ph), 3.66 (2H, s, $PhCH_2$), 3.30 (1H, d, *J* = 8.9 Hz, PhCH), 2.64 (1H, dt, *J* = 2.9, 9.6 Hz, CH), 2.47 (1H, m, CH), 1.98-1.86 (2H, m, 2 x cp ring C*H*H), 1.76-1.66 (3H, m, C*H*$(CH_3)_2$ and 2 x cp ring CH*H*), 1.57-1.54 (1H, m, cp ring C*H*H), 1.47-1.40 (1H, m, cp ring CH*H*), 0.98 (3H, d, *J* = 6.7 Hz, CH(C*H*$_3)_2$), 0.84 (3H, d, *J* = 6.7 Hz,CH(C*H*$_3)_2$) ppm; δ_C (150 MHz, $CDCl_3$) 142.2 (C, Ph), 138.9 (C, Ph), 129.3 (2 x CH, Ph), 128.5 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.8 (2 x CH, Ph), 127.7 (CH, Ph), 126.8 (CH, Ph), 118.9 (C≡N), 77.4 (*C*(CN)(^{i}Pr)), 76.6 (PhCH), 54.5 ($PhCH_2$), 52.2 (CH), 44.2 (CH), 33.1 (*C*H$(CH_3)_2$), 32.2 (CH_2), 29.0 (CH_2), 25.7 (CH_2), 19.0 (CH(*C*H$_3)_2$), 15.1 (CH(*C*H$_3)_2$) ppm; MS (ES^+) *m/z* 345 [MH^+]; HRMS (ES^+) calcd. for $C_{24}H_{29}N_2$ [MH^+]: 345.2325; found 345.2322.

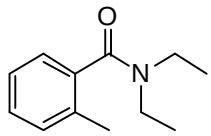
(1*R*,3a*R*,6a*S*)-2-Benzyl-octahydro-1-isopropyl-3-3-diphenylcyclopenta[*c*]pyrrole-1-carbonitrile 303



To a stirred solution of 1-benzyl-2-(5,5-diphenylpent-4-enyl)-3-(propan-2-ylidene)aziridine **204** (101 mg, 0.26 mmol) in CH_2Cl_2 (5 mL) at -30 °C was added $BF_3{\cdot}OEt_2$ (0.05 mL, 0.39 mmol). The resulting mixture was allowed to warm slowly to room temperature for 15 hours, and then quenched by the addition of saturated $NaHCO_3$ solution (10 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product, which was taken up in THF (3 mL) and cooled to 0 °C. In a separate flask, glacial AcOH (0.04 mL, 0.64 mmol) was added to a solution of TMSCN (0.05 mL, 0.38 mmol) in THF (1 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours, and then added to the stirred iminium ion solution. The resulting combined mixture was allowed to warm to room temperature for 15 hours. Water was added followed by saturated, aqueous $NaHCO_3$solution (15 mL). The mixture was extracted with Et_2O (3 x 20 mL). The combined organic washings were washed with saturated, aqueous $NaHCO_3$ solution (30 mL) and then brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (4% EtOAc in petroleum ether) afforded (1*R*,3a*R*,6a*S*)-2-benzyl-octahydro-1-isopropyl-3-3-diphenylcyclopenta[*c*]pyrrole-1-carbonitrile **303** (31.0 mg, 0.07 mmol, 28%) as a colourless oil. R_f = 0.21 (4% EtOAc in petroleum ether); ν_{max} (film) 2965, 1704, 1599, 1494, 1446, 910, 734, 703 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40-6.96 (13H, m, 13 x CH, Ph), 6.40 (2H, d, *J* = 7.2 Hz, 2 x CH, Ph), 4.38 (1H, d, *J* = 16.0 Hz, 1 x

PhC*H*H), 4.25 (1H, d, *J* = 16.0 Hz, 1 x PhCH*H*), 3.43-3.36 (1H, m, CH), 3.02-2.96 (1H, m, CH), 2.01-1.96 (2H, m, cp ring CH_2), 1.82-1.67 (2H, m, C*H*$(CH_3)_2$, and cp ring C*H*H), 1.47-1.37 (1H, m, cp ring CH*H*), 1.32-1.23 (1H, m, cp ring C*H*H), 1.17-1.11 (1H, m, cp ring CH*H*), 0.93 (3H, d, *J* = 6.7 Hz, CH(C*H*$_3)_2$), 0.32 (3H, d, *J* = 6.7 Hz, CH(C*H*$_3)_2$) ppm; δ_C (100 MHz, $CDCl_3$) 149.1 (C, Ph), 143.9 (C, Ph), 140.3 (C, Ph), 130.3 (2 x CH, Ph), 128.5 (2 x CH, Ph), 128.5 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.2 (2 x CH, Ph), 126.8 (CH, Ph), 126.5 (CH, Ph), 126.3 (CH, Ph), 122.2 (C≡N), 79.3 (*C*Ph_2), 77.1 (*C*(CN)(^{i}Pr)), 57.1 (CH), 52.0 ($PhCH_2$), 45.7 (CH), 34.2 (*C*H$(CH_3)_2$), 32.3 (CH_2), 30.2 (CH_2), 27.0 (CH_2), 19.3 (CH(*C*H$_3)_2$), 15.9 (CH(*C*H$_3)_2$) ppm; MS (ES^+) *m/z* 394 [M-C≡N^+]; HRMS (ES^+) calcd. for $C_{29}H_{32}N$ [M-C≡N^+]: 394.2529; found 394.2534.

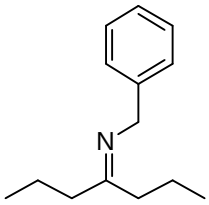
_N,N_-Diethyl-2-methylbenzamide 329[158]



2-Methylbenzoyl chloride (2.64 mL, 20.0 mmol) was added to a stirred solution of Et_2NH (2.29 mL, 22.0 mmol) and Et_3N (5.60 mL, 40.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C. A white precipitate formed. The resulting suspension was stirred for 75 minutes. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with 2M HCl (30 mL) followed by 10% NaOH solution (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by bulb-to-bulb distillation (135 °C, 0.4 mmHg) afforded *N*,*N*-diethyl-2-methylbenzamide **329** (3.25 g, 16.99 mmol, 85%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.28-7.13 (4H, m, 4 x CH, Ph), 3.58 (2H, br m, CH_2), 3.12 (2H, q, *J* = 6.7 Hz, CH_2), 2.29 (3H, s, $PhCH_3$), 1.26 (3H, t, *J* = 6.7 Hz, CH_3), 1.03 (3H, t, *J* = 6.7 Hz, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 170.8 (C=O), 137.2 (C, Ph), 133.8 (C, Ph), 130.3 (CH, Ph),

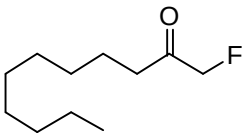
128.5 (CH, Ph), 125.8 (CH, Ph), 125.4 (CH, Ph), 42.6 (CH_2), 38.7 (CH_2), 18.6 (CH_3), 13.8 (CH_3), 12.8 (CH_3) ppm.

_N_-(Heptan-4-ylidene)(phenyl)methanamine 331[160]



4-Heptanone (10.3 mL, 71.9 mmol), benzylamine (6.6 mL, 59.9 mmol) and *p*-toluenesulfonic acid (0.58 g, 3.00 mmol) were dissolved in toluene (60 mL), attached to a Dean-Stark apparatus and heated at 140 °C for 72 hours. Upon cooling to room temperature, the toluene was removed under reduced pressure. The crude residue was dissolved in EtOAc (150 mL) and passed through a short plug of K_2CO_3. Concentration of the filtrate *in vacuo* gave the crude product. Purification by bulb-to-bulb distillation (130 °C, 0.4 mmHg) afforded *N*-(heptan-4-ylidene)(phenyl)methanamine **331** (6.25 g, 30.7 mmol, 51%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.34-7.28 (4H, m, 4 x CH, Ph), 7.24-7.17 (1H, m, CH, Ph), 4.55 (2H, s, $PhCH_2$), 2.31-2.24 (4H, m, 2 x CH_2), 1.67-1.47 (4H, m, 2 x CH_2), 0.97-0.93 (6H, m, 2 x CH_3) ppm; MS (CI) 204 [MH^+].

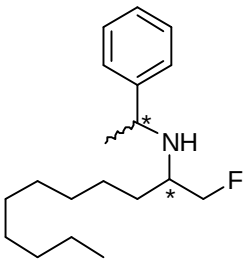
1-Fluoroundecan-2-one 342



Copper(I) iodide (72.0 mg, 0.38 mmol) was flame-dried under vacuum and then purged with N_2 (three cycles performed). THF (6 mL) was added and the mixture cooled to -30 °C, whereupon octylmagnesium chloride (2.83 mL, 5.65 mmol) was added. After 10 minutes, a solution of 2-methylene-1-(1-phenylethyl)aziridine (±)-**169** (300 mg, 1.88 mmol) in THF (3 mL) was added and the reaction mixture stirred at room temperature for 15 hours. Upon cooling to 0 °C, a solution of *N*-fluorobenzenesulfonimide (673 mg, 2.07 mmol) in THF (6 mL) was added dropwise, and the mixture heated at 45

°C for 3 hours. Upon cooling to room temperature, 10% aqueous HCl (6 mL) was added, and the mixture heated at 50 °C for 2 hours. Upon cooling to room temperature, solid NaCl was added and the mixture partitioned between Et_2O (30 mL) and saturated aqueous NH_4Cl (20 mL). The organic layer was washed successively with saturated aqueous NH_4Cl (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (1% Et_2O in petroleum ether) afforded 1-fluoroundecan-2-one **342** (40.0 mg, 0.21 mmol, 11%) as a pale yellow oil. R_f = 0.56 (10% EtOAc in petroleum ether); ν_{max} (neat) 2923, 2845, 1727, 1465, 1377, 1045, 720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.80 (2H, d, J_{HF} = 47.6 Hz, CH_2F), 2.53 (2H, dt, J_{HF} = 2.8 Hz, J_{HH} = 7.4 Hz, $CH_2C{=}O$), 1.67-1.57 (2H, m, CH_2), 1.38-1.20 (12H, m, 6 x CH_2), 0.88 (3H, m, CH_3) ppm; δ_C (75 MHz, $CDCl_3$) 206.6 (1C, d, J_{CF} = 18.8 Hz, C=O), 84.3 (1C, d, J_{CF} = 183.8 Hz, CH_2F), 37.7 (CH_2), 31.2 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 22.1 (CH_2), 22.0 (CH_2), 13.6 (CH_3) ppm; δ_F (376 MHz, $CDCl_3$) -227.4 (1F, t, J_{HF} = 47.6 Hz, CH_2F) ppm; MS (ES^-) *m/z* 187 [$M\text{-}H^+$]; HRMS (ES^-) calcd. for $C_{11}H_{20}OF$ [$M\text{-}H^+$]: 187.1493; found 187.1489.

1-Fluoro-*N*-(1-phenylethyl)undecan-2-amine 343

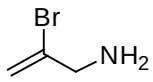


Copper(I) iodide (48.0 mg, 0.25 mmol) was flame-dried under vacuum and then purged with N_2 (three cycles performed). THF (4 mL) was added and the mixture cooled to -30 °C, whereupon octylmagnesium chloride (1.88 mL, 3.77 mmol) was added. After 10 minutes, a solution of 2-methylene-1-(1-phenylethyl)aziridine (±)-**169** (200 mg, 1.26 mmol) in THF (2 mL) was added and

the reaction mixture stirred at room temperature for 15 hours. Upon cooling to 0 °C, a solution of *N*-fluorobenzenesulfonimide (449 mg, 1.38 mmol) in THF (4 mL) was added dropwise, and the mixture heated at 45 °C for 3 hours. Upon cooling to room temperature, the mixture was added *via* canula to a stirred solution of $NaBH_4$ (145 mg, 3.77 mmol) in glacial AcOH (2.5 mL) at 10 °C. The resulting mixture was stirred for 2 hours, whereupon water (10 mL) was added followed by 10% NaOH solution (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed successively with saturated aqueous NH_4Cl solution (40 mL), saturated aqueous $NaHCO_3$ solution (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (0.5% Et_3N and 0-2% MeOH in CH_2Cl_2) afforded 1-fluoro-*N*-(1-phenylethyl)undecan-2-amine **343** (15.0 mg, 0.05 mmol, 4%) as an inseparable mixture of diastereomers (50:50). R_f = 0.53 (10% EtOAc in petroleum ether); ν_{max} (neat) 2924, 2854, 1453, 1370, 1003, 761, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35-7.20 (10H, m, 10 x $CH_{Dia\text{-}A+B}$, Ph), 4.44 (2H, ddd, J_{HF} = 48.0 Hz, J_{HH} = 9.3, 4.0 Hz, $CH_2F_{Dia\text{-}A}$), 4.28 (2H, ddd, J_{HF} = 48.0 Hz, J_{HH}= 9.3, 4.0 Hz, $CH_2F_{Dia\text{-}B}$), 3.94 (2H, q, J = 6.6 Hz, 2 x $CH_{Dia\text{-}A+B}$), 2.61-2.53 (1H, m, CH), 2.53-2.46 (1H, m, CH), 1.50-1.10 (34H, m, 2 x $NH_{Dia\text{-}A+B}$, 8 x $CH_{2Dia\text{-}A}$ and 8 x$CH_{2\ Dia\text{-}B}$), 1.34 (6H, d, J = 6.6 Hz, 2 x $CH_{3Dia\text{-}A\ +\ B}$), 0.88 (6H, t, J = 6.8 Hz, 2 x $CH_{3Dia\text{-}A\ +\ B}$) ppm; δ_C (100 MHz, $CDCl_3$) 147.8 (2 x C, Ph), 128.4 (4 x CH, Ph), 126.9 (2 x CH, Ph), 126.7 (4 x CH, Ph), 85.7 ($CH_2F_{Dia\text{-}B}$), 84.0 ($CH_2F_{Dia\text{-}A}$), 55.4 (2 x CH), 54.3 ($CH_{Dia\text{-}A}$), 54.1 ($CH_{Dia\text{-}B}$), 32.1 (2 x CH_2), 32.0 ($CH_{2Dia\text{-}A}$), 31.9 ($CH_{2Dia\text{-}B}$), 29.6 (2 x CH_2), 29.6 (2 x CH_2), 29.5 (2 x CH_2), 29.3 (2 x CH_2), 25.8 (2 x CH_2), 25.1 (2 x CH_3), 22.7 (2 x CH_2), 14.2 (2 x CH_3) ppm; δ_F

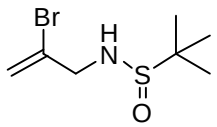
(282 MHz, $CDCl_3$) -229.8 (1F, s, CH_2F) ppm; MS (ES^+) *m/z* 294 [MH^+]; HRMS (ES^+) calcd. for $C_{19}H_{33}FN$ [MH^+]: 294.2592; found 294.2580.

