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# **Synthesis and Chemistry of Methyleneaziridines Bearing Aryl Groups**

by

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A Thesis submitted in partial fulfilment of the requirement for the  
degree of Doctor of Philosophy in Chemistry

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## **Declaration**

Except where indicated, the work in this thesis is an account of my own independent research at the University of Warwick and at AstraZeneca, Macclesfield, carried out between October 2008 and October 2012. I certify that no material within this thesis has been submitted for a prior degree or a degree at another university.

Signed:

Date:

## Abstract

This thesis describes the synthesis of methyleneaziridines bearing aryl groups and investigates some of their chemistry, focusing on thermal rearrangements and metal catalysed reactions. The inclusion of an *N*-aryl group is desirable as it is thought it might facilitate new types of reactions to be developed for use in organic synthesis.

In chapter one, the synthesis of methyleneaziridines with *N*-EWGs and *N*-aryl groups is investigated. Starting by exploring the possibility of using copper-catalysed nitrene cyclisation, a common method for the synthesis of aziridines, the synthesis of *N*-tosyl and *N*-trroc methyleneaziridines was attempted. This led into the synthesis of *N*-mesityl methyleneaziridine which was achieved in 85% yield by ring closure of *N*-(2-iodopro-2-en-1-yl)-2,4,6-trimethylaniline using sodium amide in ammonia. The effect of the leaving group (Br vs I) on the relative rates of such ring closure reactions was explored and it was established that iodides cyclise at a higher rate.

Chapter two describes the thermal rearrangement of *N*-mesityl methyleneaziridines. A kinetic study was conducted to show the increased propensity for *N*-mesityl methyleneaziridine to rearrange to the cyclopropylimine, compared to *N*-alkyl methyleneaziridines. The application of this rearrangement for the preparation of cyclopropylamines was explored.

Chapter three looks at metal-catalysed reactions of methyleneaziridines. It was shown that *N*-mesityl methyleneaziridine will participate in a palladium-catalysed reaction. Carbonylation reaction of methyleneaziridines, as reported by Alper<sup>1</sup> and Pauson-Khand reactions were also explored. A novel methyleneaziridine containing cobalt/alkyne complex was produced in 40% yield.



## Acronyms and Abbreviations

Ac	Acetyl
acac	Acetylacetone
Alk	Alkyl
Anal.	Analysis
Ar	Aryl
Bn	Benzyl
br	Broad
Bu	Butyl
Calcd.	Calculated
cat.	Catalytic
CataCXium <sup>®</sup> A	Di(1-adamantyl)- <i>n</i> -butylphosphine
cf.	Confer
CI	Chemical ionisation
COSY	Correlation spectroscopy
Cy	Cyclo
$\delta$	Chemical shift
d	Doublet
DFT	Density Functional Theory
DMAc	Dimethylacetamide
DMF	Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMSO	Dimethylsulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane

dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,2-Bis(diphenylphosphino)propane
dr	Diastereomeric ratio
E	Electrophile
E2	Bimolecular elimination
ee	Enantiomeric excess
EI	Electron impact
ES	Electrospray
Et	Ethyl
Eq.	Molar equivalents
EWG	Electron withdrawing group
GC-MS	Gas chromatography mass spectrometry
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple-Quantum Correlation
HRMS	High resolution mass spectroscopy
Hz	Herz
<i>i</i> -	Iso
Ir	Infrared
L	Ligand
LA	Lewis acid
Lit.	Literature value
LRMS	Low resolution mass spectroscopy
m	Multiplet
M	Metal

Me	Methyl
MeCN	Acetonitrile
MHz	Megahertz
MS	Mass spectroscopy
ms	Molecular sieves
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect
Nu	Nucleophile
<i>o</i> -	<i>ortho</i> -
<i>p</i> -	<i>para</i> -
Ph	Phenyl
ppm	Parts per million
Pr	Propyl
Py	Pyridine
q	Quartet
quant	Quantitative
RDS	Rate determining step
R <sub>f</sub>	Retention factor
rt	Room temperature
<i>s</i> -	<i>sec</i> -
s	singlet
sat.	Saturated
SM	Starting material
S <sub>N</sub> 2	Bimolecular nucleophilic substitution

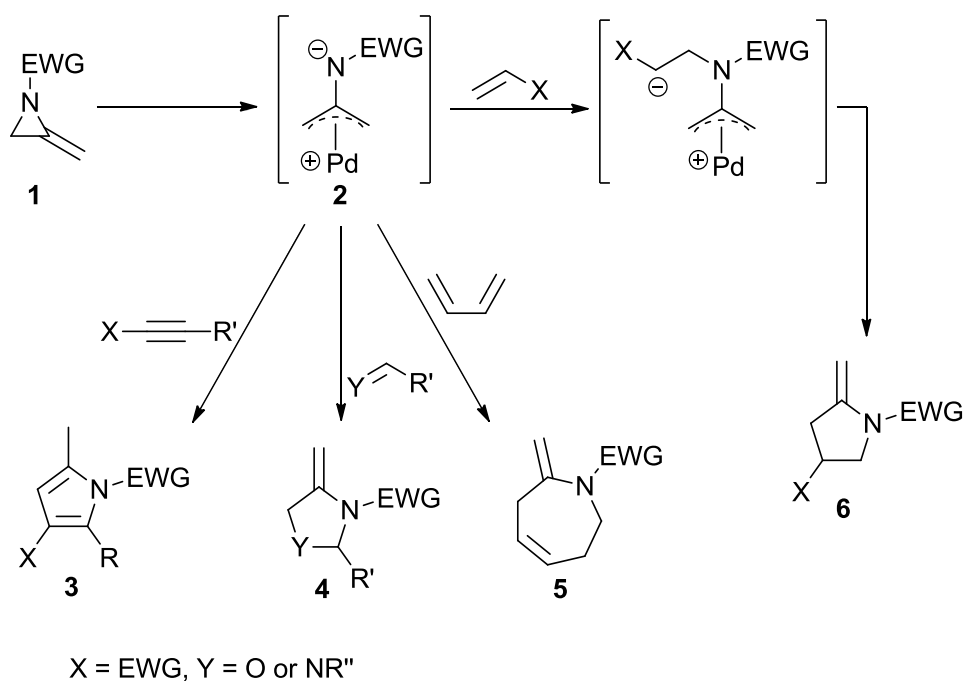
<i>t</i> -	<i>tert</i> -
T	Temperature
TBAF	Tetra- <i>n</i> -butylammonium fluoride
Tf	Triflate
TLC	Thin layer chromatography
THF	Tetrahydrofuran
TMANO	Trimethylamine <i>N</i> -oxide
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TPA	Tris(2-pyridylmethyl)amine
Troc	2,2,2-Trichlorethoxycarbonyl
Ts	Tosyl
w/v	Weight per unit volume

# **Chapter 1:**

## **Synthesis of Methyleneaziridines**

### **Bearing *N*-Aryl Groups**

This thesis describes the synthesis of methyleneaziridines bearing aryl groups and investigates aspects of their chemistry. At the outset, it was hoped that the inclusion of a group, such as an electron withdrawing group (EWG) **1** on the nitrogen atom of methyleneaziridines might facilitate new types of reactions to be developed for use in organic synthesis. For example, zwitterionic intermediate **2**, formed upon opening with palladium, was anticipated to be stabilised by an electron withdrawing group on the nitrogen atom, therefore making its formation easier. This intermediate would potentially give rise to a variety of new cycloaddition reactions not accessible using *N*-alkyl methyleneaziridines (Scheme 1.1). Analogies with conventional Pd-TMM chemistry are apparent.<sup>2,3</sup>



Scheme 1.1.

In this chapter we investigate the synthesis of methyleneaziridines bearing EWGs and aryl groups. Nitrene cyclisation, a well-established method for aziridine

synthesis, was initially investigated, followed by an alternative sodium amide induced cyclisation method commonly used for the preparation of methyleneaziridines. This led onto a study investigating the effect of the leaving group on the rate of such cyclisations.

### 1.1. Introduction

Aziridine **7** (R = H), the simplest of the three-membered nitrogen-containing heterocycles, was first synthesised in 1888 by Gabriel.<sup>4</sup> The original synthesis involved the ring-closure of 2-chloroethylamine; a strategy that remains important in aziridine synthesis today. Since their discovery, aziridines and their chemistry has been widely studied.<sup>5,6,7</sup> As is typical for three-membered rings, aziridines are highly strained systems, which, coupled with the inclusion of an electronegative nitrogen atom dominates their chemistry. A large number of ring-opening reactions have been developed<sup>8</sup> but aziridines also have the ability to undergo intramolecular rearrangements,<sup>9,10</sup> ring-expansion<sup>11,12</sup> and cycloaddition reactions.<sup>13</sup> This versatility of reactivity has made aziridines important intermediates in many chemical transformations.



Figure 1.1.

Methyleneaziridines **8** are a subclass of the aziridine family, containing an exocyclic double bond. The synthesis of methyleneaziridines was first reported in

1951 through the ring-closure of (2-bromoallyl)-*n*-butylamine with sodium amide in liquid ammonia.<sup>14</sup> Like aziridines, methyleneaziridines are highly strained compounds. Consequently, methyleneaziridines are excellent precursors to a variety of different compounds; which has made them interesting and useful substrates to investigate (*vide infra*).

## 1.2. Reactivity of Methyleneaziridines

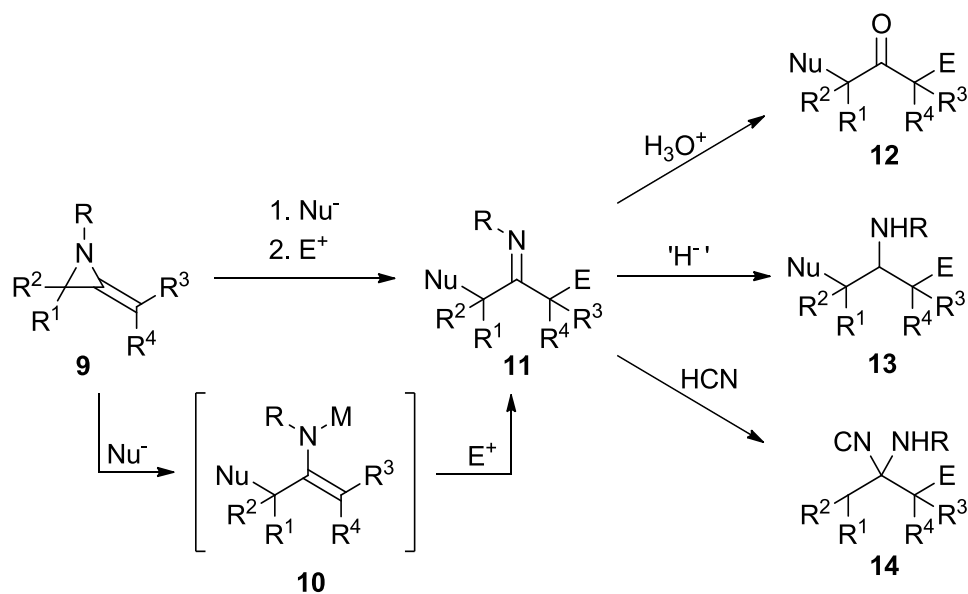
Methyleneaziridines undergo a variety of interesting and, more importantly, useful transformations, including multicomponent reactions, cycloadditions and radical rearrangements.<sup>15</sup> Methyleneaziridines can be functionalised at three different locations; on the nitrogen atom, at the saturated C-3 position of the ring or on the exocyclic double bond. Combined with different ring opening and/or cycloaddition reactions, this allows a wide variety of products to be accessible from methyleneaziridines. These are briefly discussed in the following subsections.