2-Bromoprop-2-en-1-amine 369[174]



A solution of hexamethylenetetramine (12.1 g, 85.2 mmol) in $CHCl_3$ (80 mL) was heated at reflux temperature whilst a solution of 2,3-dibromopropene (10.0 mL, 77.4 mmol) in $CHCl_3$ (20 mL) was added over a 60 minute period. The resulting mixture was heated at reflux temperature for 4 hours. Upon cooling to room temperature, the mixture was filtered, the filter cake washed with ice-cold $CHCl_3$ and dried *in vacuo* to afford the crude quaternary ammonium salt. The ammonium salt was dissolved in a solution of concentrated HCl (60 mL), water (50 mL) and EtOH (235 mL), and stirred at room temperature for 72 hours. The solvents were removed under reduced pressure, the residue dissolved in water (150 mL) and basified with 10% NaOH solution. The aqueous phase was saturated with NaCl and then extracted with Et_2O (3 x 200 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by bulb-to-bulb distillation (50 °C, 20 mmHg) afforded 2-bromoprop-2-en-1-amine **369** (6.55 g, 48.2 mmol, 62%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 5.78 (1H, d, *J* = 1.9 Hz, =C*H*H), 5.48 (1H, d, *J* = 1.9 Hz, =CH*H*), 3.47 (2H, s, CH_2), 1.86 (2H, br s, NH_2) ppm; δ_C (75 MHz, $CDCl_3$) 136.6 (=CH_2), 115.4 (CBr), 51.0 (CH_2) ppm.

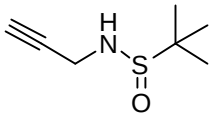
***N*-(*tert*-Butylsulfinyl)-2-bromoprop-2-en-1-amine 375**



An ice-cold solution of *tert*-butylsulfinyl chloride (0.94 mL, 7.35 mmol) in CH_2Cl_2 (25 mL) was added dropwise to a stirred solution of 2-bromoprop-2-en-1-amine **369** (500 mg, 3.68 mmol) and Et_3N (5.15

mL, 36.76 mmol) in CH_2Cl_2 (35 mL) at 0 °C. The resulting mixture was allowed to slowly warm to room temperature for 15 hours. The mixture was diluted with saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (1% Et_3N and 60% EtOAc in petroleum ether) afforded *N*-(*tert*-butylsulfinyl)-2-bromoprop-2-en-1-amine **375** (670 mg, 2.79 mmol, 76%) as an off-white solid. mp 48-50 °C (from EtOAc/petroleum ether); R_f = 0.31 (60% EtOAc in petroleum ether); ν_{max} (neat) 3185, 2958, 2360, 1638, 1362, 1046, 894 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.94-5.93 (1H, m, =C*H*H), 5.60-5.59 (1H, m, =CH*H*), 4.02 (1H, dd, *J* = 15.7, 6.2 Hz, C*H*H), 3.92 (1H, dd, *J* = 15.7, 6.7 Hz, CH*H*), 3.57 (1H, br t, NH), 1.26 (9H, s, $C(CH_3)_3$) ppm; δ_C (75 MHz, $CDCl_3$) 130.6 (CBr), 118.7 ($=CH_2$), 56.3 ($C(CH_3)_3$), 53.5 (CH_2), 22.6 ($C(CH_3)_3$) ppm; MS (CI) *m/z* 240 [MH^+, ^{79}Br], 242 [MH^+, ^{81}Br]; HRMS (ES^+) calcd. for $C_7H_{14}BrNNaOS$ [MNa^+, ^{79}Br]: 261.9872; found 261.9863, [MNa^+, ^{81}Br]: 263.9851; found 263.9844; Anal. calcd. for $C_7H_{14}BrNOS$: C, 35.01; H, 5.88; N, 5.83; Br, 33.27; S, 13.35%; found: C, 35.06; H, 5.89; N, 5.79; Br, 32.53; S, 13.23%.

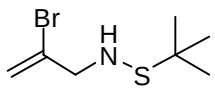
2-Methyl-propane-2-sulfinic acid prop-2-ynyl amide 381



Iron(III) nitrate nonahydrate (3.00 mg, 8.33 µmol), sodium (383 mg, 16.7 mmol) and *N*-(*tert*-butylsulfinyl)-2-bromoprop-2-en-1-amine **375** (400 mg, 1.67 mmol) were reacted together in ammonia (10 mL) at -33 °C for 1 hour, in accordance with general method A. After work-up, purification by bulb-to-bulb distillation (135 °C, 0.4 mmHg) afforded 2-methyl-propane-2-sulfinic acid prop-2-ynyl amide **381** (151 mg, 0.95 mmol, 57%) as a

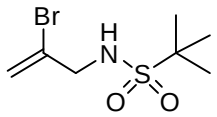
pale, yellow oil. R_f = 0.42 (80% EtOAc in petroleum ether); ν_{max} (neat) 3207, 2958, 2361, 2117, 1655, 1364, 1047 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.96 (1H, ddd, *J* = 17.0, 5.6, 2.5 Hz, C*H*H), 3.87 (1H, ddd, *J* = 17.0, 6.3, 2.5 Hz, CH*H*), 3.43 (1H, br t, NH), 2.34 (1H, t, *J* = 2.5 Hz, CH), 1.24 (9H, s, $C(CH_3)_3$) ppm; δ_C (75 MHz, $CDCl_3$) 79.5 (C≡), 72.1 (C≡), 55.5 ($C(CH_3)_3$), 34.0 (CH_2), 21.9 ($C(CH_3)_3$) ppm; MS (CI) *m/z* 160 [MH^+]; HRMS (ES^+) calcd. for $C_7H_{13}NNaOS$ [MNa^+]: 182.0610; found 182.0612.

_N_-(_tert_-Butylsulfenyl)-2-bromoprop-2-en-1-amine 382



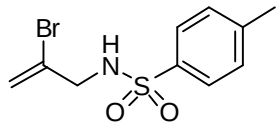
To a stirred solution of *t*-butyldisulfide (0.37 mL, 1.86 mmol) in $CHCl_3$ (2 mL) at -20 °C, was added sulfuryl chloride (0.15 mL, 1.86 mmol). A bright yellow solution resulted. The mixture was allowed to warm to room temperature, and then stirred for 1 hour whereupon the mixture was concentrated *in vacuo*. The residue was dissolved in THF (1 mL) and added to a stirred solution of 2-bromoprop-2-en-1-amine **369** (505 mg, 3.71 mmol) and Et_3N (2.60 mL, 18.57 mmol) in THF (10 mL) at 0 °C. The resulting mixture was allowed to stir at room temperature for 15 hours. The white triethylamine hydrochloride salt was filtered and the filtrate concentrated *in vacuo* to give the crude product. Purification on basic alumina (0-2% Et_2O in petroleum ether) afforded *N*-(*tert*-butylsulfenyl)-2-bromoprop-2-en-1-amine **382** (8.0 mg, 0.036 mmol, 2%) as an oil. R_f = 0.36 (4% Et_2O in petroleum ether); ν_{max} (neat) 3328, 2958, 1630, 1454, 1361, 1162, 1054, 894 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.89-5.88 (1H, m, =C*H*H), 5.59-5.58 (1H, m, =CH*H*), 3.76 (2H, d, *J*= 5.8 Hz, CH_2), 2.96 (1H, br s, NH), 1.39 (9H, s, $C(CH_3)_3$) ppm; δ_C (125 MHz, $CDCl_3$) 129.4 (CBr), 117.8 (=CH_2), 57.5 (CH_2), 49.9 ($C(CH_3)_3$), 29.6 ($C(CH_3)_3$) ppm.

_N_-(_tert_-Butylsulfonyl)-2-bromoprop-2-en-1-amine 388



To a stirred solution of *N*-(*tert*-butylsulfinyl)-2-bromoprop-2-en-1-amine **375** (124 mg, 0.52 mmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (150 mg, 0.67 mmol). The resulting mixture was stirred at room temperature for 15 hours, and then diluted with a 1:1 mixture of saturated, aqueous $NaHSO_3$ and $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (2 x 20 mL) The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (30% EtOAc in petroleum ether) afforded *N*-(*tert*-butylsulfonyl)-2-bromoprop-2-en-1-amine **388** (59.0 mg, 0.23 mmol, 44%) as a white solid. mp 108-110 °C; R_f = 0.54 (30% EtOAc in petroleum ether); ν_{max} (neat) 3262, 2698, 2359, 1634, 1431, 1296, 1123, 1074, 841 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.95-5.93 (1H, m, =C*H*H), 5.62-5.61 (1H, m, =CH*H*), 4.24 (1H, br t, NH), 4.00 (2H, d, *J* = 6.5 Hz, CH_2), 1.41 (9H, s, $C(CH_3)_3$) ppm; δ_C (75 MHz, $CDCl_3$) 128.9 (CBr), 118.0 ($=CH_2$), 59.6 ($C(CH_3)_3$), 51.4 (CH_2), 23.6 ($C(CH_3)_3$) ppm; MS (EI) *m/z* 254 [M^+, ^{79}Br], 256 [M^+, ^{81}Br]; HRMS (ES^+) calcd. for $C_7H_{14}BrNNaO_2S$ [MNa^+, ^{79}Br]: 277.9821; found 277.9817, [MNa^+, ^{81}Br]: 279.9800; found 279.9793.

2-Bromo-_N_-tosylprop-2-en-1-amine 359



To a stirred solution of 2-bromoprop-2-en-1-amine **369** (507 mg, 3.73 mmol) and Et_3N (0.55 mL, 3.91 mmol) in THF (3.5 mL) was added a solution of *p*-toluenesulfonyl chloride (761 mg, 3.91 mmol) in THF (3.5 mL). A white precipitate formed. The resulting mixture was stirred at room temperature for 15 hours and then diluted with water (10 mL). The mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts

were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification on silica (5-50% EtOAc in petroleum ether) afforded 2-bromo-*N*-tosylprop-2-en-1-amine **359** (732 mg, 2.52 mmol, 68%) as a white solid. R_f = 0.49 (30% EtOAc in petroleum ether); ν_{max} (neat) 3254, 1632, 1598, 1320, 1158, 1051, 734 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.2 Hz, 2 x CH, Ph), 7.32 (2H, d, *J* = 8.2 Hz, 2 x CH, Ph), 5.81-5.79 (1H, m, =C*H*H), 5.48-5.47 (1H, m =CH*H*), 4.93 (1H, br t, *J* = 6.6 Hz, NH), 3.85 (2H, d, *J* = 6.6 Hz, CH_2), 2.44 (3H, s, CH_3), ppm; δ_C (100 MHz, $CDCl_3$) 143.8 (C, Ph), 137.0 (C, Ph), 129.8 (2 x CH, Ph), 128.0 (CBr), 127.2 (2 x CH, Ph), 119.0 (=CH_2), 50.9 (CH_2), 21.6 (CH_3) ppm; MS (CI) *m/z* 290 [MH^+, ^{79}Br], 292 [MH^+, ^{81}Br]; HRMS (ES^+) calcd. for $C_{10}H_{12}BrNNaO_2S$ [MNa^+, ^{79}Br]: 311.9664; found 311.9668, [MNa^+, ^{81}Br]: 313.9644; found 313.9645.

References

[1] T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles: Structures, Reactions, Synthesis and Applications*, Wiley-VCH: Weinheim, **2003**.

[2] W. R. Pitt, D. M. Barry, B. G. Perry, C. R. Groom, *J. Med. Chem.*, **2009**, *52*, 2952.

[3] R. R. Gupta, A. Hassner, *Synthesis of Heterocycles via Cycloadditions I*, Springer-Verlag Berlin Heidelberg, **2008**.

[4] *Cycloaddition Reactions in Organic Synthesis*, S. Kobayashi, and K. A. Jørgensen, Eds. Wiley-VCH: Weinheim, **2002.**

[5] W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Oxford, **1990**.

[6] (a) R. Huisgen, *Angew. Chem. Int. Ed. Engl*., **1963**, *2*, 565; (b) R. Huisgen, *Angew. Chem. Int. Ed. Engl*., **1963**, *2*, 633.

[7] R. Huisgen, *Angew. Chem. Int. Ed. Engl*., **1968**, *7*, 321.

[8] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.*, **2001**, *40*, 2004.

[9] R. Huisgen, *J. Org. Chem*., **1976**, *41*, 403.

[10] K. V. Gothelf, K. A. Jørgensen, *Chem. Rev*., **1998**, *98*, 863.

[11] K. N. Houk, J. Gonzáles, Y. Li, *Acc. Chem. Res*., **1995**, *28*, 81.

[12] R. Huisgen, *J. Org. Chem*., **1968**, *33*, 2291.

[13] (a) R. A. Firestone, *J. Org. Chem*., **1968**, *33*, 2285; (b) R. A. Firestone, *J. Org. Chem*., **1972**, *37*, 2181-2191; (c) R. A. Firestone, *Tetrahedron*, **1977**, *33*, 3009.

[14] K. N. Houk, R. A. Firestone, L. L. Munchausen, P. H. Mueller, B. H. Arison, L. A. Garcia, *J. Am. Chem. Soc*., **1985**, *107*, 7227.

[15] R. B. Woodward, R, Hoffman, *The Conservation of Orbital Symmetry*, Verlag Chemie: Weinheim, Germany, **1970**.

[16] R. Huisgen, R. Weinberger, *Tetrahedron Lett.*, **1985**, *26*, 5119.

[17] (a) R. Huisgen, G. Mloston, E. Langhaus, *J. Am. Chem. Soc*., **1986**, *108*, 6401; (b) *J. Org. Chem.*, **1986**, *51*, 4085-4087; (c) *Tetrahedron Lett*., **1989**, *30*, 5373.

[18] I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, Chichester, **1976**.

[19] (a) R. Sustmann, *Tetrahedron Lett*., **1971**, *12*, 2717; (b) R. Sustmann, H. Trill, *Angew. Chem. Int. Ed*., **1972**, *11*, 838; (c) R. Sustmann, *Pure Appl. Chem*., **1974**, *40*, 579; (d) K. N. Houk, in *1,3-Dipolar Cycloaddition Chemistry*, A. Padwa, Ed. John Wiley and Sons: New York, **1984**.

[20] D. H. Ess, K. N. Houk, *J. Am. Chem. Soc*., **2008**, *130*, 10187.

[21] X. E. Hu, *Tetrahedron*, **2004**, *60*, 2701.

[22] C. Luigi, B. Franco, L. P. Piero, *Synthesis*, **1994**, 287.

[23] a) C. Gaebert, C. Siegner, J. Mattay, M. Toubartz, S. Steenken, *J. Chem. Soc., Perkin Trans. 2*, **1998**, 2735; b) P. D. Pohlhaus, R. K. Bowman, J. S. Johnson, *J. Am. Chem. Soc.*, **2004**, *126*, 2294.

[24] A. Paasche, M. Arnone, R. F. Fink, T. Schirmeister, B. Engels, *J. Org. Chem.*, **2009**, *74*, 5244.

[25] a) E. Vedejs, F. G. West, *Chem. Rev.*, **1986**, *86*, 941; b) Y. Terao, M. Aono, K. Achiwa, *Heterocycles*, **1988**, *27*, 981.

[26] R. Grigg, *Chem. Soc. Rev.*, **1987**, *16*, 89.

[27] a) A. Padwa, S. F. Hornbuckle, *Chem. Rev.*, **1991**, *91*, 263; b) A. Padwa, M. D. Weingarten, *Chem. Rev.*, **1996**, *96*, 223; c) K. G. Rasmussen, K. A. Jørgensen, *J. Chem. Soc., Perkin Trans. 1*, **1997**, 1287.

[28] H. W. Heine, R. Peavy, *Tetrahedron Lett.*, **1965**, *6*, 3123.

[29] A. Padwa, L. Hamilton, *Tetrahedron Lett.*, **1965**, *6*, 4363.

[30] (a) R. Huisgen, W. Scheer, H. Huber, *J. Am. Chem. Soc.*, **1967**, *89*, 1753; (b) R. Huisgen, W. Scheer, G. Szeimies, H. Huber, *Tetrahedron Lett.*, **1966**, *7*, 397.

[31] R. B. Woodward, R. Hoffman, *J. Am. Chem. Soc.*, **1965**, *87*, 395.

[32] I. Coldham, R. Hufton, *Chem. Rev.*, **2005**, *105*, 2765.

[33] Irradiation from a high-pressure mercury lamp, 10-15 °C, 24 h.

[34] SeO_2, 200 °C, Sealed Tube.

[35] H. W. Heine, R. Peavy, A. J. Durbetaki, *J. Org. Chem.*, **1966**, *31*, 3924.

[36] T. Uchida, *J. Chem. Soc., Perkin Trans. 1*, **1978**, *11*, 1315.

[37] K. Matsumoto, H. Iida, T. Uchida, Y. Yabe, A. Kakehi, J. W. Lown, *Can. J. Chem.*, **1994**, *72*, 2108.

[38] R. Huisgen, W. Scheer, H. Mäder, *Angew. Chem., Int. Ed. Engl.*, **1969**, *8*, 602.

[39] P. J. S. Gomes, C. M. Nunes, A. A. C. C. Pais, T. M. V. D. Pinho e Melo, L. G. Arnaut, *Tetrahedron Lett.*, **2006**, *47*, 5475.

[40] a) A. Boruah, B. Baruah, D. Prajapati, J. S. Sandhu, A. C. Ghosh, *Tetrahedron Lett.*, **1996**, *37*, 4203; b) F. G. Brunetti, M. A. Herrero, J. Muñoz, S. Giordani, A. Diaz-Ortiz, S. Filippone, G. Ruaro, M. Meneghetti, M. Prato, E. Vázquez, *J. Am. Chem. Soc.*, **2007**, *129*, 14580; c) S. M. M. Lopes, A. M. Beja, M. R. Silva, J. A. Paixão, F. Palacios, T. M. V. D. Pinho e Melo, *Synthesis*, **2009**, *14*, 2403.

[41] P. D. Pohlhaus, R. K. Bowman, J. S. Johnson, *J. Am. Chem. Soc.*, **2004**, *126*, 2294.

[42] S. Wang, Y. Zhu, Y. Wang, P. Lu, *Org. Lett.*, **2009**, *11*, 2615.

[43] J. H. Ahn, M. S. Shin, S. H. Jung, S. K. Kang, K. R. Kim, S. D. Rhee, W. H. Jung, W. H. Jang, S. J. Kim, J. R. Woo, J. H. Lee, H. G. Cheon, S. S. Kim, *J. Med. Chem.*, **2006**, *49*, 4781.

[44] a) K. H. Meyer, K. Schuster, *Chem. Ber*., **1922**, *55*, 819; b) S. Swaminathan, K. V. Narayanan, *Chem. Rev*., **1971**, *71*, 429.

[45] a) M. A. Kuznetsov, A. S. Pan'kova, A. V. Ushkov, S. I. Selivanov, *Russ. J. Org. Chem*., **2008**, *44*, 1780; b) M. A. Kuznetsov, A. V. Ushkov, S. I. Selivanov, A. S. Pan'kova, A. Linden. *Russ. J. Org. Chem*., **2009**, *45*, 1200.

[46] H. Person, K. Luanglath, M. Baudru, A. Foucaud, *Bull. Soc. Chim. Fr*., **1976**, 1989.

[47] J. Charrier, H. Person, A. Foucaud, *Tetrahedron Lett*., **1979**, *16*, 1381.

[48] O. A. Attanasi, P. Davoli, G. Favi, P. Filippone, A. Forni, G. Moscatelli, F. Prati, *Org. Lett*., **2007**, *9*, 3461.

[49] A. S. Pan'kova, V. V. Voronin, M. A. Kuznetsov, *Tetrahedron Lett*., **2009**, *50*, 5990.

[50] a) M. Rossini, R. Budriesi, M. G. Bixel, M. L. Bolognesi, A. Chiarini, F. Hucho, P. Krogsgaard-Larsen, A. Mellor, I. R. Minarini, V. Tumiatti, P. N. R. Usherwood, C. Melchiorre, *J. Med. Chem.*, **1999**, *42*, 5212; b) P. N. Confalone, E. M. Huie, *J. Am. Chem. Soc*., **1984**, *106*, 7175.

[51] A. V. Ushkov, M. A. Kuznetsov, A. Linden, H. Heimgartner, *Helv. Chim. Acta*., **2010**, *93*, 847.

[52] a) G. Mlostoń, A. Linden, H. Heimgartner, *Helv. Chim. Acta.*, **1998**, *81*, 558; b) K. Urbaniak, R, Szymański, J. Romański, G. Mlostoń, M. Domagala, A. Linden, H. Heimgartner, *Helv. Chim. Acta.*, **2004**, *87*, 496; c) G. Mlostoń, K. Urbaniak, M. Domagala, A. Pfitzner, M. Zabel, H. Heimgartner, *Helv. Chim. Acta.*, **2009**, *92*, 2631.

[53] a) F. M. R. Laia, T. M. V. D. Pinho e Melo, *Tetrahedron Lett*., **2009**, *50*, 6180; b) F. M. R. Laia, A. L. Cardoso, A. M. Beja, M. R. Silva, T. M. V. D. Pinho e Melo, *Tetrahedron*, **2010**, *66*, 8815.

[54] a) B. R. Henke, A. J. Kouklis, C. H. Heathcock, *J. Org. Chem*., **1992**, *57*, 7056; b) P. DeShong D. A. Kell, D. R. Sidler, *J. Org. Chem*., **1985**, *50*, 2309; c) A. Padwa, H. Ku, *J. Org. Chem*., **1979**, *44*, 255; d) D. Wenkert, S. B. Ferguson, B. Porter, A. Qvarnstrom, A. T. McPhail, *J. Org. Chem*., **1985**, *50*, 4114.

[55] S. Takano, Y. Iwabuchi, K. Ogasawara, *J. Am. Chem. Soc*., **1987**, *109*, 5523.

[56] a) J. W, Lown, K. Matsumoto, *J. Chem. Soc. D*., **1970**, 692; b) A. Padwa, E. Vega, *J. Org. Chem*., **1975**, *40*, 175.

[57] a) K. Ishii, M. Kido, M. Noji, S. Sugiyama, *Org. Biomol. Chem*., **2008**, *6*, 3186; b) P. Garner, W. B. Ho, S. K. Grandhee, W. J. Youngs, V. O. Kennedy, *J. Org. Chem*., **1991**, *56*, 5893.

[58] a) K. Ishii, M. Noji, Y. Shimada, S. Sugiyama, *J. Chem. Soc*., *Perkin Trans. 1*, **2000**, 3022; b) K. Ishii, T. Sone, Y. Shimada, T. Shigeyama, M. Noji, S. Sugiyama, *Tetrahedron*, **2004**, *60*, 10887; c) K. Ishii, T. Sone, T. Shigeyama, M. Noji, S. Sugiyama, *Tetrahedron*, **2006**, *62*, 10865.

[59] P. Dauban, G. Malik, *Angew. Chem. Int. Ed*., **2009**, *48*, 2.

[60] T. Hiyama, H. Koide, S. Fujita, H. Nozaki, *Tetrahedron*, **1973**, *29*, 3137.

[61] a) J. Wu, X. Sun, H-G. Xia, *Tetrahedron Lett*., **2006**, *47*, 1509; b) M. K. Ghorai, K. Ghosh, K, Das, *Tetrahedron Lett*., **2006**, *47*, 5399.

[62] J. M. Concellón, E. Riego, J. R. Suárez, S. Garcia-Granda, M. R. Diaz, *Org. Lett*., **2004**, *6*, 4499.

[63] a) S. Gandhi, A. Bisai, B. A. Bhanu Prasad, V. K. Singh, *J. Org. Chem*., **2007**, *72*, 2133; b) B. A. Bhanu Prasad, G. Pandey, V. K. Singh, *Tetrahedron Lett*., **2004**, *45*, 1137.

[64] V. K. Yadav, V. Sriramurthy, *J. Am. Chem. Soc*., **2005**, *127*, 16366.

[65] a) M-R. Schneider, A. Mann, M. Taddei, *Tetrahedron Lett*., **1996**, *37*, 8493; b) S. C. Bergmeier, S. L. Fundy, P. P. Seth, *Tetrahedron Lett*., **1999**, *55*, 8025; c) I. Ungureanu, C. Bologa, S. Chayer, A. Mann, *Tetrahedron Lett*., **1999**, *40*, 5315; d) M-R. Schneider, P. Klotz, I, Ungureanu, A. Mann, C-G. Wermuth, *Tetrahedron Lett*., **1999**, *40*, 3873; e) D. J. Lapinsky, S. C. Bergmeier, *Tetrahedron*, **2002**, *58*, 7109-7117; f) S. H. Krake, S. C. Bergmeier, *Tetrahedron*, **2010**, *66*, 7337.

[66] a) S. C. Bergmeier, S. J. Katz, J. Huang, H. McPherson, P. J. Donoghue, D. D. Reed, *Tetrahedron Lett*., **2004**, *45*, 5011; b) J. S. Yadav, B. V. Subba Reddy, S. K. Pandey, P. Srihari, I. Prathap, *Tetrahedron Lett*., **2001**, *42*, 9089.

[67] B. Kang, A. W. Miller, S. Goyal, S. T. Nguyen, *Chem. Commun*., **2009**, 3928.

[68] R. J. Madhushaw, C-C. Hu, R-S. Liu, *Org Lett*., **2002**, *4*, 4151.

[69] I. Ungureanu, P. Klotz, A. Mann, *Angew. Chem. Int. Ed*., **2000**, *39*, 4615.

[70] J. Fan, L. Gao, Z. Wang, *Chem. Commun*., **2009**, 5021.

[71] P. A. Wender, D. Strand, *J. Am. Chem. Soc*., **2009**, *131*, 7528.

[72] W. Zhu, G. Cai, D. Ma, *Org. Lett*., **2005**, *7*, 5545.

[73] C. Gaebert, J. Mattay, *Tetrahedron*, **1997**, *53*, 14297.

[74] O. Kitagawa, Y. Yamada, H. Fujiwara, T. Taguchi, *Angew. Chem. Int. Ed*., **2001**, *40*, 3865.