### 1.2.1. Multicomponent Reactions

Methyleneaziridines participate in a number of multicomponent reactions. Ring-opening with Grignard reagents in the presence of CuI (20 mol%) at room temperature leads to the formation of the corresponding metallocenamine (Scheme 1.2).<sup>16,17</sup> Addition of an electrophile gives the ketimine **11** which can then be hydrolysed to give the ketone **12**,<sup>16,17</sup> reduced to give the amine **13**<sup>18,19</sup> or reacted with cyanide to give  $\alpha$ -aminonitriles **14** which can be further reduced to form



diamines.<sup>20</sup> This approach has successfully been employed to synthesise a variety of compounds via multiple C-C bond formation (Figure 1.2.).



Scheme 1.2.

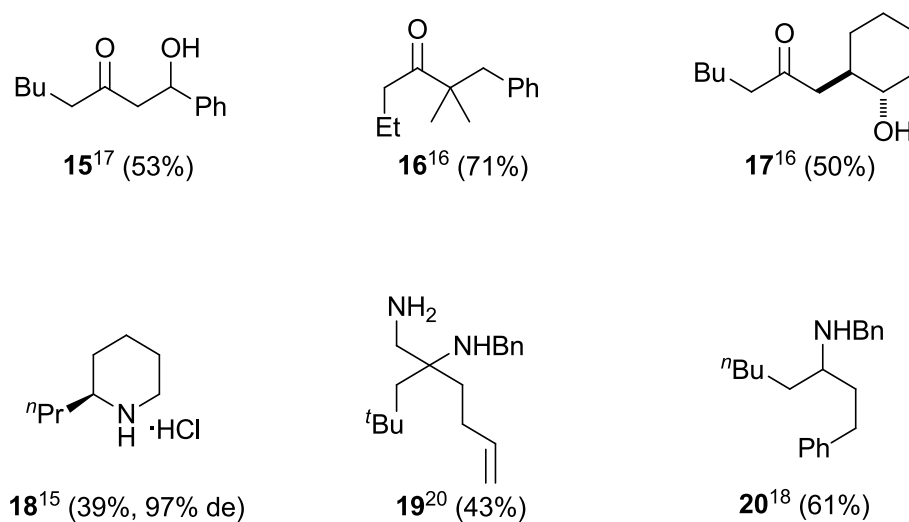


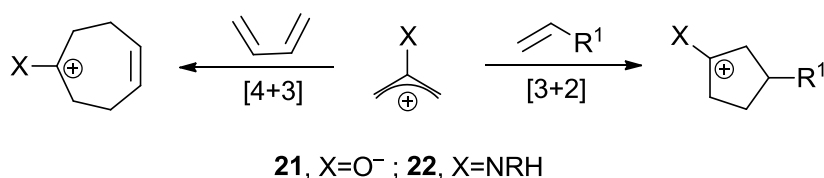
Figure 1.2.

### 1.2.2. Cycloadditions

A number of simple cycloaddition reactions of methyleneaziridines are known. The [2+2] cycloaddition of methyleneaziridines include reactions with tetracyanoethylene, forming 1,1,2,2-tetracyano-5-azaspiro[3.2]hexanes<sup>21</sup> and with singlet oxygen to produce 1,2-dioxetanes.<sup>22</sup> Methyleneaziridines also undergo cycloadditions with alkyl and sulfonyl azides to afford triazoles and 2-(sulfonylimino)azetidines, respectively.<sup>23</sup> These reactions have been rationalised as [3+2] cycloadditions followed by rearrangement of the resultant spirotriazolines.

#### 1.2.2.1. [4+3] Cycloadditions

Shipman *et al.* have shown the possibility of using methyleneaziridines in cycloaddition processes. It was recognised that methyleneaziridines might serve as novel precursors to 2-aminoallyl cations **22**. These intermediates are known to undergo [4+3] cycloadditions with 1,3-dienes<sup>24,25</sup> and [3+2] cycloadditions with olefins (Scheme 1.3).<sup>26,27</sup>

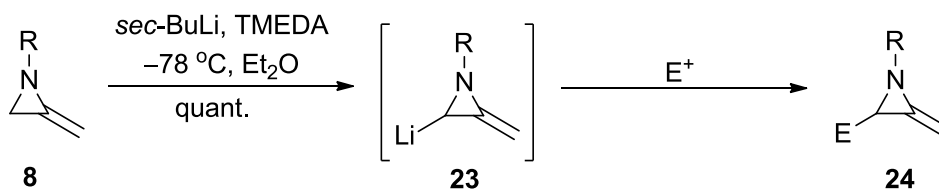


**Scheme 1.3.**

Cations **21** and **22** closely resemble trimethylenemethane (TMM) and its synthetic equivalents; synthons for the formation of five-membered rings.<sup>28</sup> These *N*-

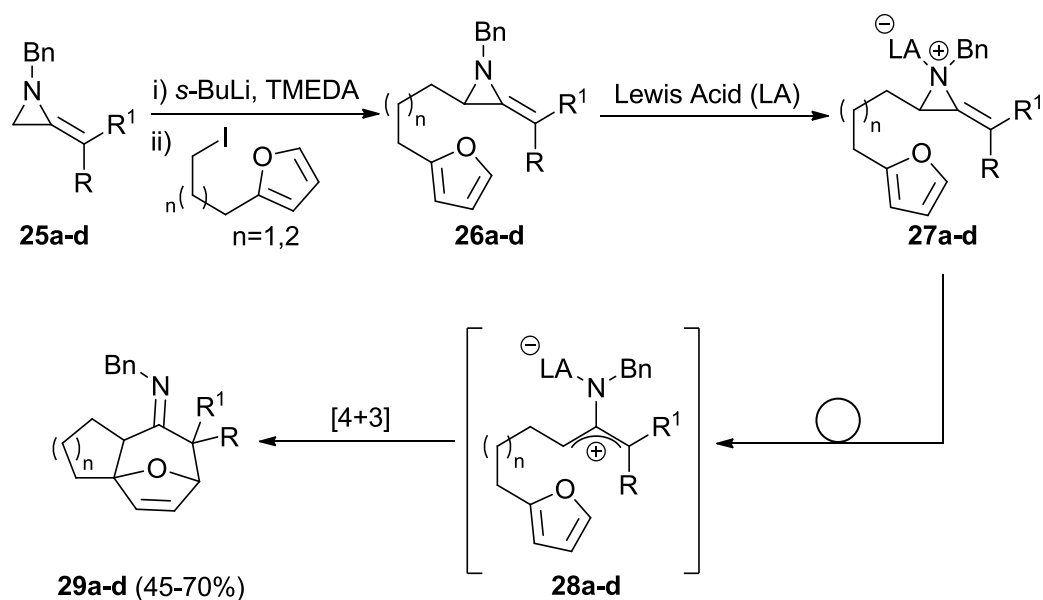
substituted cations can offer some advantages over the oxygen analogues, most importantly their ability to allow enantiocontrolled processes by incorporation of chiral non-racemic *N*-substituents.<sup>29</sup> However, as general and reliable methods for cation generation are rare, very few papers describe the use of 2-aminoallyl cations in synthesis.<sup>29</sup>

The ability to incorporate functionality into methyleneaziridines by alkylating at the C-3 position is crucially important in these types of reactions. When methyleneaziridines are subjected to *sec*-butyllithium, lithiation occurs at the C-3 position, and the resulting anion **23** can subsequently be alkylated with a variety of electrophiles (Scheme 1.4).<sup>30,31</sup>



Scheme 1.4.

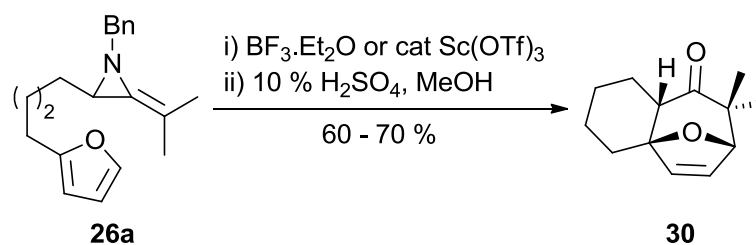
Shipman *et al.* have successfully formed 2-aminoallyl cations by Lewis acid promoted opening of C-3 substituted methyleneaziridine **25**, and subsequently used it to form seven membered rings.<sup>32</sup> The complexation of methyleneaziridine **26** with a suitable Lewis acid [i.e. BF<sub>3</sub>·OEt<sub>2</sub> or catalytic Sc(OTf)<sub>3</sub>] generates the strained and reactive intermediate **27** which then undergoes opening to **28** prior to [4+3] cycloaddition with the tethered 1,3-diene to give the cycloheptenone imine **29** (Scheme 1.5).



**a**,  $R=R^1=\text{Me}$ ; **b**,  $R=R^1=-(\text{CH}_2)_5-$ ; **c**,  $R=\text{H}$ ,  $R^1=\text{Me}$ ; **d**,  $R=\text{Me}$ ,  $R^1=\text{H}$

Scheme 1.5.