[75] M. Nakagawa, M. Kawahara, *Org. Lett*., **2000**, *2*, 953.

[76] a) A. W. Miller, S. T. Nguyen, *Org. Lett*., **2004**, *6*, 2301; b) Y. M. Shen, W. L. Duan, M. Shi, *Eur. J. Org. Chem*., **2004**, 3080; c) A. Sudo, Y. Morioka, E. Koizumi, F. Sanda, T. Endo. *Tetrahedron Lett*., **2003**, *44*, 7889; d) M. T. Hancock, A. R. Pinhas, *Tetrahedron Lett*. **2003**, *44*, 5457; e) A. Sudo, Y. Morioka, F. Sanda, T. Endo, *Tetrahedron Lett*., **2004**, *45*, 1363; f) Y. Du, Y. Wu, A-H. Liu, L-N. He, *J. Org. Chem*., **2008**, *73*, 4709; g) H. Kawanami, Y. Ikushima, *Tetrahedron Lett*., **2002**, *43*, 3841; h) P. Tascedda, E. Duñach, *Chem. Commun*., **2000**, 449.

[77] a) Y. Wu, L-N. He, Y. Du, J-Q. Wang, C-X. Miao, W. Li, *Tetrahedron*, **2009**, *65*, 6204; b) X-Y. Dou, L-N. He, Z-Z. Yang, J-L. Wang, *SYNLETT*, **2010**, *14*, 2159; c) H-F. Jiang, J-W. Ye, C-R. Qi, L-B. Huang, *Tetrahedron Lett*., **2010**, *51*, 928.

[78] W. H. Mu, G. A. Chasse, D. C. Fang, *J. Phys. Chem. A*., **2008**, *112*, 6708.

[79] D. C. D. Butler, G. A. Inman, H. Alper, *J. Org. Chem*., **2000**, *65*, 5887.

[80] a) R. Nomura, T. Nakano, Y. Nishio, S. Ogawa, A. Ninagawa, H. Matsuda, *Chem. Ber*., **1989**, *122*, 2407; b) J-Y. Wu, Z-B. Luo, L-X. Dai, X-L. Hou, *J. Org. Chem*., **2008**, *73*, 9137; c) J. E. Ney, J. P. Wolfe, *J. Am . Chem. Soc*., **2006**, *128*, 15415; d) J-O. Baeg, H. Alper, *J. Org. Chem*., **1992**, *57*, 157; e) J-O. Baeg, H. Alper, *J. Am. Chem. Soc*., **1994**, *116*, 1220; f) J-O. Baeg, C. Bensimon, H. Alper, *J. Am. Chem. Soc*., **1995**, *117*, 4700; g) H. Maas, C. Bensimon, H. Alper, *J. Org. Chem*., **1998**, *63*, 17; h) B. M. Trost, D. R. Fandrick, *J. Am. Chem. Soc*., **2003**, *125*, 11836; i) C. Dong, H. Alper, *Tetrahedron: Asymmetry*, **2004**, *15*, 1537; j) U. K. Nadir, N. Basu, *Tetrahedron Lett*., **1992**, *33*, 7949; k) U. K. Nadir, N. Basu, *J. Org. Chem*., **1995**, *60*, 1458; l) M. S. Kim, Y-W. Kim, H. S. Hahm, J. W. Jang, W. K. Lee, H-J. Ha, *Chem. Commun*., **2005**, 3062; m) K. Zhang, P. R. Chopade, J. Louie, *Tetrahedron Lett*., **2008**, *49*, 4306.

[81] B. M. Trost, D. R. Fandrick, *Org. Lett*., **2005**, *7*, 823.

[82] T. Munegumi, I. Azumaya, T. Kato, H. Masu, S. Saito, *Org. Lett*., **2006**, *8*, 379.

[83] B. M. Trost, A. R. Sudhakar, *J. Am. Chem. Soc*., **1987**, *109*, 3792.

[84] D. Craig, R. McCague, G. A. Potter, M. R. V. Williams, *SYNLETT*, **1998**, 55.

[85] R. Bambal, R. D. W. Kemmit, *J. Organomet. Chem*., **1989**, *362*, C18.

[86] a) B. M. Trost, T. M. Nanninga, *J. Am. Chem, Soc*., **1985**, *107*, 1293; b) B. M. Trost, S. Schneider, *Angew. Chem. Int. Ed. Engl*., **1989**, *28*, 213; c) B. M. Trost, *Angew. Chem. Int. Ed. Engl*., **1986**, *25*, 1.

[87] a) S. J. Hedley, W. J. Moran, A. H. G. P. Prenzel, D. A. Price, J. P. A. Harrity, *SYNLETT*, **2001**, *10*, 1596; b) S. J. Hedley, W. J. Moran, D. A. Price, J. P. A. Harrity, *J. Org. Chem*., **2003**, *68*, 4286; c) W. J. Moran, K. M. Goodenough, P. Raubo, J. P. A. Harrity, *Org. Lett*., **2003**, *5*, 3427; d) J. P. A. Harrity, O. Y. Provoost, *Org. Biomol.*

Chem., **2005**, *3*, 1349; e) K. M. Goodenough, P. Raubo, J. P. A. Harrity, *Org. Lett*., **2005**, *7*, 2992; f) O. Y. Provoost, S. J. Hedley, A. J. Hazelwood, J. P. A. Harrity, *Tetrahedron Lett*., **2006**, *47*, 331; g) O. Y. Provoost, A. J. Hazelwood, J. P. A. Harrity, *Beilstein J. Org. Chem*. **2007**, *3*, 8.

[88] a) B. M. Trost, T. M. Nanninga, *J. Am. Chem. Soc*., **1985**, *107*, 1293; b) B. M. Trost, S. Schneider, *Angew. Chem. Int. Ed. Engl*., **1989**, *28*, 213; c) B. M. Trost, *Angew. Chem. Int. Ed. Engl*., **1986**, *25*, 1.

[89] M. Shipman, *SYNLETT*, **2006**, 3205.

[90] a) R. C. Cookson, B. Halton, I. D. R. Stevens, C. T. Watts, *J. Chem. Soc. C*, **1967**, 928; b) M. Shipman, T. M. Ross, A. M. Z. Slawin, *Tetrahedron Lett*., **1999**, *40*, 6091.

[91] a) J. K. Crandell, L. C. Crawley, J. B. Komin, *J. Org. Chem*., **1975**, *40*, 2045; b) N. De Kimpe, D. De Smaele, Z. Sakonyi, *J. Org. Chem*., **1997**, *62*, 2448.

[92] T. Akasaka, Y. Nomura, W. Ando, *J. Org. Chem*., **1988**, *53*, 1670.

[93] a) R. Schmid, H. Schmid, *Helv. Chim. Acta*, **1974**, *57*, 1883; b) N. De Kimpe, M. Palamareva, R. Verhe, L. De Buyck, N. Schamp, *J. Chem. Res. (S)*,**1986**, 190; c) J. Oh, J. Lee, S-J. Jin. J. K. Cha, *Tetrahedron Lett*., **1994**, *35*, 3449; d) J. Lee, J. Oh, S-J. Jin, J-R. Choi, J. L. Atwood, J. K. Cha, *J. Org. Chem*., **1994**, *59*, 6955; e) H. Kim, C. Ziani-Cherif, J. Oh, J. K. Cha, *J. Org. Chem*., **1995**, *60*, 792; f) S-J. Jin, J-R. Choi, J. Oh, D. Lee, J. K. Cha, *J. Am. Chem. Soc*., **1995**, *117*, 10914; g) A. S. Kende, H. Huang, *Tetrahedron Lett*., **1997**, *38*, 3353; h) M. Harmata, *Chem. Commun*., **2010**, *46*, 8886.

[94] a) A. H. Stoll, S. B. Blakey, *J. Am. Chem. Soc*., **2010**, *132*, 2108; b) A. H. Stoll, S. B. Blakey, *Chem. Sci*., **2011**, *2*, 112.

[95] a) B. M. Trost, *Angew. Chem*., **1986**, *98*, 1; b) M. Harmata, *Tetrahedron*, **1997**, *53*, 6235; c) E. Nakamura, S. Yamago, *Acc. Chem. Res*., **2002**, *35*, 867.

[96] a) H. M. R. Hoffman, *Angew. Chem., Int. Ed. Engl*., **1984**, *23*, 1; b) C. B. W. Stark, U. Eggert, H. M. R. Hoffman, *Angew. Chem., Int. Ed.*, **1998**, *37*, 1266; c) C. B. W. Stark, S. Pierau, R. Wartchow, H. M. R. Hoffman, *Chem. Eur. J*., **2000**, *6*, 684.

[97] G. Prié, N. Prévost, H. Twin, S. A. Fernandes, J. R. Hayes, M. Shipman, *Angew. Chem. Int. Ed*., **2004**, *43*, 6517-6519.

[98] H. Twin, Ph.D Thesis, University of Exeter, **2002**.

[99] C. B. Pollard, R. F. Parcell, *J. Am. Chem. Soc*., **1951**, *73*, 2925; For the correct structural assignments, see: A. T. Bottini, J. D. Roberts, *J. Am. Chem. Soc*., **1957**, *79*, 1462.

[100] a) E. M. Bingham, J. C. Gilbert, *J. Org. Chem*., **1975**, *40*, 224; b) J. B. P. A. Wijnberg, P. G. Wiering, H. Steinberg, *Synthesis*, **1981**, 901; c) K. A. Tehrani, N. De Kimpe, *Tetrahedron Lett*., **2000**, *41*, 1975.

[101] D. S. Ennis, J. Ince, S. Rahman, M. Shipman, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2047.

[102] J. Ince, T. M. Ross, M. Shipman, D. S. Ennis, *Tetrahedron: Asymmetry*, **1996**, *7*, 3397.

[103] a) N. Prévost, M. Shipman, *Org. Lett*., **2001**, *3*, 2383; b) N. Prévost, M. Shipman, *Tetrahedron*, **2002**, *58*, 7165.

[104] J. Ince, T. M. Ross, M. Shipman, A. M. Z. Slawin, D. S. Ennis, *Tetrahedron*, **1996**, *52*, 7037.

[105] J. F. Hayes, N. Prévost, I. Prokeš, H. Twin, M. Shipman, A. M. Z. Slawin, *Chem. Commun*., **2003**, 1344.

[106] J. F. Margathe, M. Shipman, S. C. Smith, *Org. Lett*., **2005**, *7*, 4987.

[107] J. F. Hayes, M. Shipman, A. M. Z. Slawin, H. Twin, *Heterocycles*, **2002**, *58*, 243.

[108] J. J. Shiers, M. Shipman, J. F. Hayes, A. M. Z. Slawin, *J. Am. Chem. Soc*., **2004**, *126*, 6868.

[109] A. T. Bottini, R. E. Olsen, *J. Am. Chem. Soc*., **1962**, *84*, 195.

[110] J. J. Shiers, Ph.D Thesis, University of Warwick, **2005**.

[111] C. Montagne, N. Prévost, J. J. Shiers, G. Prié, S. Rahman, J. F. Hayes, M. Shipman, *Tetrahedron*, **2006**, *62*, 8447.

[112] L. Skattebol, *Acta Chem. Scand*., **1963**, *17*, 1683.

[113] H. Lütjens, S. Nowotny, P. Knochel, *Tetrahedron: Asymmetry*, **1995**, *6*, 2675.

[114] E. M. E. Viseux, P. J. Parsons, J. B. J. Pavey, *SYNLETT*, **2003**, *6*, 871.

[115] C. F. Hiskey, H. L. Slates, N. L. Wendler, *J. Org. Chem*., **1956**, *21*, 429.

[116] a) H. Quast, C. A. Weise Vélez, *Angew. Chem., Int. Ed. Engl*., **1974**, *13*, 342; b) H. Quast, C. A. Weise Vélez, *Angew. Chem., Int. Ed. Engl*., **1978**, *17*, 213; c) C. Montagne, N. Prévost, G. Prie, S. Rahman, J. Ince, J. F. Hayes, M. Shipman, *Tetrahedron*, **2006**, *62*, 8447.

[117] C. Montagne, M. Shipman, *Unpublished results*.

[118] The lithiation/alkylation methodogy is limited to the formation of monosubstituted products at C-3. Attempts to subject the monosubstituted products to the same lithiation/alkylation sequence failed to provide the expected 3,3-disubstituted derivatives.

[119] K. M. Gericke, D. I. Chai, M. Lautens, *Tetrahedron*, **2008**, *64*, 6002.

[120] M. V. Baker, D. H. Brown, B. W. Skelton, A. H. White, *J. Chem. Soc., Dalton Trans*., **2000**, 4607.

[121] B. Portevin, C. Tordjman, P. Pastoureau, J. Bonnet, G. De Nanteuil, *J. Med. Chem.*, **2000**, *43*, 4582.

[122] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett*., **1975**, *50*, 4467.

[123] R. Matsubara, T. F. Jamison, *J. Am. Chem. Soc*., **2010**, *132*, 20, 6880.

[124] T. Zheng, R. S. Narayan, J. M. Schomaker, B. Borhan, *J. Am. Chem. Soc*., **2005**, *127*, 6946.

[125] J. M. Humphrey, E. P. Arnold, T. A. Chappie, J. B. Feltenberger, A. Nagel, W. Simon, M. Suarez-Contreras, N. J. Tom, B. T. O'Neill, *J. Org. Chem*., **2009**, *74*, 4525.

[126] D. J. Hart, V. Leroy, *Tetrahedron*, **1995**, *51*, 5757.

[127] J. F. Biellmann, J. B. Ducep, J. L. Schmitt, J. J. Vicens, Tetrahedron, 1976, 32, 1061.

[128] D. M. Smith, M. E. Pulling, J. R. Norton, *J. Am. Chem. Soc*., **2007**, *129*, 770.