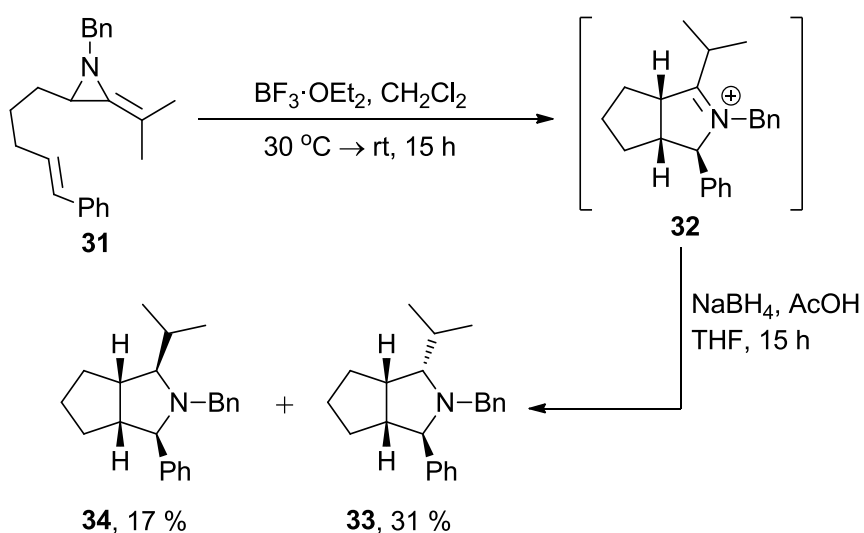
By incorporating an acid work-up, ketone-containing products can be isolated (Scheme 1.6). For example, heating methyleneaziridine **26a** with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  or catalytic  $\text{Sc}(\text{OTf})_3$  followed by an aqueous  $\text{H}_2\text{SO}_4$  work-up gave tricyclic ketone **30** as a single diastereomer.<sup>32</sup>



Scheme 1.6.

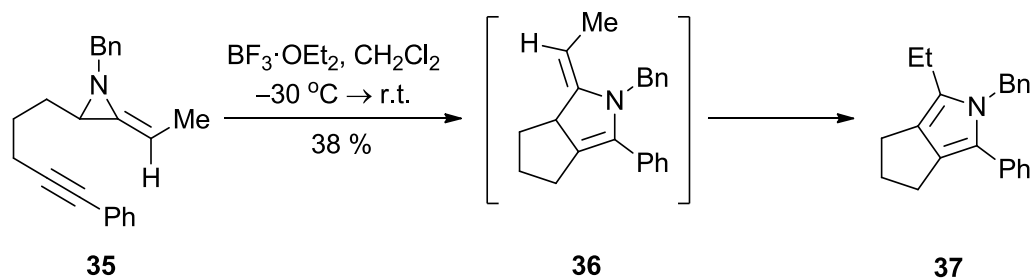
### 1.2.2.2. [3+2] Cycloadditions

More recently, Shipman *et al.* have described Lewis acid catalysed intramolecular [3+2] ‘cycloadditions’ of methyleneaziridines with alkenes or alkynes.<sup>33</sup> This methodology allows access to complex nitrogen heterocycles starting from readily available methyleneaziridines. For example, when methyleneaziridine **31** was subjected to  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , it was converted into iminium ion **32** which was further reduced to **33** and **34** in 48% combined yield (Scheme 1.7). Evidence was produced to suggest that these ‘cycloadditions’ proceed in a highly asynchronous manner.



Scheme 1.7.

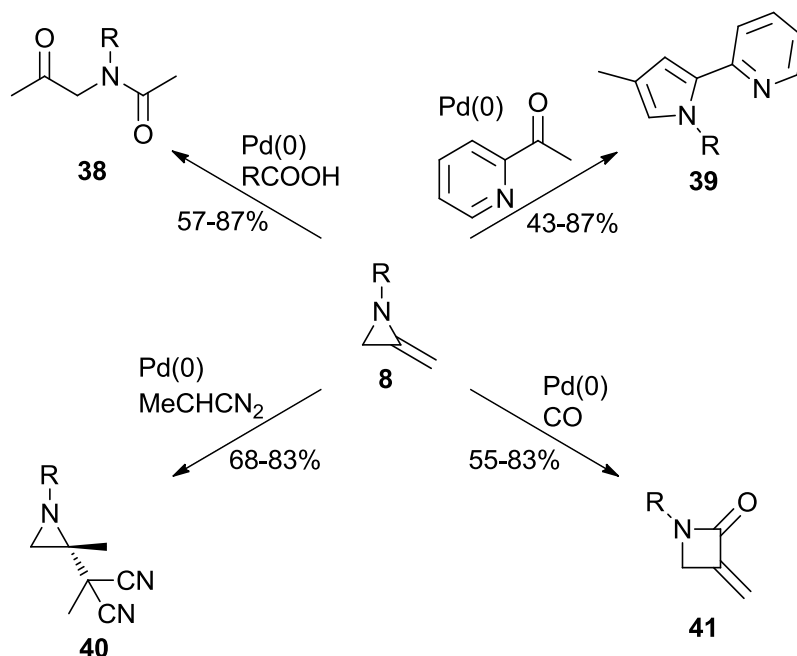
When an alkyne is used as the acceptor in the [3+4] cycloaddition, the resulting *bisenamine* was expected to be unstable, and under the reaction conditions, isomerise to the corresponding pyrrole. This was shown to be the case and **37** was formed in 38 % yield (Scheme 1.8).



Scheme 1.8.

### 1.2.3. Palladium Catalysed Reactions

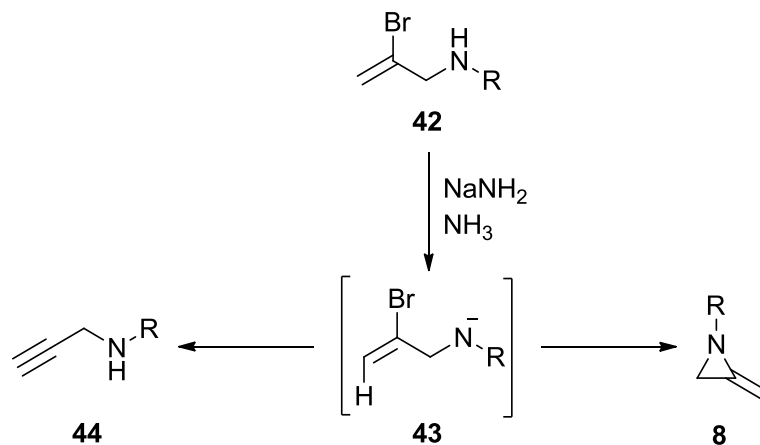
Although methyleneaziridines have been widely studied, their application in metal catalysed reactions is very limited. Some success has been achieved with a variety of carbopalladation reactions, as developed by the Nakamura group. Examples include the synthesis of pyrrole **39**,<sup>34,35</sup> bisnitrile **40**<sup>36</sup> and  $\alpha$ -amino ketone **38**<sup>37</sup> (Scheme 1.9). A second, less common, palladium catalysed reaction involves the insertion of palladium into the N-C bond to give  $\alpha$ -methylene- $\beta$ -lactams **41** after subsequent insertion of carbon monoxide.<sup>1</sup>



Scheme 1.9.

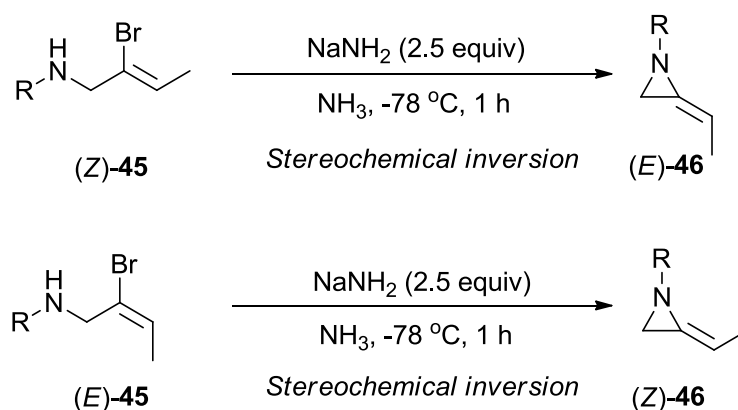
### 1.3. Synthesis of Methyleneaziridines

The first reported synthesis of a methyleneaziridine involved the ring-closure of (2-bromoallyl)-*n*-butylamine with sodium amide in liquid ammonia.<sup>14</sup> An iron(III) catalyst is required for the formation of sodium amide, commonly Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O or FeCl<sub>3</sub>.<sup>15</sup> The main side reaction is competing elimination to form the corresponding alkyne (Scheme 1.10). In some cases, it is possible to suppress alkyne formation by lowering the reaction temperature.



Scheme 1.10.

The cyclisation was originally believed to go through an allene intermediate as proposed by Bottini and Olsen.<sup>38</sup> However Shipman *et al.* have shown this mechanism does not normally operate. They did this by showing that the reaction proceeds with net stereochemical inversion at the alkene carbon (Scheme 1.11). Such an outcome is inconsistent with an allene intermediate.<sup>39</sup>



Scheme 1.11.

The sodium amide induced ring-closure has been used successfully for the synthesis of a large number of methyleneaziridines in moderate to good yields



(Figure 1.3).<sup>39,40,41,42,43,44</sup> However, this methodology has its limitations, and is only suitable for the synthesis of *N*-alkyl derivatives.

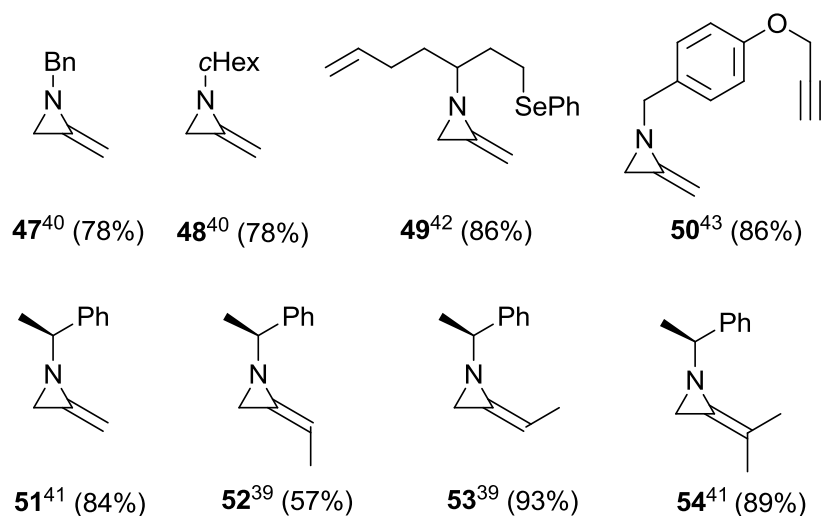
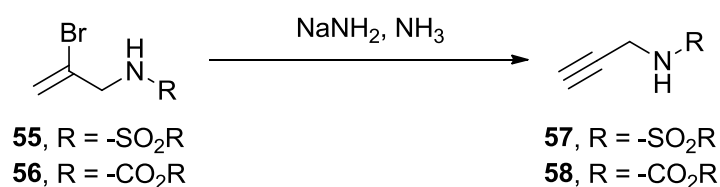


Figure 1.3.