[129] W. Biernacki, A. Gdula, *Synthesis*, **1979**, 37.

[130] K. Mori, T. Sugai, Y. Maeda, T. Okasaki, T. Noguchi, H. Naito, *Tetrahedron*, **1985**, *41*, 5307.

[131] G. Belanger, F. Levesque, J. Paquet, G. Barbe, *J. Org. Chem.*, **2005**, *70*, 291.

[132] W. F. Bailey, K. V. Gavaskar, *Tetrahedron*, **1994**, *50*, 5957.

[133] E. M. Campi, J. M. Chong, W. R. Jackson, M. Van Der Schoot, *Tetrahedron*, **1994**, *50*, 8, 2533.

[134] M. R. Siebert, J. M. Osbourn, K. M. Brummond, D. J. Tantillo, *J. Am. Chem. Soc*., **2010**, *132*, 11952.

[135] S. E. Denmark, Z. Wang, *Organic Syntheses*, **2005**, *81*, 54.

[136] M. Konno, T. Nakae, S. Sakuyama, Y. Odagaki, H. Nakai, N. Hamanaka, *Bioorg. Med. Chem*., **1997**, *5*, 1649.

[137] S. Tsuchida, A. Kaneshige, T. Ogaka, H. Baba, Y. Yamamoto, K. Tomioka, *Org. Lett*., **2008**, *10*, 3635.

[138] G. Liu, S. S. Stahl, *J. Am. Chem. Soc*., **2007**, *129*, 6328.

[139] A. R. Thornton, V. I. Martin, S. B. Blakey, *J. Am. Chem. Soc*., **2009**, *131*, 2434.

[140] bp = -6 °C.

[141] Two equivalents of methylamine provided mono- and dialkylated products in a ratio of 23:77 respectively.

[142] For selected reviews on MCRs, see: a) A. Dömling, I. Ugi, *Angew. Chem., Int. Ed. Engl*., **2000**, *39*, 3168; b) R. V. A. Orru, M. DeGreef, *Synthesis* **2003**, 1471; c) J. Zhu, *Eur. J. Org. Chem*., **2003**, 1133; A. Dömling, *Chem. Rev*., **2006**, *106*, 17; d) C. Hulme, V. Gore, *Curr. Med Chem*., **2003**, *1*, 51; e) C. Simon, T. Constantieux, J. Rodriguez, *Eur. J.*

Org. Chem., **2004**, 4957; f) D. J. Ramón, M. Yus, *Angew. Chem. Int. Ed*., **2005**, *44*, 1602; g) J. D. Sunderhaus, S. F. Martin, *Chem. Eur. J*., **2009**, *15*, 1300.

[143] a) P. Biginelli, *Chem. Ber*., **1891**. *24*, 1317; b) P. Biginelli, *Chem. Ber*., **1893**, *26*, 447.

[144] C. Mannich, W. Krosche, *Arch. Pharm*., (*Weinheim Ger*.), **1912**, *250*, 647.

[145] M. Passerini, *Gazz. Chim. Ital*., **1923**, *52*, 126.

[146] a) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, *J. Chem. Soc., Perkin Trans. 1*, **1971**, 36; b) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, M. I. Foreman, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 977.

[147]A. Strecker, *Liebigs Ann. Chem*., **1850**, *75*, 27.

[148] a) I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner, *Angew. Chem*., **1959**, *71*, 386; b) I. Ugi, C. Steinbrückner, *Angew. Chem*., **1960**, *72*, 267.

[149] N. Elders, D. van der Born, L. J. D. Hendrickx, B. J. J. Timmer, A. Krause, E. Janssen, F. J. J. de Kanter, E. Ruijter, R. V.A. Orru, *Angew. Chem. Int. Ed*., **2009**, *48*, 5856.

[150] a) N. Elders, R. F. Schmitz, F. J. J. de Kanter, E. Ruijter, M. B. Groen, R. V. A. Orru, *J. Org. Chem*., **2007**, *72*, 6135; b) R. S. Bon, C. Hong, M. J. Bouma, R. F. Schmitz, F. J. J. de Kanter, M. Lutz, A. L. Spek, R. V. A. Orru, *Org. Lett*., **2003**, *5*, 3759; c) R. S. Bon, B. van Vliet, N. E. Sprenkels, R. F. Schmitz, F. J. J. de Kanter, C. V, Stevens, M. Swart, F. M. Bickelhaupt, M. B. Groen, R. V. A. Orru, *J. Org. Chem*., **2005**, *70*, 3542; d) N. Elders, F. J. J. de Kanter, E. Ruijter, M. B. Groen, R. V. A. Orru, *Chem. Eur. J*., **2008**, *14*, 4961.

[151] N. Elders, E. Ruijter, F. J. J. de Kanter, E. Janssen, M. Lutz, A. L. Spek, R. V. A. Orru, *Chem. Eur. J*., **2009**, *15*, 6096.

[152] C. Montagne, J. J. Shiers, M. Shipman, *Tetrahedron Lett*., **2006**, *47*, 9207.

[153] C. C. A. Cariou, G. J. Clarkson, M. Shipman, *J. Org. Chem*., **2008**, *73*, 9762.

[154] a) J. F. Hayes, M. Shipman, H. Twin, *Chem. Commun*., **2000**, 1791; b) J. F. Hayes, M. Shipman, H. Twin, *J. Org. Chem*., **2002**, *67*, 935.

[155] J. J. Shiers, G. J. Clarkson, M. Shipman, J. F. Hayes, *Chem. Commun*., **2006**, 649.

[156] P. M. Mumford, G. J. Tarver, M. Shipman, *J. Org. Chem*., **2009**, *74*, 3573.

[157] J. F. Hayes, M. Shipman, H. Twin, *Chem. Commun*., **2001**, 1784.

[158] M. Buswell, I. Fleming, U. Ghosh, S. Mack, M. Russell, B. P. Clark, *Org. Biomol. Chem.*, **2004**, *2*, 3006.

[159] a) R. D. Clark, Jahangir, *J. Org. Chem*., **1987**, *52*, 5378; b) R. D. Clark, Jahangir, *J. Org. Chem*., **1988**, *53*, 2378; c) Jahangir, L. E. Fisher, R. D. Clark, J. M. Muchowski, *J. Org. Chem*., **1989**, *54*, 2992.

[160] S. P. G. Costa, H. L. S. Maia, S. M. M. A. Pereira-Lima, *Org. Biomol. Chem*., **2003**, *1*, 1475.

[161] Clark and Jahangir found that quenching at low temperature was necessary in order to eliminate possible side reactions, see ref. 17a.

[162] B. E. Smart, *J. Fluorine Chem*., **2001**, *109*, 3.

[163] a) K. Uneyama, *Organofluorine Chemistry*, Blackwell: Oxford, **2006**; b) J. T. Welch, *Tetrahedron*, **1987**, *43*, 3123; c) T. Hiyama, *Organofluorine Compounds*, H. Yamamoto, Ed.; Springer-Verlag: Berlin, 2000; d) K. L. Kirk, *Curr. Top. Med. Chem*., **2006**, *6*, 1447; e) A. G. Myers, J. K. Barbay, B. Zhong, *J. Am. Chem. Soc*., **2001**, *123*, 7207.

[164] (a) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH: Weinheim, **2004**; (b) *Advances in Organic Synthesis, Vol. 2*, Atta-Ur Rahman, K. K. Laali, Eds., Bentham Science: Hilversum, **2006**.

[165] J. T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, John Wiley and Sons: New York, **1991**.

[166] G. Verniest, E. Van Hende, R. Surmont, N. De Kimpe, *Org. Lett*., **2006**, *8*, 4767.

[167] M. Mąkosza, R. Bujok, *J. Fluorine Chem*., **2005**, *126*, 209.

[168] J. A. Ellman, *Pure Appl. Chem*., **2003**, *75*, 39 and references therein.

[169] a) J. C. Barrow, P. L. Ngo, J. M. Pellicore, H. G. Selnick, P. G. Nantermet, *Tetrahedron Lett*., **2001**, *42*, 2051; b) G. K. S. Prakash, M. Mandal, G. A. Olah, *Angew. Chem., Int. Ed*., **2001**, *40*, 589; c)) G. K. S. Prakash, M. Mandal, G. A. Olah, *Org. Lett*., **2001**, *3*, 2847; d) G. K. S. Prakash, M. Mandal, *J. Am. Chem. Soc*., **2002**, *124*, 6538; e) F. A. Davis, S. Lee, H. Zhang, D. L. Fanelli, *J. Org. Chem*., **2000**, *65*, 8704; f) S. Mabic, A. A. Cordi, *Tetrahedron*, **2001**, *57*, 8861; g) Y. Lee, R. B. Silverman, *Org. Lett*., **2000**, *2*, 303; h) N. Plobeck, D. Powell, *Tetrahedron Asymmetry*, **2002**, *13*, 303; i) D. A. Pflum, D. Krishnamurthy, Z. Han, S. A. Wald, C. H. Senanayake, *Tetrahedron Lett*., **2002**, *43*, 923; j) A. W. Shaw, S. J. de Solms, *Tetrahedron Lett*., **2001**, *42*, 7173; h) L. S. Lin, I. E. Kopka, R. A. Mumford, P. A. Magriotis, T. Lanza, Jr., P. L. Durette, T. Kamenecka, D. N. Young, S. E. De Laszlo, E. McCauley, G. Van Riper, U. Kidambi, L. A. Egger, X. Tong, K. Lyons, S. Vincent, R. Stearns, A. Colletti, Y. Teffera, J. Fenyk-Melody, J. A. Schmidt, M. MacCoss, W. K. Hagmann. *Bioorg. Med. Chem. Lett*., **2002**, *12*, 611.

[170] T. Kochi, T. P. Tang, J. A. Ellman, *J. Am. Chem. Soc*., **2002**, *124*, 6518.

[171] For selected reviews on the Horner-Wadsworth-Emmons reaction, see: a) W. S. Wadsworth Jr., *Org. React*., **1977**, *25*, 73; b) J. Boutagy, R. Thomas, *Chem. Rev*. **1974**, *74*, 87; c) B. E. Maryanoff, A. B. Reitz, *Chem. Rev*., **1989**, *89*, 863; d) S. E. Kelly, *Comp.*

Org. Syn., **1991**, *1*, 729; e) B. Iorga, F. Eymery, V. Mouriès, P. Savignac, *Tetrahedron*, **1998**, *54*, 14637.

[172] C. A. M. Cariou, M. Shipman, *Unpublished work*.

[173] P. M. Mumford, Ph.D Thesis, University of Warwick, **2009**.

[174] A. T. Bottini, V. Dev, J. Klinck, *Organic Syntheses*, **1963**, *43*, 6.

[175] P. Sun, S. M. Weinreb, *J. Org. Chem*., **1997**, *62*, 8604.

[176] S. Kikuchi, H. Konishi, Y. Hashimoto, *Tetrahedron*, **2005**, *61*, 3587.

[177] W. R. Bowman, D. N. Clark, R. J. Marmon, *Tetrahedron*, **1994**, *50*, 1275.

[178] N. Kharasch, S. J. Potempa, H. L. Wehrmeister, *Chem. Rev*., **1946**, *39*, 269.

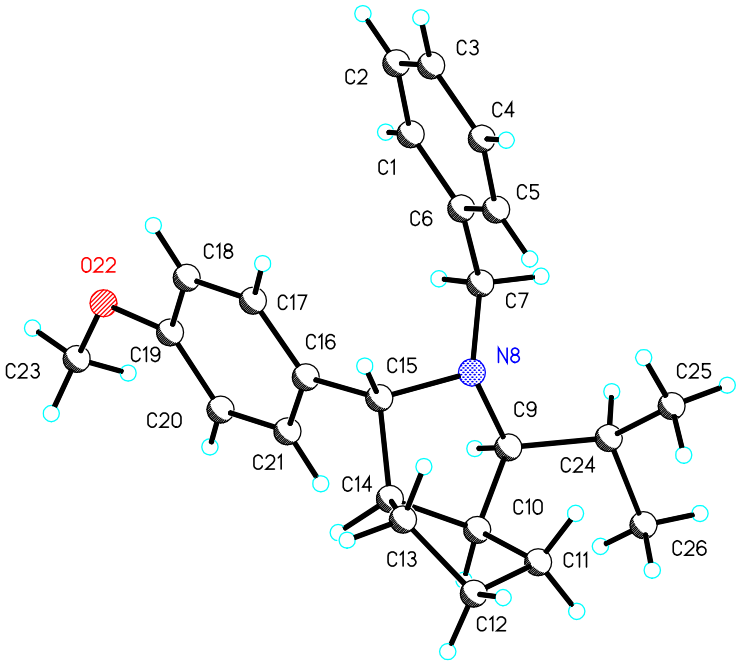
[179] J. Klose, C. B. Reese, Q. Song, *Tetrahedron*, **1997**, *53*, 14411.

[180] H. Brintzinger, K. Pfannstiel, H. Koddebusch, K. E. Kling, *Chem. Ber*., **1950**, *82*, 87.

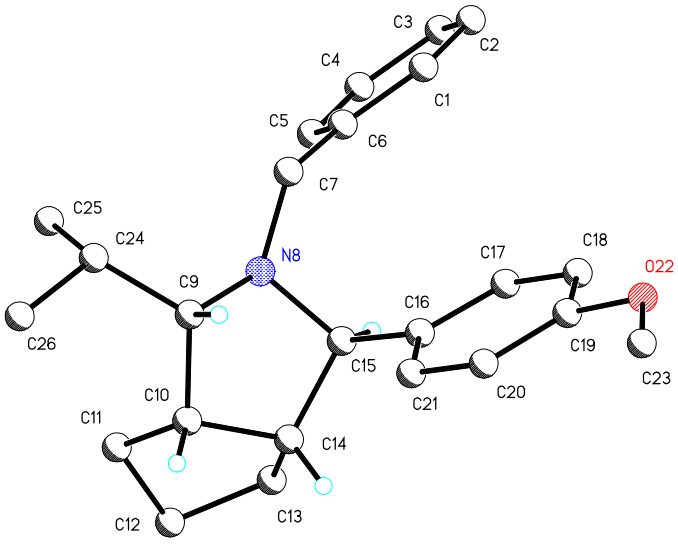
[181] H. Miyauchi, S. Chiba, K. Fukamizu, K. Ando, K. Narasaka, *Tetrahedron*, **2007**, *63*, 5940.

[182] J. Ince, Ph.D Thesis, University of Exeter, **1997**.

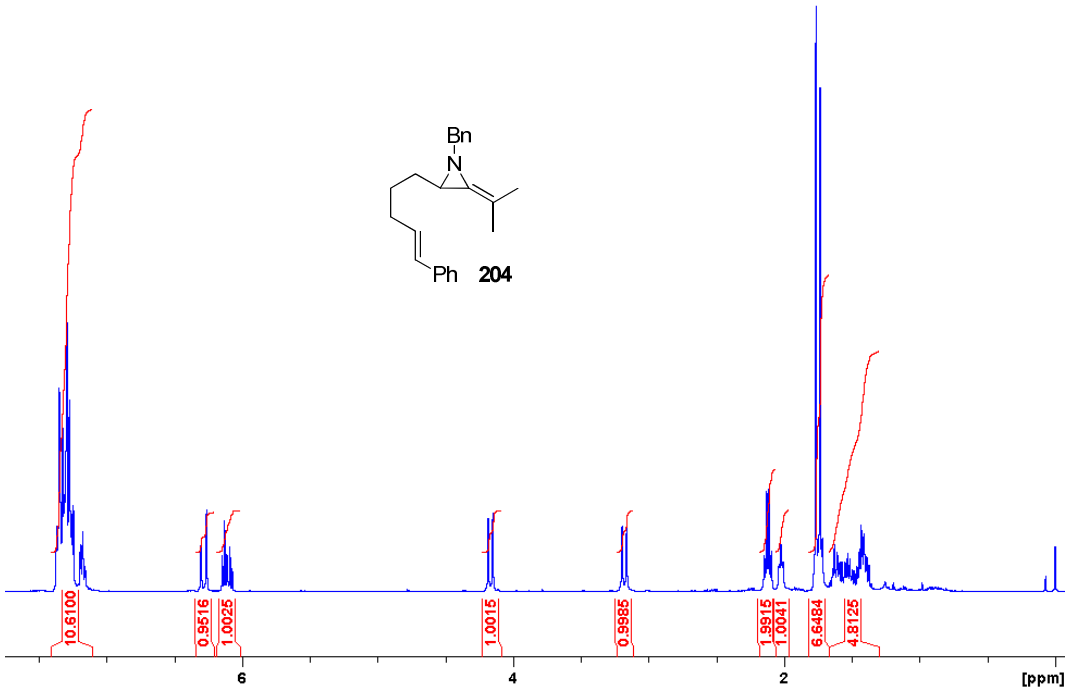
Appendix



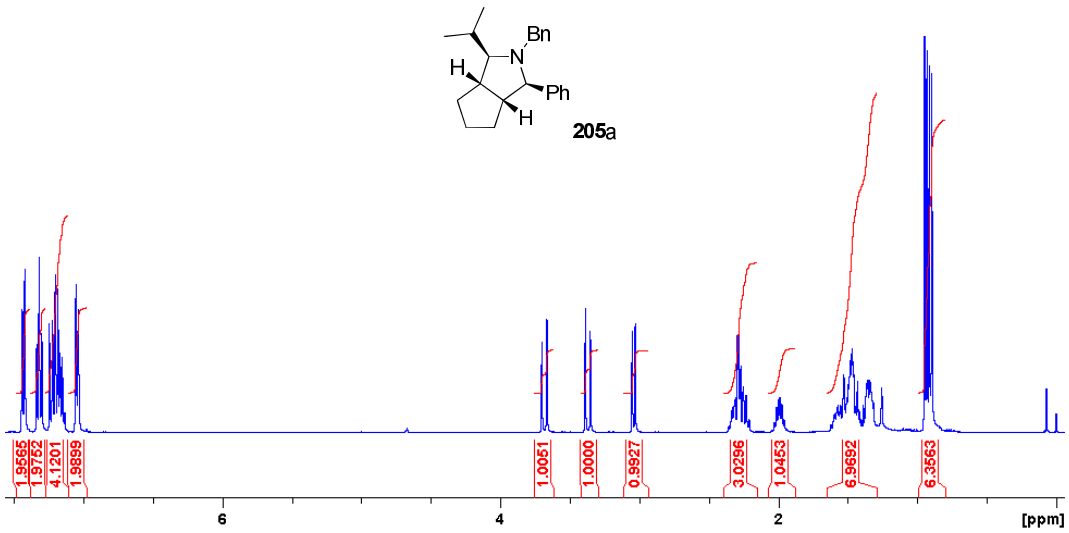
Solid state structure of (1*S*,3*R*,3a*R*,6a*S*)-2-benzyl-octahydro-1-isopropyl-3-(4-methoxyphenyl)cyclopenta[*c*]pyrrole **268b** with atom numbering.



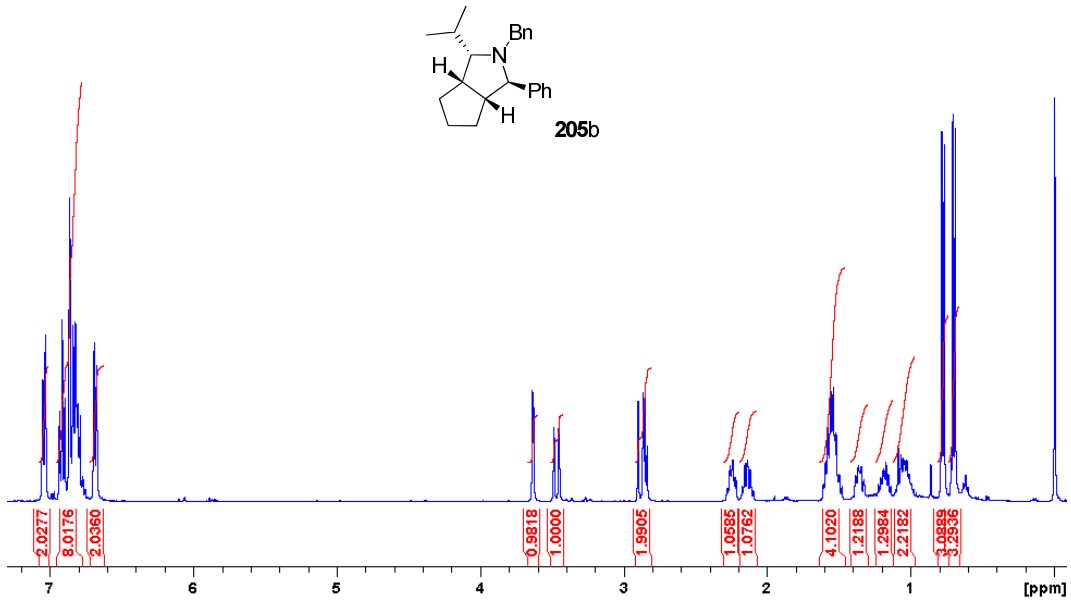
Solid state structure of **268b** with atom numbering, depicting only the chiral hydrogen atoms.



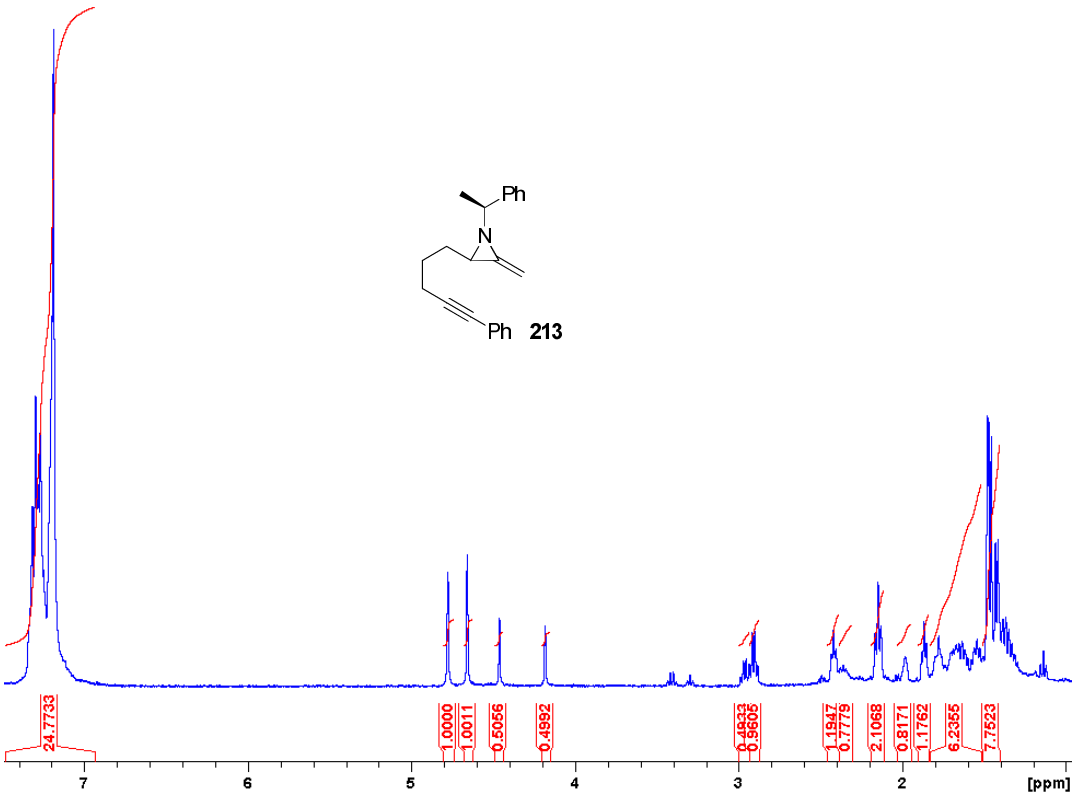
^{1}H NMR spectrum of 204 in $CDCl_3$ at 400 MHz



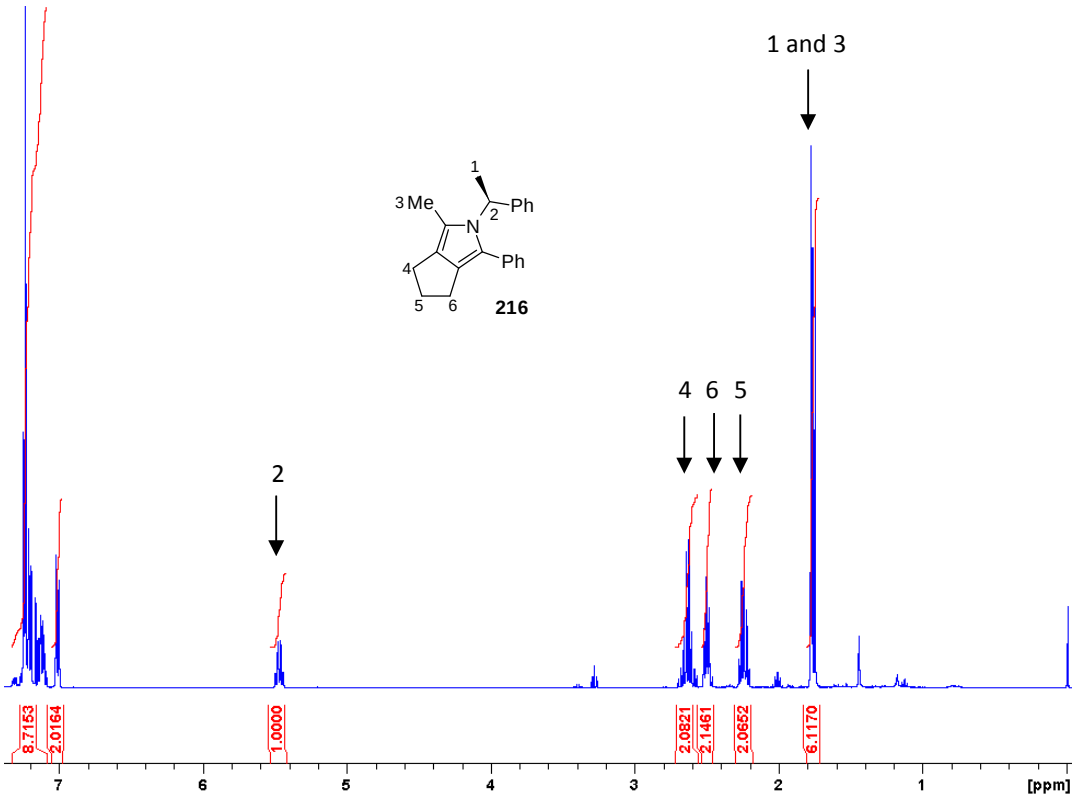
^{1}H NMR spectrum of 205a in $CDCl_3$ at 400 MHz