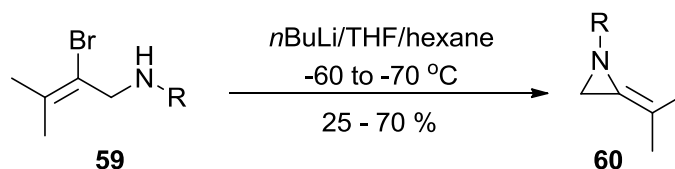
Other groups on the nitrogen atom (such as esters or sulfonamides) result in the formation of the corresponding alkyne via an elimination process (Scheme 1.12).<sup>44</sup>



Scheme 1.12.

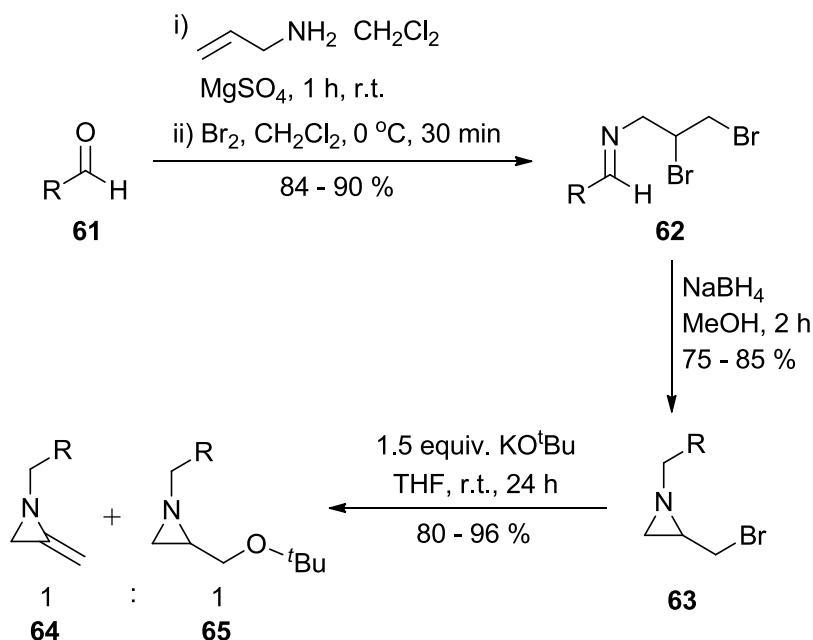
Less forcing conditions have been developed for the cyclisation by Steinberg *et al.*<sup>45</sup> They have shown that using *n*-butyllithium the cyclisation proceeds with 25–70% yield (Scheme 1.13). However it appears to only be suitable for *gem*-dimethyl substituted methyleneaziridines, which cannot undergo the competitive

elimination. When R = adamantanyl this method gave 35% yield of **60** (R = adamantyl). This is lower than the corresponding cyclisation achieved using NaNH<sub>2</sub> in NH<sub>3</sub> (50% yield).<sup>46</sup>



Scheme 1.13.

De Kimpe has reported base-induced 1,2-dehydrobromination of 2-(bromo-methyl)aziridines **63** using potassium *tert*-butoxide as a route to methyleneaziridines (Scheme 1.14).<sup>47</sup>

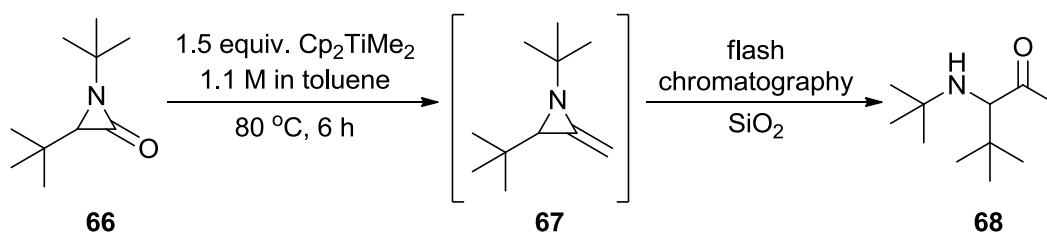


Scheme 1.14.

The synthesis is three steps starting from the corresponding aldehyde. The final step, forming the methyleneaziridine, is high yielding however methyleneaziridine

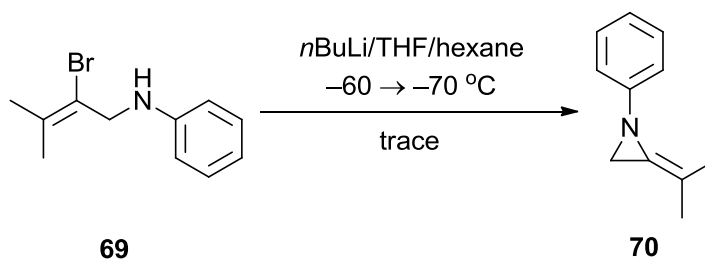
**64** is formed as a 1 : 1 mixture with 2-(*tert*-butoxymethyl)-aziridine **65** formed as a result of S<sub>N</sub>2 displacement.

De Kimpe has also described the dimethyl titanocene mediated methylenation of  $\alpha$ -lactams yielding methyleneaziridines (Scheme 1.15).<sup>48</sup> However, only one example of this method being used for the synthesis of a methyleneaziridine has been described.



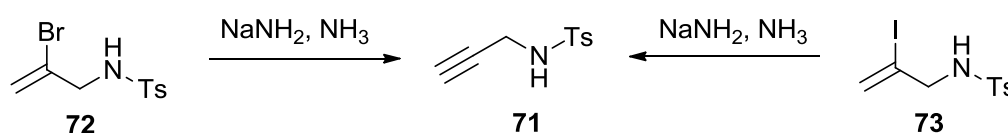
Scheme 1.15.

It should be stressed that all the above methods have only been used to synthesise *N*-alkyl methyleneaziridines. Steinberg attempted to synthesise *N*-phenyl methyleneaziridine **70** using *n*-butyllithium, however only a trace of **70** was observed (Scheme 1.16).<sup>45</sup>



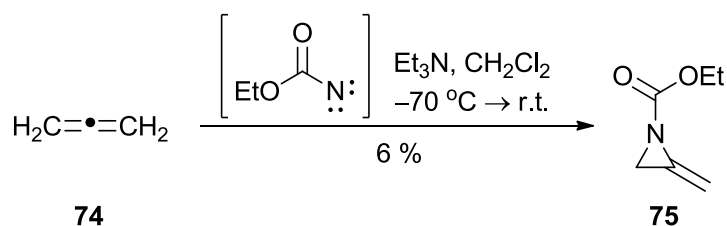
Scheme 1.16.

Attempts have been made to synthesise methyleneaziridines containing EWGs. Unfortunately, when bromide **72** is cyclised under the sodium amide conditions only alkyne **71** is produced (Scheme 1.17).<sup>44</sup> More recently, it was thought that if the bromide was replaced with an iodide, this might promote the cyclisation and suppress elimination. Unfortunately this was not the case and again only alkyne **71** was formed (Scheme 1.17).<sup>49</sup>



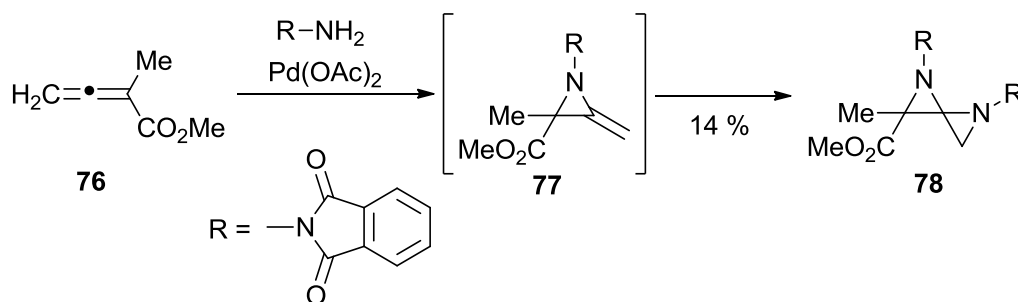
Scheme 1.17.

In 1975, Bingham and Gilbert reported the synthesis of *N*-carbethoxymethyleneaziridine (**75**).<sup>50</sup> They made **75** in 6% yield by reacting allene (**74**) with carbethoxynitrene (Scheme 1.18). They choose *N*-(*p*-nitrobenzenesulfonyl)-urethane as the nitrene source as it is known to generate singlet and/or triplet nitrenes depending on the conditions used. The authors reported low product stability with polymerisation taking place, which may account for the very poor yield.



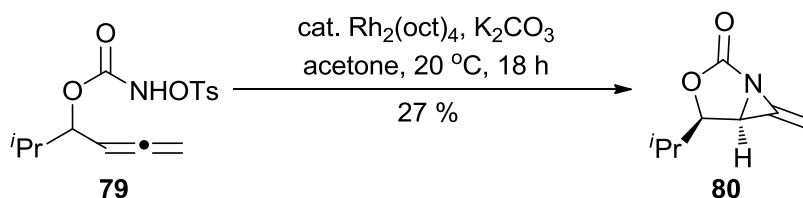
Scheme 1.18.

Inspired by this work, Atkinson and Malpass attempted to make methyleneaziridine **77** by reacting 2-methylbuta-2,3-dienoate and phthalimido-nitrene in the presence of  $\text{Pb}(\text{OAc})_4$ .<sup>51</sup> However, the product formed was diazaspiro[2,2]pentane (**78**) (Scheme 1.19). Presumably, the aziridination took place but **77** underwent a second aziridination giving spiro-cycle **78**.



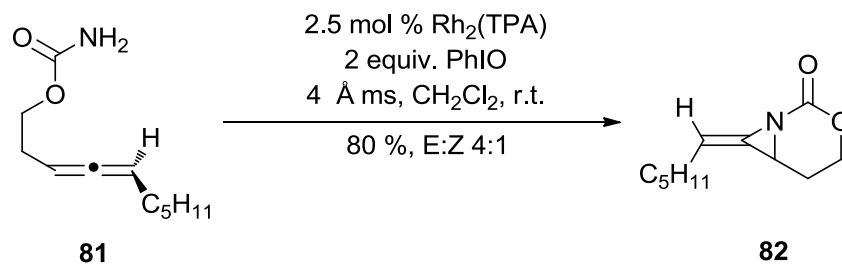
Scheme 1.19.

More recently there have been examples of intermolecular nitrene aziridinations forming methyleneaziridines. Robertson *et al.* have reported the synthesis of methyleneaziridine **80** in 27% yield (Scheme 1.20).<sup>52</sup>



Scheme 1.20.