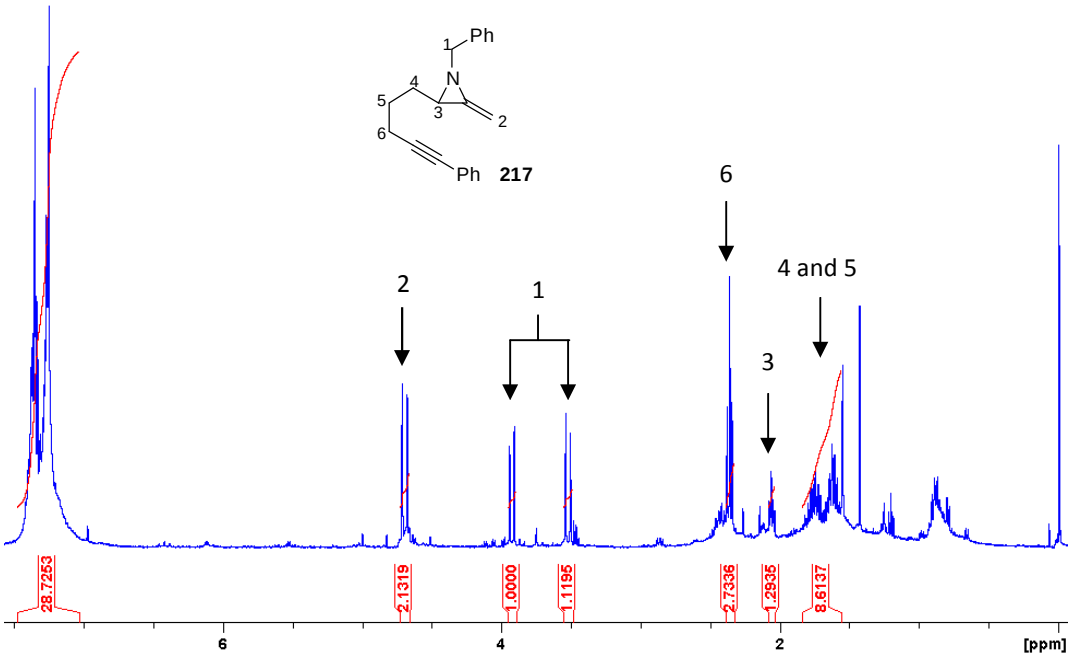
^{1}H NMR spectrum of 205b in C_6D_6 at 400 MHz



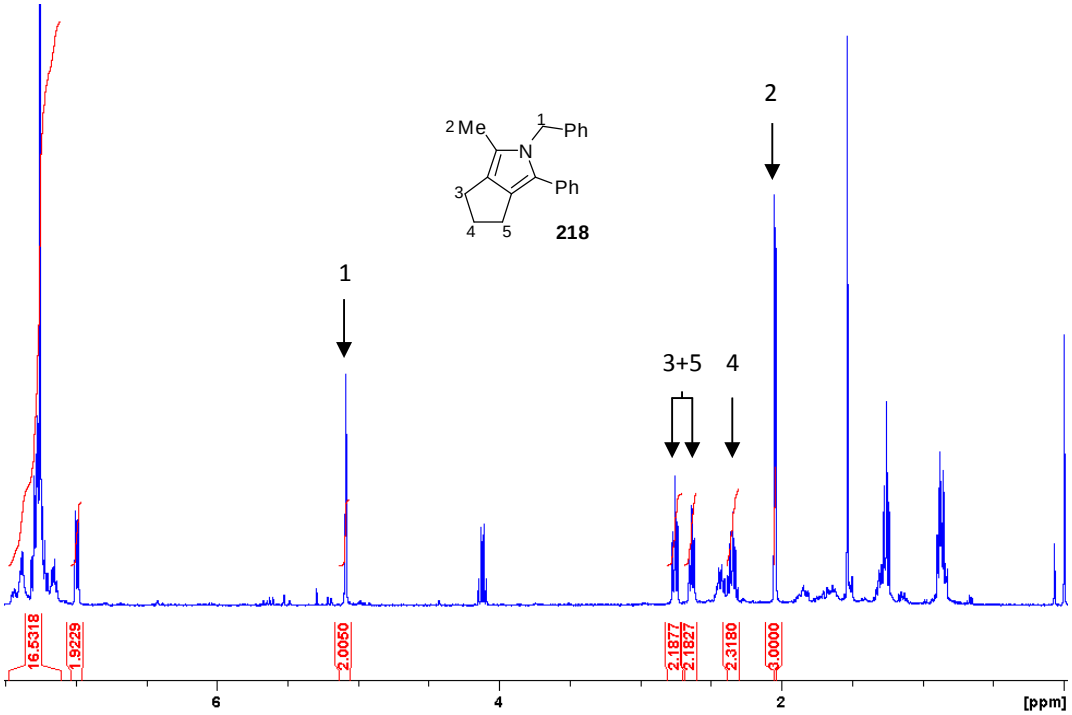
^{1}H NMR spectrum of 213 in $CDCl_3$ at 400 MHz



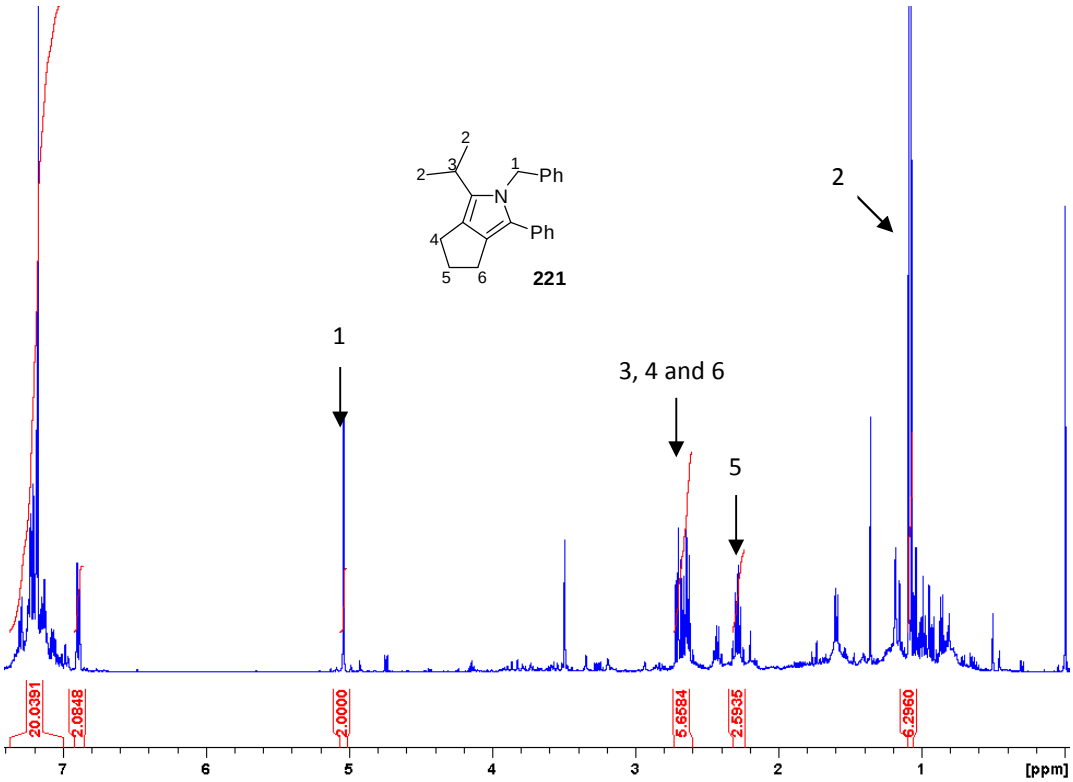
^{1}H NMR spectrum of 216 in $CDCl_3$ at 400 MHz



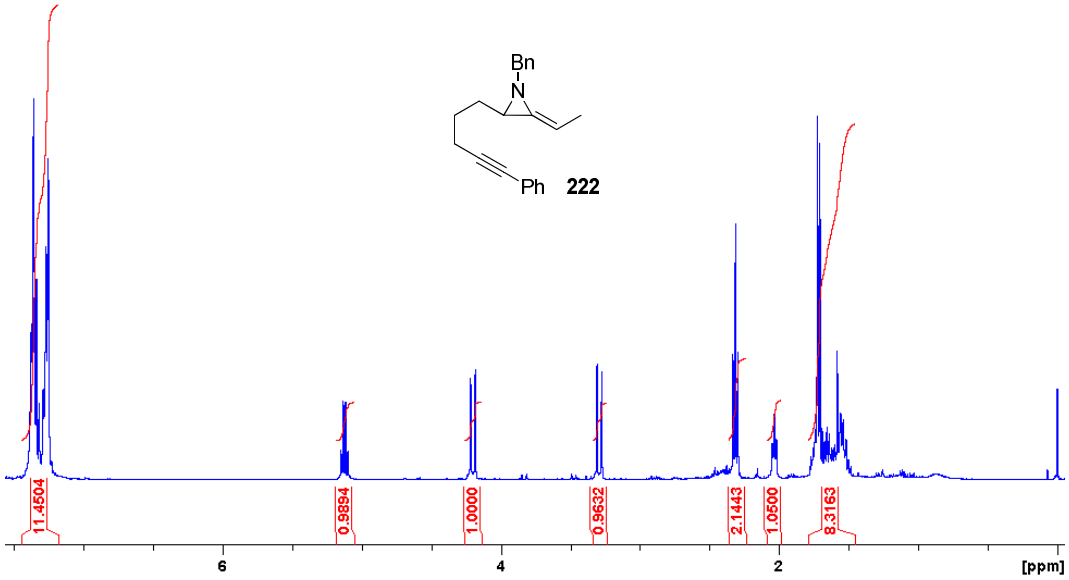
^{1}H NMR spectrum of 217 in $CDCl_3$ at 400 MHz



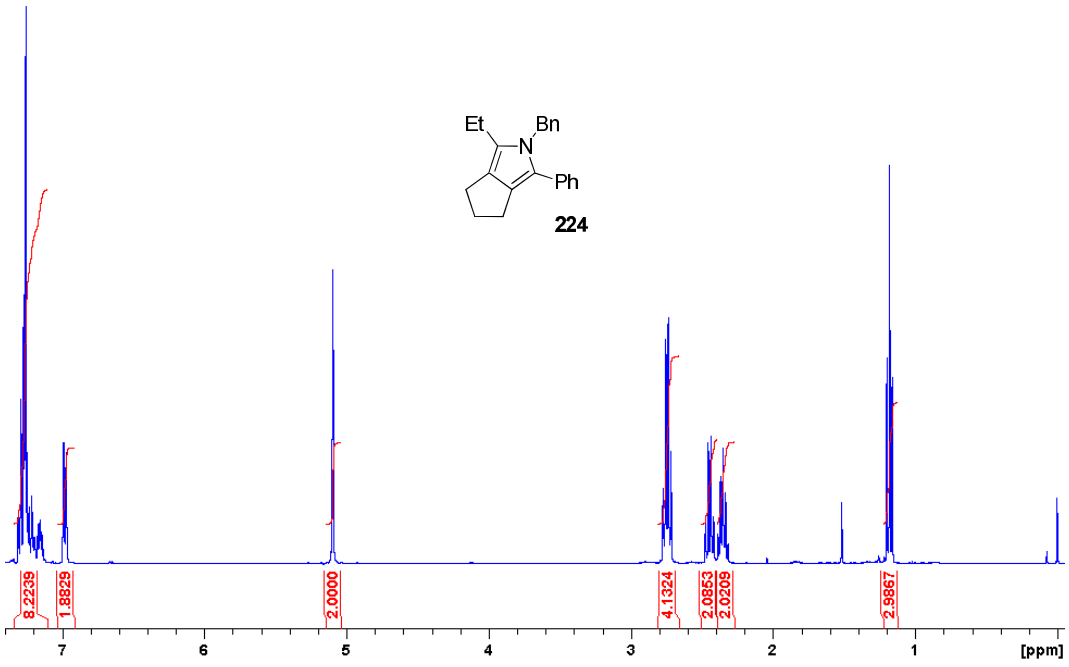
^{1}H NMR spectrum of 218 in $CDCl_3$ at 400 MHz



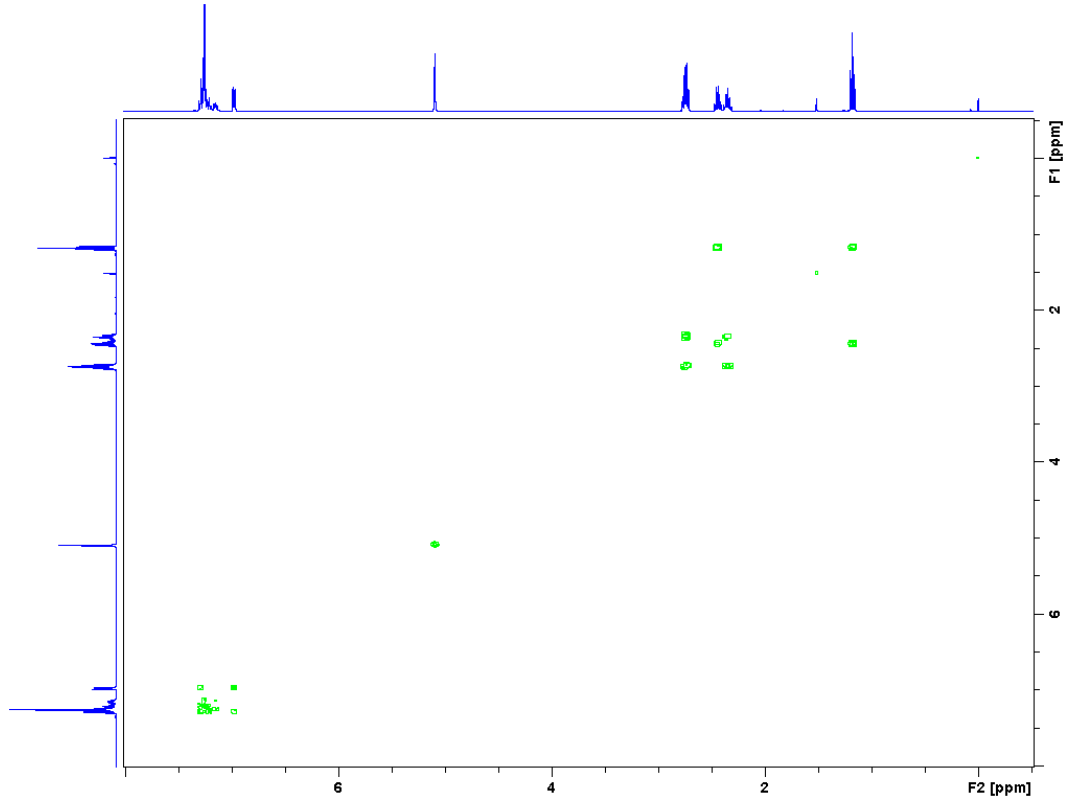
^{1}H NMR spectrum of 221 in $CDCl_3$ at 400 MHz