Schomaker has also recently published work showing that rhodium catalysed aziridination of substituted allenes, such as **81**, can be used to form bicyclic methyleneaziridines including **82** (Scheme 1.21).<sup>53</sup>

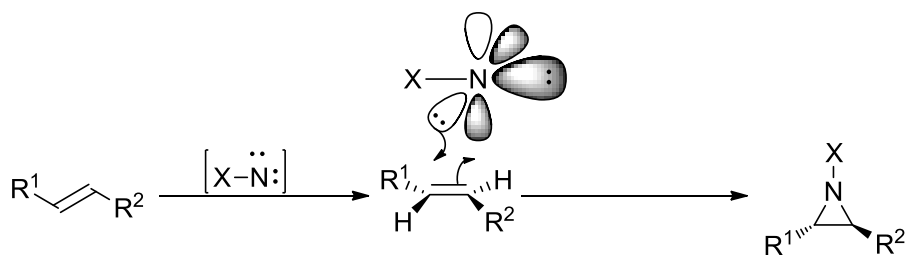


Scheme 1.21.

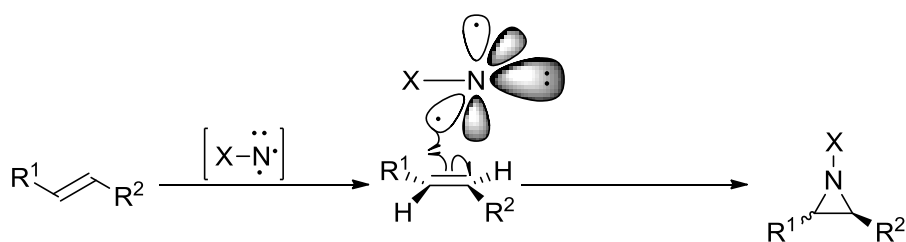
### 1.3.1. Aziridination Reactions of Alkenes

There are several methods for synthesising aziridines and they can be grouped into two general classes: addition and cyclisation processes.<sup>5,54</sup> Addition processes include reaction of nitrenes or nitrene equivalents with alkenes ( $C_2+N_I$  reactions) or addition of carbenes or carbenoids to imines ( $C_I N_I+C_I$  reactions).<sup>55</sup> Cyclisation processes include the ring-closure of amino alcohols or equivalents.<sup>4,56</sup> Bingham and Gilbert utilised the  $C_2+N_I$  nitrene addition to allene (**74**) to form methyleneaziridine **75** (Scheme 1.21).

Nitrenes can exist in two forms, namely singlet and triplet nitrenes. When reacting with 1,2-disubstituted alkenes only singlet nitrenes react stereospecifically as the aziridine ring is formed in a single step (Scheme 1.22). Conversely, triplet nitrenes react in a stepwise process which results in a loss of stereocontrol (Scheme 1.23).<sup>54</sup>



Scheme 1.22.

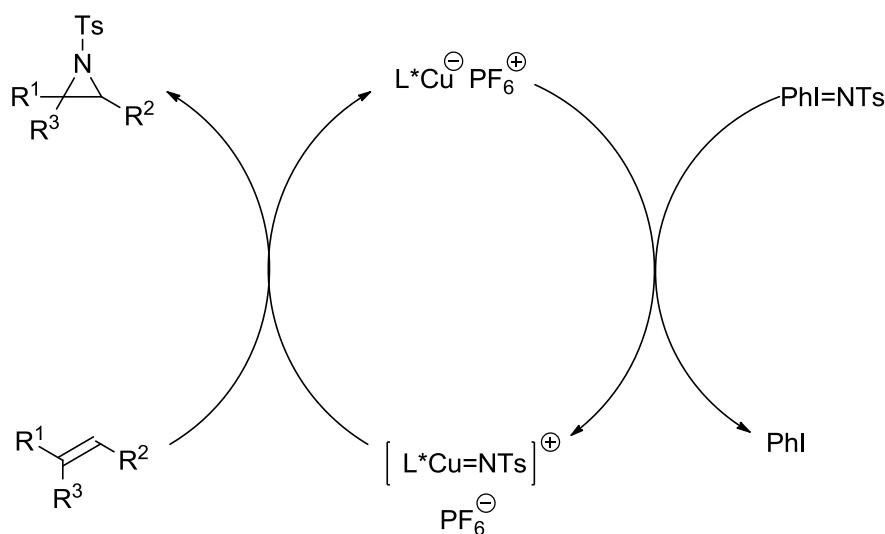


Scheme 1.23.

Traditionally, nitrenes are generated by thermal or photochemical decomposition of the corresponding azide. These methods give mixtures of singlet and triplet nitrenes and hence mixtures of the *cis* and *trans* products.<sup>54</sup>

In 1967, Kwart *et al.* first reported that Cu(I) salts were capable of mediating aziridination of alkenes.<sup>57</sup> Unfortunately, the method was limited in scope and was not adopted for general use. In the early 1980's metalloporphyrins were shown to catalyse the aziridination of alkenes using *N*-tosyliminophenyl iodine (PhI=NTs) as the nitrene precursor (Scheme 1.24),<sup>54</sup> More recently, Evans described the use of Cu(I) and Cu(II) in the aziridination of alkenes with PhI=NTs.<sup>58</sup> Electron-rich and electron-poor alkenes were shown to undergo aziridinations using PhI=NTs in 55–95% yield. Jacobsen *et al.* have also

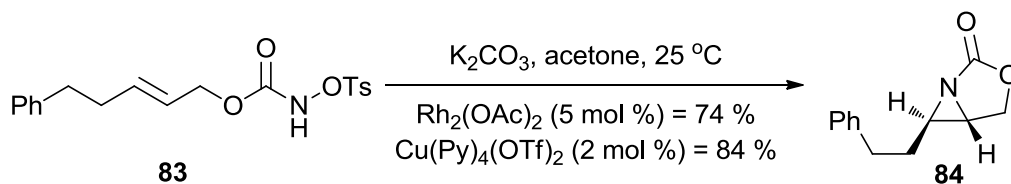
described copper catalysed aziridinations, and have gathered evidence that these reactions proceed through a discrete copper-nitrene complex.<sup>59</sup>



**Scheme 1.24.**

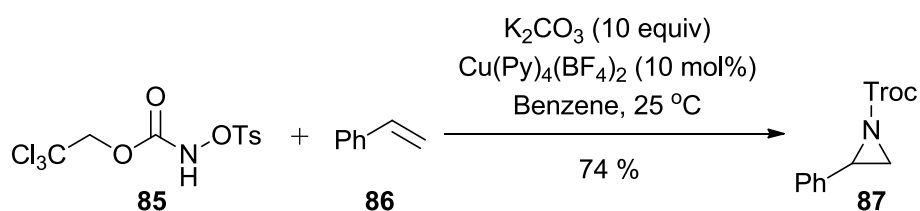
One downside to using PhI=NTs as the nitrene source is the generation of a full equivalent of iodobenzene. An alternative has been investigated by Lebel *et al.* (Scheme 1.25).<sup>60</sup> They have shown that *N*-tosyloxycarbamate reagents can be used in *intra*- and intermolecular alkene aziridinations. Alkene **83** was shown to form **84** by intramolecular aziridination (Scheme 1.25). Rh<sub>2</sub>(OAc)<sub>2</sub> had already been shown to catalyse such reactions<sup>61,62</sup> and indeed in this case Rh<sub>2</sub>(OAc)<sub>2</sub> made a significant difference in yield compared to the uncatalysed process (74% cf <10% yield). However rhodium is expensive and so copper complexes were also investigated. Cu(Py)<sub>4</sub>(Otf)<sub>2</sub> gave excellent results with low catalyst loading.





Scheme 1.25.

The intermolecular reaction worked well and **87** was isolated in 74% yield when  $\text{Cu}(\text{Py})_4(\text{BF}_4)_2$  was used as the catalyst (Scheme 1.26).

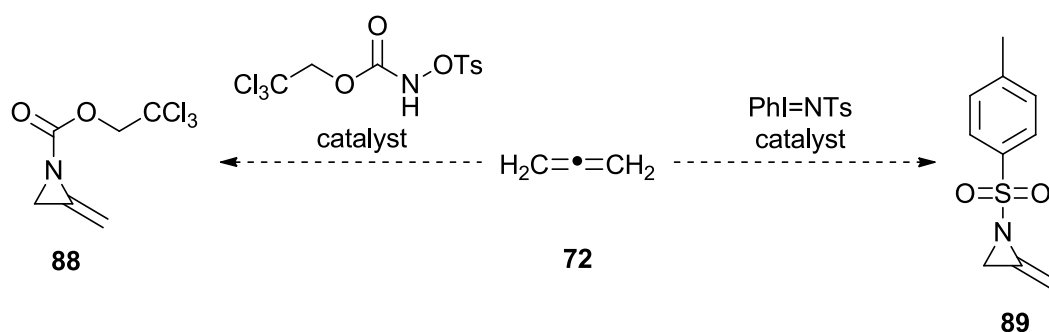


Scheme 1.26.

In summary, it can be seen from the literature that nitrene cyclisations are a reliable and convenient method for synthesising aziridines. Our aim was to utilise this method in the attempt to synthesise methyleneaziridines bearing EWGs using allene as the alkene component.

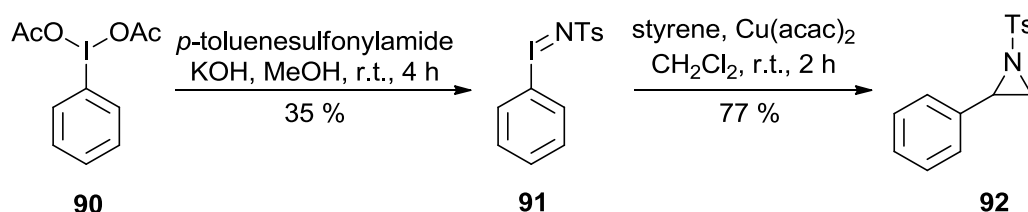
#### 1.4. Aziridination Reactions of Allene (74)

As  $\text{PhI=NTs}$  **91** is well known to be a good nitrene precursor for aziridination of alkenes, we decided that it would be a good starting place for our own studies. If allene (**74**) could be aziridinated using this method, methyleneaziridine **89** would be produced (Scheme 1.27). Conversely, using trichloroethyl *N*-tosylcarbamate **85**, methyleneaziridine **88** would be formed (Scheme 1.27). This molecule closely resembles methyleneaziridine **75** however the inclusion of the  $-\text{CCl}_3$  raises the molecular weight, which may help reduce the volatility of the product and aid isolation.



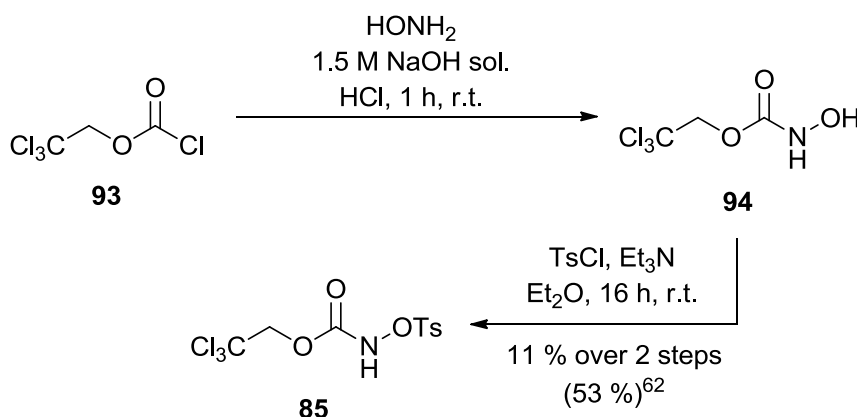
Scheme 1.27.

$\text{PhI=NTs}$  (**91**) was synthesised following the literature procedure,<sup>63</sup> whereby *p*-toluenesulfonylamide and iodobenzene diacetate (**90**) were reacted with potassium hydroxide in methanol to give **91** in 35% yield (Scheme 1.28). To test the quality of the  $\text{PhI=NTs}$  (**91**) and to become familiarised with aziridination reactions, styrene was reacted with **91** and  $\text{Cu}(\text{acac})_2$  to give aziridine **92** in 77% yield (Scheme 1.28).<sup>64</sup>



Scheme 1.28.

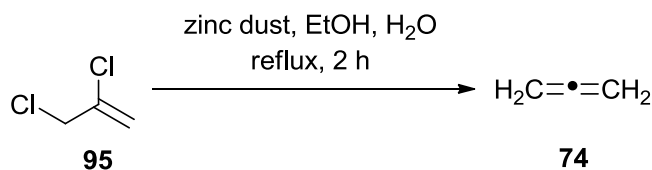
*N*-Tosyl carbamate **85** was synthesised in two steps from 2,2,2-trichloroethyl chloroformate (**93**) and hydroxylamine under basic conditions (Scheme 1.29). The resulting *N*-hydroxy-carbamate **94** was directly reacted with *p*-toluenesulfonyl chloride and triethylamine to give **85** in 11% yield over the two steps. Although the yield for this process was lower than that reported,<sup>62</sup> sufficient material was available to proceed.



Scheme 1.29.

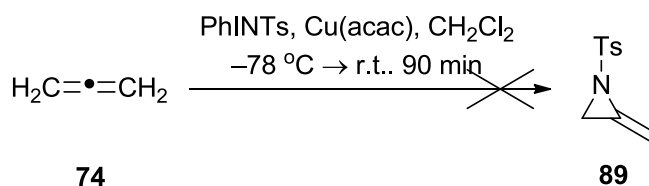
Due to its high cost (£422/Mol),<sup>65</sup> allene (**74**) was synthesised from 2,3-dichloropropene (**95**) and zinc dust in ethanol/water mix (Scheme 1.30).<sup>66</sup> The gaseous allene (**74**) was passed through a calcium chloride trap to remove any remaining water, then collected as a colourless liquid using a dry ice/acetone trap.

By bubbling the resulting allene (**74**) through  $\text{CDCl}_3$  it was possible to obtain  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, confirming the liquid to be pure allene (**74**).<sup>67</sup>



Scheme 1.30.

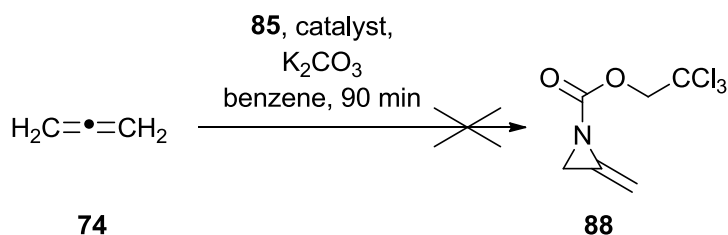
The first aziridination attempted was with  $\text{PhI}=\text{NTs}$  (**91**) using the conditions used for styrene (Scheme 1.28).<sup>64</sup> The reaction was conducted in a re-sealable tube and the allene (**74**), in excess, was added via cannula into  $\text{PhI}=\text{NTs}$  (**91**) and  $\text{Cu}(\text{acac})_2$  in  $\text{CH}_2\text{Cl}_2$  precooled to  $-78\text{ }^\circ\text{C}$ ; the tube was sealed, allowed to warm to room temperature and stirred for 90 min (Scheme 1.31). Unfortunately, no signals attributable to aziridine **89** were seen in the crude  $^1\text{H}$  NMR spectrum.



Scheme 1.31.

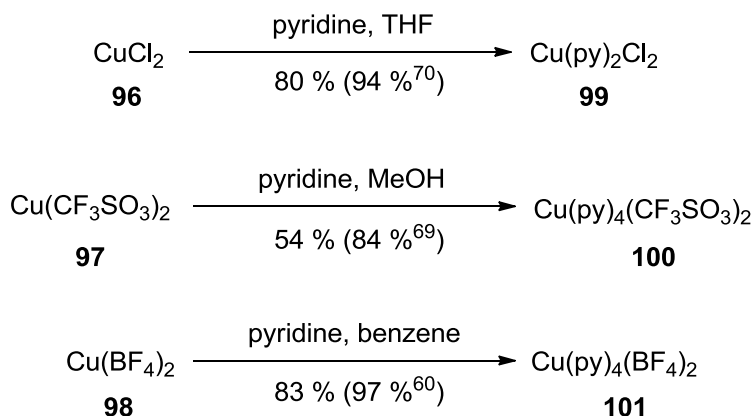
As  $\text{Cu}(\text{OTf})_2$  and  $\text{Rh}(\text{OAc})_2$  are both known to be good catalysts for aziridinations,<sup>64,68,61</sup> they were chosen for investigating reactions with *N*-tosyl carbamate **85**. These studies were conducted in benzene following the best conditions reported by Lebel (Scheme 1.32).<sup>60</sup> Control experiments without

catalyst were also conducted. In all cases,  $^1\text{H}$  NMR spectroscopy showed no evidence of the formation of aziridine **88**, however no starting material remained.



Scheme 1.32.

Next, we investigated alternative catalysts. Copper(II) catalysts **99**, **100** and **101** proved most successful in Lebel's work.<sup>60</sup> These catalysts were synthesised following literature methods (Scheme 1.33).<sup>60,69,70</sup>

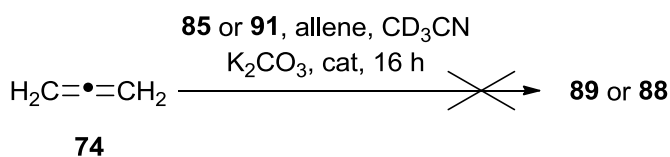


Scheme 1.33.

Concerned that the aziridine products may be volatile, we sought to eliminate the need to change solvents prior to NMR analysis. Acetonitrile is known to be a good solvent for aziridinations.<sup>64</sup> Using  $\text{CD}_3\text{CN}$ , we were able to demonstrate that allene (**74**) is soluble in it and remained in solution at room temperature for

significant periods of time. Hence, we decided to use CD<sub>3</sub>CN in subsequent experiments.

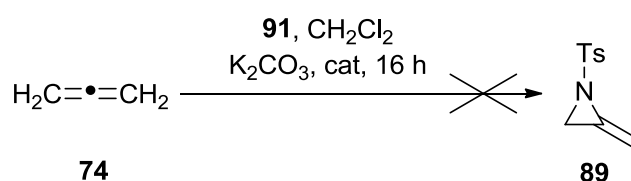
Two sets of reactions were conducted; one using PhI=NTs (**91**), allene (**74**), CD<sub>3</sub>CN and catalyst and one using *N*-tosyl carbamate **85**, allene (**74**), CD<sub>3</sub>CN and catalyst (Scheme 1.34). In both cases, the allene was used in excess. The catalysts used were: Rh<sub>2</sub>(OAc)<sub>4</sub>, Cu(Py)<sub>4</sub>(BF<sub>4</sub>)<sub>2</sub>, Cu(Py)<sub>4</sub>(OTf)<sub>2</sub>, Cu(Py)<sub>2</sub>Cl<sub>2</sub>, and Cu(acac)<sub>2</sub>. The allene was bubbled through a stock solution of CD<sub>3</sub>CN and a 1 mL aliquot of the allene/CD<sub>3</sub>CN solution taken for each reaction. The reactions were analysed by <sup>1</sup>H NMR and GC–MS. All the reactions with PhI=NTs contained iodobenzene, tosylamide and allene after 16 h. For the reactions containing *N*-tosyl carbamate **85**, unreacted starting material and other unidentified signals were observed which were not consistent with aziridine **88**.



Scheme 1.34.

Undeterred, a second catalyst screen was conducted using PhI=NTs, this time using non-deuterated dichloromethane as solvent (Scheme 1.35). Again, the allene was bubbled through the solvent and 1 mL aliquots combined with the above catalysts. <sup>1</sup>H NMR analysis revealed that the reactions with Cu(Py)<sub>4</sub>(OTf)<sub>2</sub> and Cu(Py)<sub>2</sub>Cl<sub>2</sub> contained only tosylamide, and the reactions with Rh<sub>2</sub>(OAc)<sub>4</sub>, Cu(Py)<sub>4</sub>(BF<sub>4</sub>)<sub>2</sub> and Cu(acac)<sub>2</sub> all contained tosylamide and a peak that was in the

correct region for the alkene hydrogens (6.6 ppm). However, by using HMQC experiments, it was possible to determine that these hydrogens were not attached to a carbon atom, and so the formation of aziridine **89** was discounted.



Scheme 1.35.

With no positive results, we decided to abandon this approach, and chose to explore the synthesis of methyleneaziridines with alternative *N*-substituents.

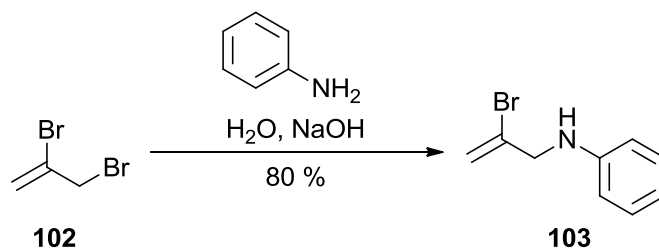
## 1.5. Synthesis of *N*-Aryl-2-methyleneaziridines

*N*-Aryl substituents, although not as electron deficient as sulfonamides and esters, are more electron withdrawing than the *N*-alkyl substituents. Hence they could still modify the reactivity of the methyleneaziridines, such that new reaction manifolds (such as those depicted in scheme 1.1) could become available.