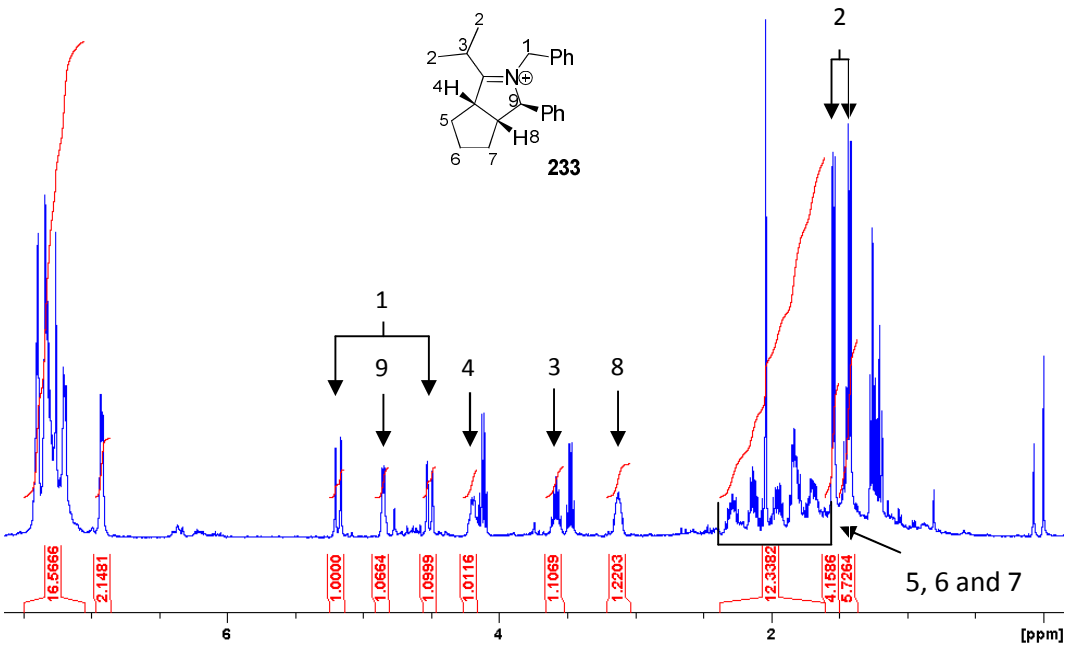
^{1}H NMR spectrum of 222 in $CDCl_3$ at 400 MHz



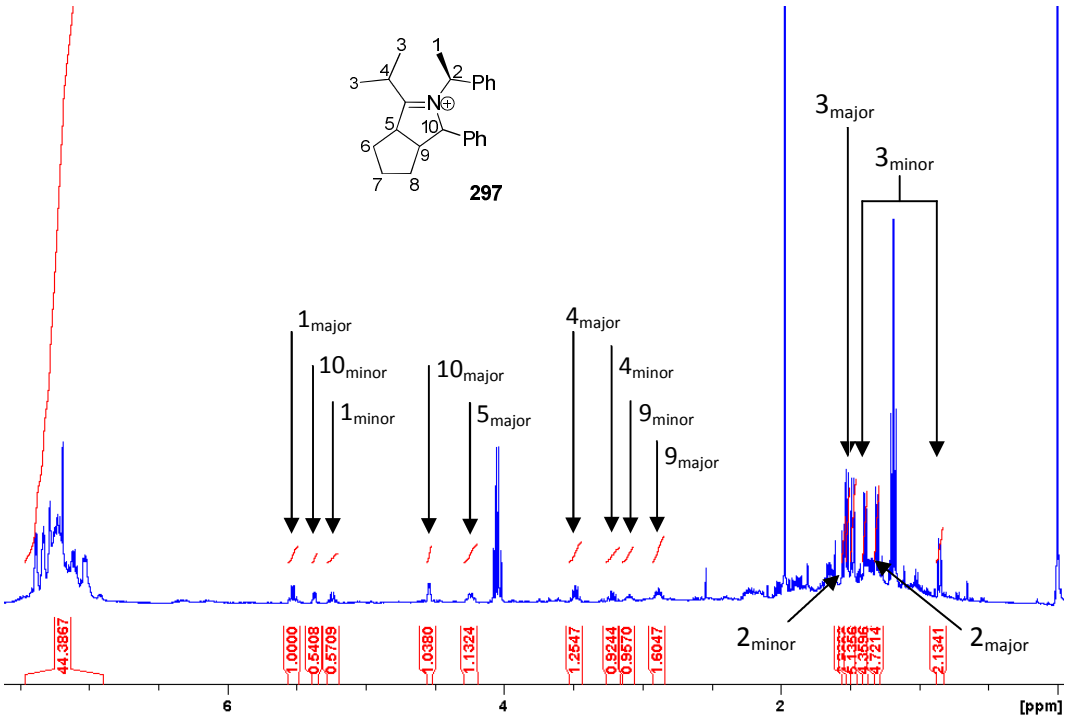
^{1}H NMR spectrum of 224 in $CDCl_3$ at 400 MHz



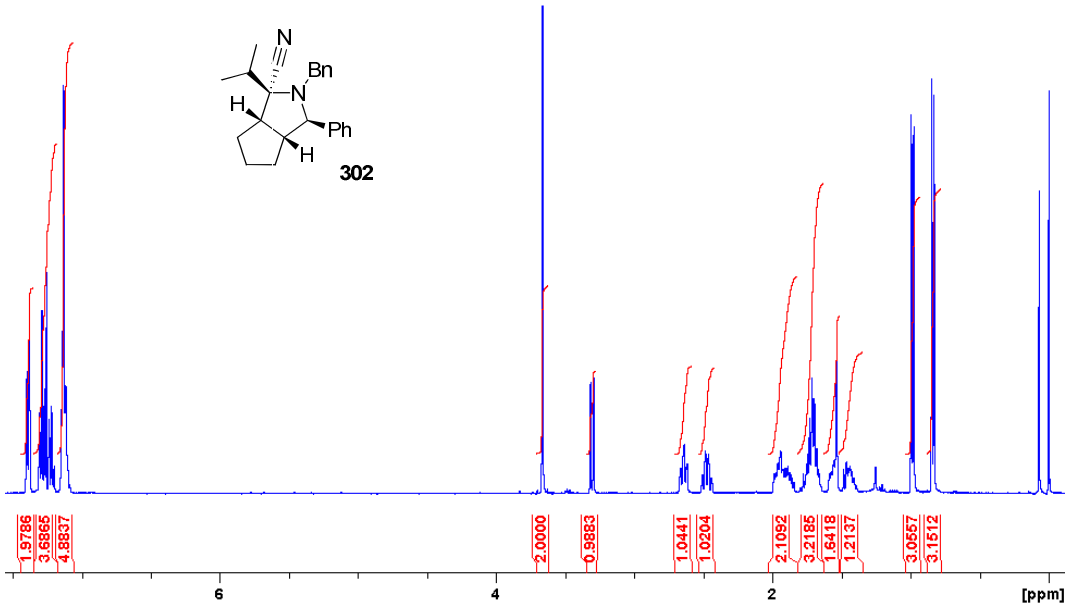
COSY NMR spectrum of 224 in $CDCl_3$ at 400 MHz



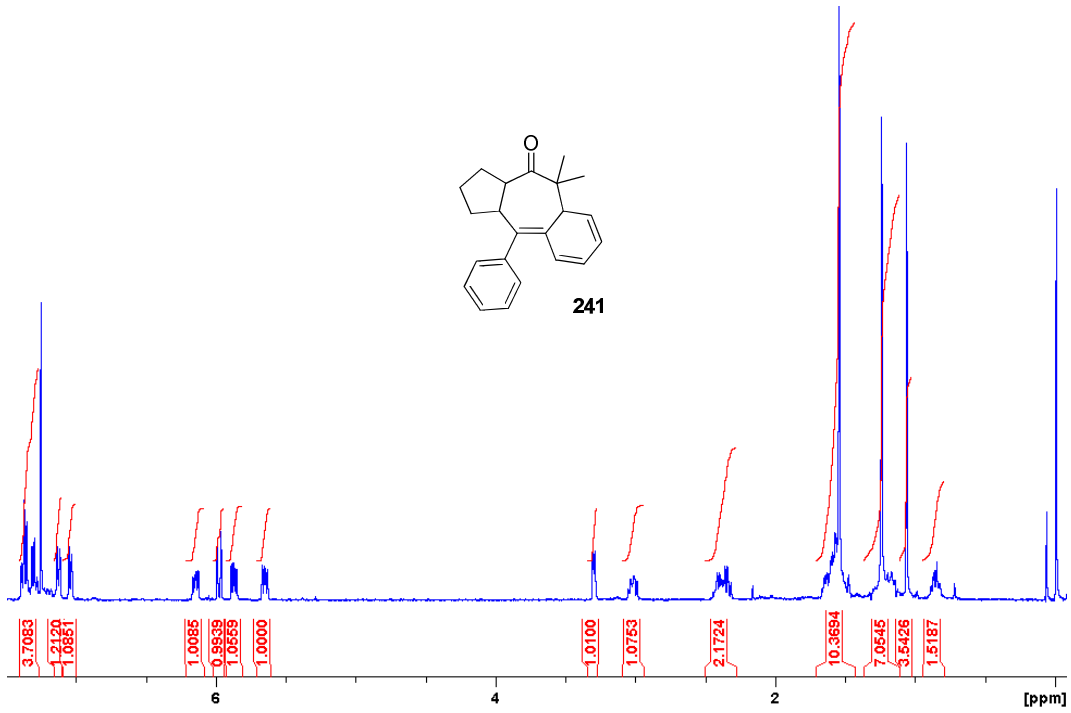
^{1}H NMR spectrum of 233 in $CDCl_3$ at 400 MHz



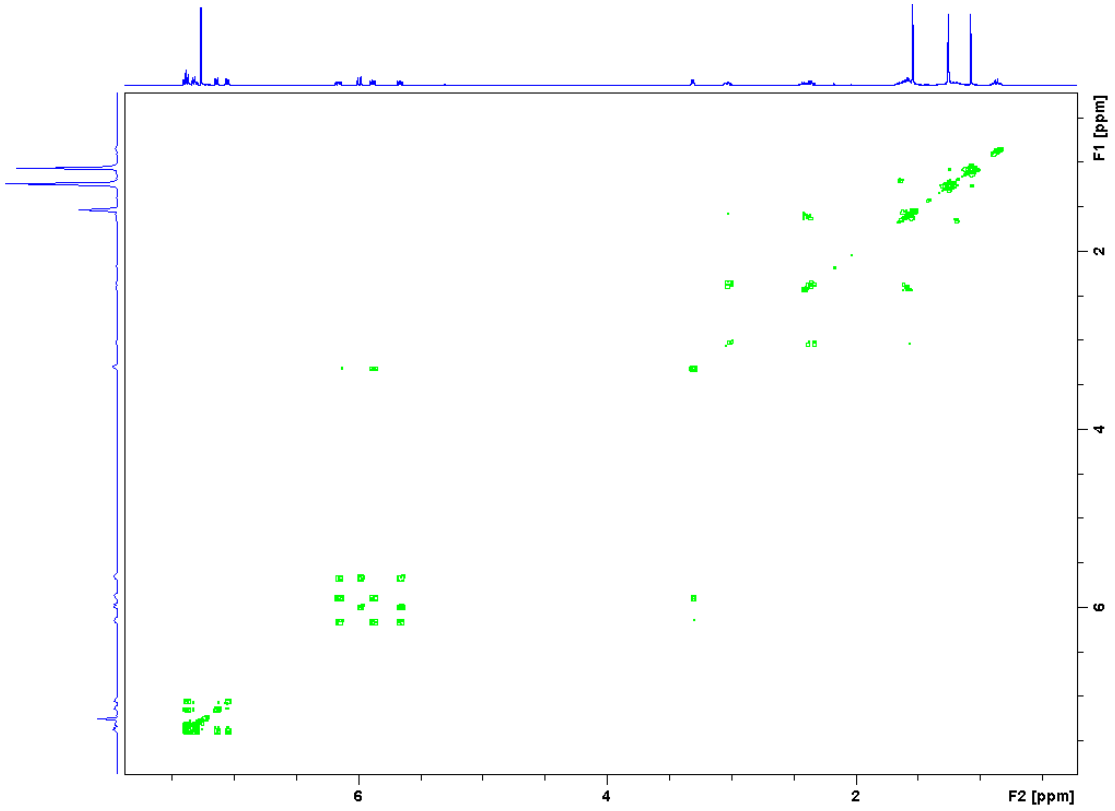
^{1}H NMR spectrum of 297 in $CDCl_3$ at 400 MHz



^{1}H NMR spectrum of 302 in $CDCl_3$ at 400 MHz



^{1}H NMR spectrum of 241 in $CDCl_3$ at 400 MHz



COSY NMR spectrum of 241 in $CDCl_3$ at 400 MHz