### 1.5.1. Attempted Synthesis of *N*-Phenyl-2-methyleneaziridine (**104**).

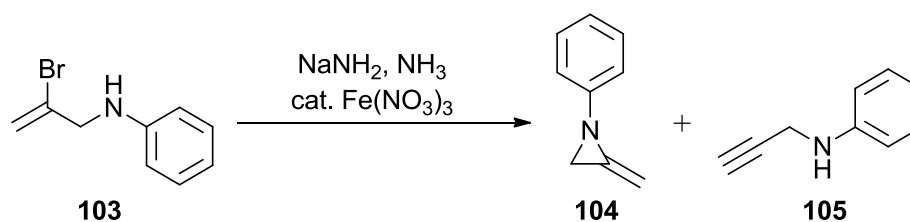
#### 1.5.1.1. Cyclisation of Bromide Precursor **103**

As the synthesis of *N*-aryl methyleneaziridine had not been reported, the possibility of synthesising them using the Pollard and Parcel method seemed like an appropriate place to begin. Thus, bromide **103**<sup>71</sup> was synthesised from 2,3-dibromopropene and aniline in 80% yield (Scheme 1.36).



Scheme 1.36.

Initial attempts at cyclising bromide **103** with NaNH<sub>2</sub> in liquid ammonia failed, with only the corresponding alkyne **105** observed (Entry 1, Table 1.1). Adjusting the reaction conditions, −78 °C for 1 h using 3.5 equivalents of sodium amide, small signals at 4.8 and 5.0 ppm assignable to methyleneaziridine **104** were observed giving us some encouragement (Entry 2, Table 1.1). Unfortunately, this corresponded to just 2% conversion, along with some alkyne (6%), with mostly starting **103** (92%). Increasing the reaction length led to exclusive formation of the alkyne (Entry 3, Table 1.1).

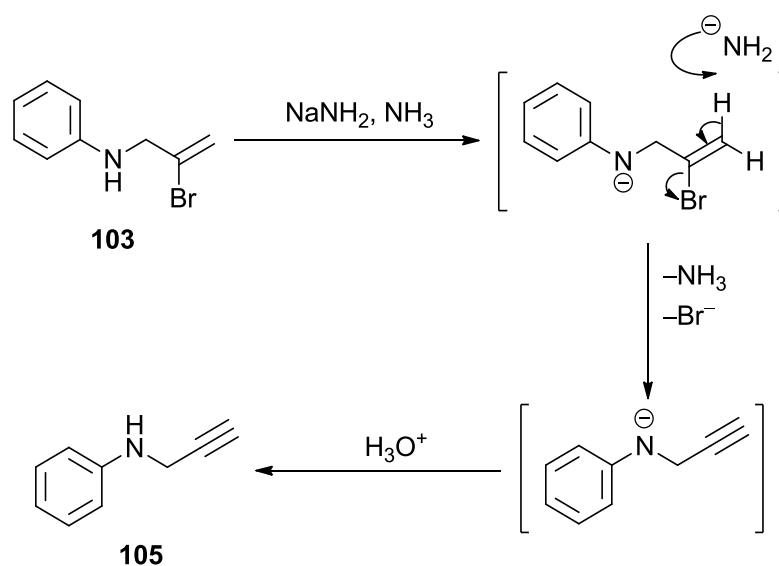


Entry	Equiv. NaNH <sub>2</sub>	T (°C)	t (h)	103 : 104 : 105
1	3.5	−33	1	0 : 0 : 100
2	3.5	−78	1	92 : 2 : 6
3	5	−78	5	0 : 0 : 100

Table 1.1.



As discussed previously, Shipman *et al.* have produced evidence to suggest that these cyclisations proceed via an unusual 'S<sub>N</sub>2 like' process.<sup>39</sup> After initial amine deprotonation, the cyclisation proceeds with inversion of the stereochemistry (Scheme 1.11). When the *N*-substituent contains an electron withdrawing group e.g. an ester, sulfonamide or even a phenyl group, stabilisation of the negative charge will reduce the nucleophilicity of the nitrogen atom, lowering the propensity to cyclise. Competitive elimination can then occur leading to the alkyne (Scheme 1.37). In the case of bromide **103**, alkyne formation is clearly the favoured pathway.



Scheme 1.37.

### 1.5.1.2. Computational Predictions

Although bromine is a good leaving group it is well known that iodine is a better leaving group in S<sub>N</sub>2 processes. Iodine is bigger than bromine, making it more

diffuse and so making the bond between it and carbon weaker.<sup>72</sup> Of course, changing to iodide may make the competing E2-elimination faster, but, we felt that this modification merited investigation.

DFT calculations conducted for us by Prof. Kaori Ando at the University of Gifu, Japan supported this hypothesis (Table 1.2).<sup>73</sup> By comparing the Gibbs energies for the transition states, the calculations indicate that when X = Cl or Br and R = SO<sub>2</sub>Me the reaction would not take place below room temperature as the values are high, 24.3 and 25.4 kcal/mol respectively.

Experimentally, we know that when X = Br and R = Ph the cyclisation is very poor even though the calculations suggests the  $\Delta G$  transition state is relatively low (13.9 kcal/mol). This indicates that any of the reactions with an activation barrier above this will likely not occur, such as the cyclisation where X = I and R = SO<sub>2</sub>Me (18.2 kcal/mol).

X	R	106 $\Delta G$ (kcal/mol)	107 $\Delta G$ (kcal/mol)	108 $\Delta G$ (kcal/mol)
Cl	Me	0	5.09	-44.6
Cl	Ph	0	13.3	-26.9
Cl	SO <sub>2</sub> Me	0	24.3	-6.3
Br	Me	0	5.12	-40.1
Br	Ph	0	13.9	-20.3
Br	SO <sub>2</sub> Me	0	25.4	-0.13
I	Me	0	0.48	-45.7
I	Ph	0	6.87	-30.3
I	SO <sub>2</sub> Me	0	18.2	-9.18

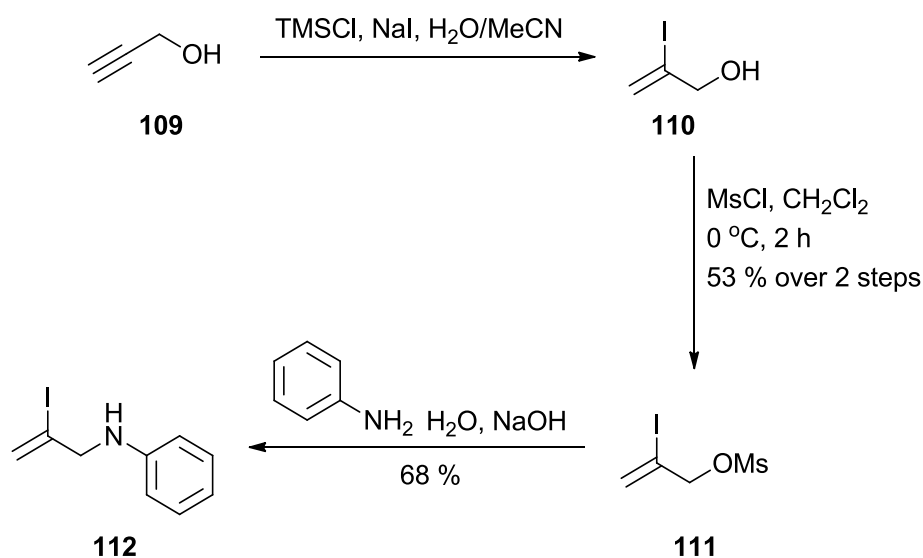
**Table 1.2.** Calculated using EtOH as the implicit solvent ( $\epsilon = 24.85$ ) to model the properties of NH<sub>3</sub> ( $\epsilon = 22.4$  at  $-33$  °C). B3LYP/6-31+G\* CPCM, for iodide, lanl2dz basis set was used.

However, the value for X = I and R = Ph is 6.87 kcal/mol which is significantly less than the value for X = Br and R = Ph, and crucially, is similar to the value for X = Br and R = Me (5.12 kcal/mol), a cyclisation known to proceed successfully. This indicates that this cyclisation (X = I, R = Ph) may take place under typical reaction conditions (NaNH<sub>2</sub>, NH<sub>3</sub>,  $-33$  °C).

### 1.5.1.3. Cyclisation of Iodide Precursor 112

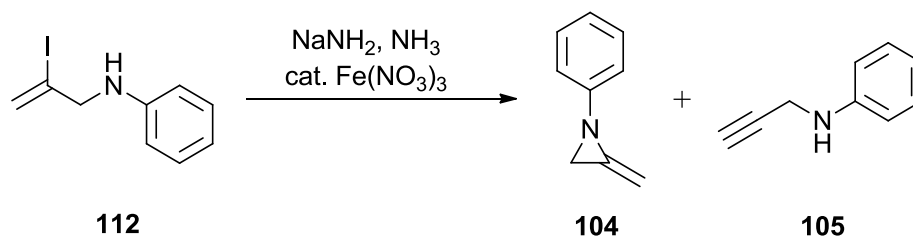
With this encouraging information, we embarked on the synthesis of the iodide **112**. Starting from propargyl alcohol (**109**), the iodine atom was installed<sup>74</sup> before

mesylation of the hydroxyl group<sup>75</sup> to give mesylate **111** in 53% over the two steps (Scheme 1.38). Due to the volatility of alcohol **110**, and the reactivity of mesylate **111**, no purification was undertaken of these materials. Further alkylation of aniline with mesylate **111** was successfully performed to give iodide **112** in 68% yield (Scheme 1.38).



Scheme 1.38.

Next, with iodide **112** in hand, the cyclisation was attempted using the best conditions identified for bromide **103**. Using 3.5 equivalents of sodium amide, for 1 h at  $-78$  °C, the amount of methyleneaziridine increased significantly as evidenced by <sup>1</sup>H NMR spectroscopy (Entry 1, Table 1.3). However, the increase in the formation of alkyne was also marked; from 6% up to 65%. Encouraged, we sought to further optimise the conditions such that methyleneaziridine formation becomes the major reaction pathway.

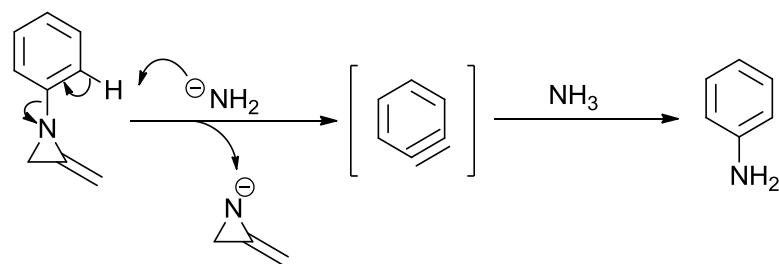


Entry	Equiv. NaNH <sub>2</sub>	T (°C)	t (h)	112 : 104 : 105 <sup>a</sup>
1	3.5	−78	1	13 : 22 : 65
2	2	−78	4	24 : 40 : 36
3	2	−100	5	40 : 20 : 40

**Table 1.3.** <sup>a</sup> ratio determined by <sup>1</sup>H NMR spectroscopy

It has been shown that for the cyclisations involving *N*-alkyl substituents, two equivalents of sodium amide are required with 2.5 equivalents often being optimal.<sup>18</sup> In this case, reducing the number of equivalents to 2 equivalents had a positive impact (Table 1.3, Entry 2). Lowering the temperature still further, to −100 °C did not improve the reaction with less conversion to products (Table 1.3, Entry 3).

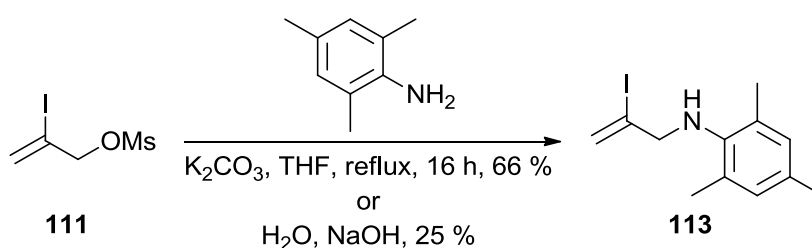
A major concern with this reaction was the presence of a side product which led to an over integration in the aromatic region of the <sup>1</sup>H NMR spectrum. It was postulated that benzyne formation may be occurring under the reaction conditions. This idea was supported by GC–MS analysis which gave a peak with a molecular weight consistent with aniline. Assuming iodide **112** is fully deprotonated under the reaction conditions, benzyne formation from the cyclisation precursor seems unlikely, suggesting it arises from methyleneaziridine **104** (Scheme 1.39).



Scheme 1.39.

### 1.5.2. Synthesis of *N*-Mesityl-2-methyleneaziridines

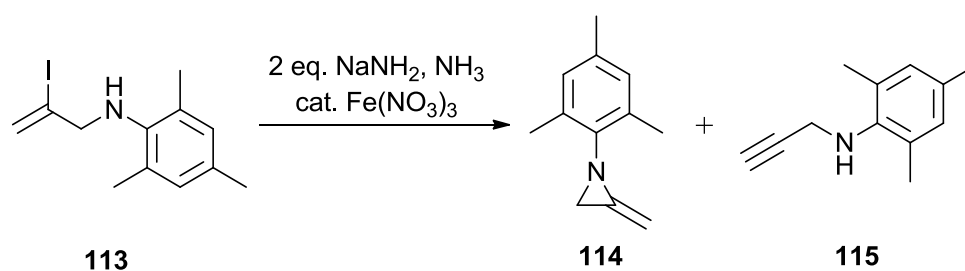
If benzyne formation was the problem, blocking the *o*-positions should suppress this side reaction. To test this idea, mesylate **111** was reacted with 2,4,6-trimethylaniline to give iodide **113** in 66% yield (Scheme 1.40). Lower yields were observed using NaOH, in contrast to the reaction with aniline.



Scheme 1.40.

Using conditions similar to those described above for iodide **112**, namely 2 equivalents of sodium amide, at  $-78^{\circ}\text{C}$  for 5.5 h, 67% conversion to methyleneaziridine **114** was achieved. Crucially, no over-integration of the aromatic region was observed and the remaining material was unreacted iodide **113**.

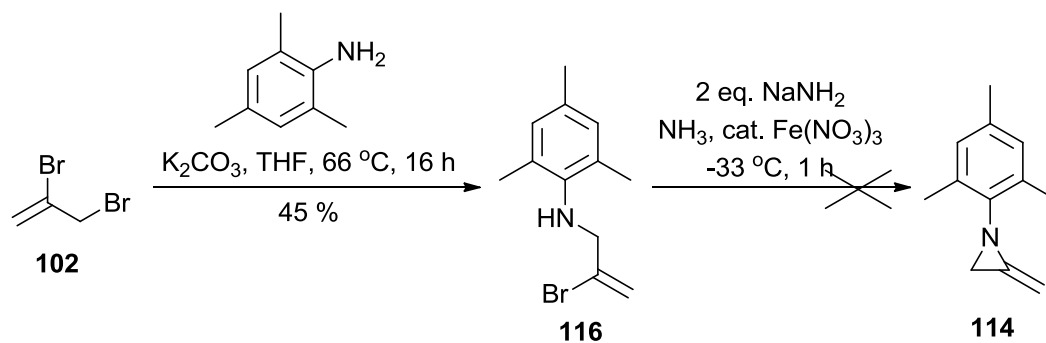
Performing the reaction at  $-33\text{ }^{\circ}\text{C}$  for a shorter reaction time, complete consumption of starting material was achieved. However, significant quantities of alkyne **115** were produced (Table 1.4, Entry 2). The best result was achieved reducing the reaction time to 1 h which gave 90% conversion to methyleneaziridine **114** (Table 1.4, Entry 3). Curiously these results perhaps suggest that alkyne formation is arising from the methyleneaziridine (*vide infra*).



Entry	T ( $^{\circ}\text{C}$ )	t (h)	<b>113</b> : <b>114</b> : <b>115</b> <sup>a</sup>
1	$-78$	5.5	33 : 67 : 0
2	$-33$	2.5	0 : 63 : 37
3	$-33$	1	0 : 90 : 10

Table 1.4. <sup>a</sup> ratio determined by  $^1\text{H}$  NMR spectroscopy

We wanted to confirm that iodide **113** was the most suitable precursor for this reaction and so bromide **116** was also synthesised and subjected to the cyclisation conditions. As had been seen for bromide **103** only alkyne **115** was formed (Scheme 1.41).



Scheme 1.41.

It is known that purification by column chromatography of unsubstituted *N*-alkyl methyleneaziridines leads to poor mass recovery.<sup>15</sup> This was also the case for methyleneaziridine **114**. Attempts to use basic alumina or florisil<sup>®</sup> also proved fruitless. The most common method of purification for unsubstituted *N*-alkyl methyleneaziridines is bulb-to-bulb distillation.<sup>15</sup> Unfortunately, the inclusion of an aryl group reduced the thermal stability of the methyleneaziridine, and attempts to purify it by this method were unsuccessful. This is discussed in more detail in Chapter 2.

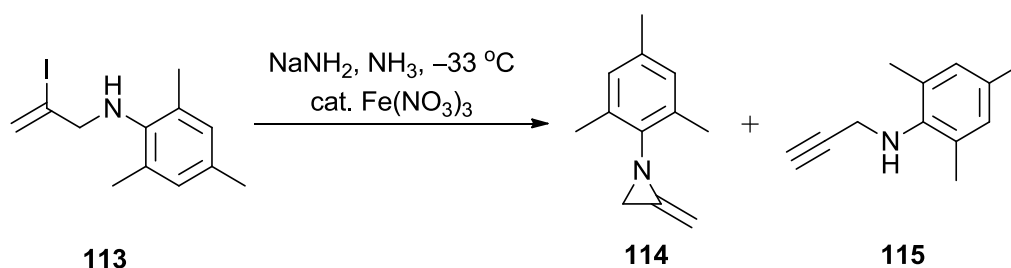
It is also worth noting a difference in the work-up conditions was required for methyleneaziridine **114**. *N*-Alkyl methyleneaziridines are subjected to an acid wash (0.1 M acetic acid) to remove the more basic alkyne by-product. We expected that this method would not work for *N*-aryl based systems, as alkyne **115** would be unlikely to protonate in the presence of weak acid. Indeed, acidic washing only led to the disappearance of the methyleneaziridine presumably as a result of degradation.



As separation of methyleneaziridine **114** from alkyne **115** was not possible, the reaction needed to be more carefully optimised so that essentially pure **114** could be produced directly.

We further investigated the reaction duration (Table 1.5, Entries 1-6). All reactions were run with 2 equiv. of sodium amide at  $-33^{\circ}\text{C}$ . Entry 1 is taken from Table 1.4. No starting material is recovered until the reaction time is cut to 5 minutes, indicating that the cyclisation is fast at  $-33^{\circ}\text{C}$ . It was expected that the ratio of **114** : **115** would not change as the reaction length was shortened however some variation was seen. When the reaction scale was doubled (entries 7 – 8) the amount of alkyne noticeably increased.

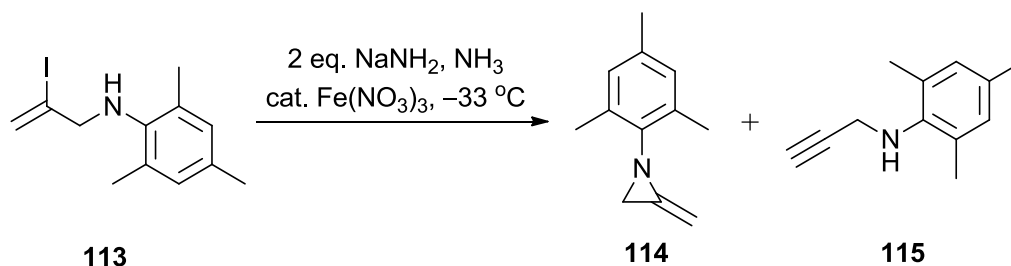
As it is difficult to accurately measure the volume of ammonia condensed into the flask, the reaction concentrations are hard to precisely control. Small changes in concentration could account for the variability in these results upon scale up.



Entry	Scale (mmol)	t (min)	113 : 114 : 115 <sup>a</sup>
1	3.32	60	0 : 90 : 10
2	3.32	50	0 : 96 : 4
3	3.32	40	0 : 87 : 13
4	3.32	30	0 : 90 : 10
5	3.32	10	0 : 95 : 5
6	3.32	5	10 : 75 : 15
7	6.64	40	0 : 74 : 26
8	6.64	50	0 : 67 : 33

**Table 1.5.** <sup>a</sup> ratio determined by <sup>1</sup>H NMR spectroscopy

Concentration effects were further explored (Table 1.6). Methyleneaziridine formation is clearly favoured at higher concentrations. This is counterintuitive if the cyclisation is the RDS as it is an intramolecular process. One might expect the competing intermolecular elimination to be favoured at higher concentrations.

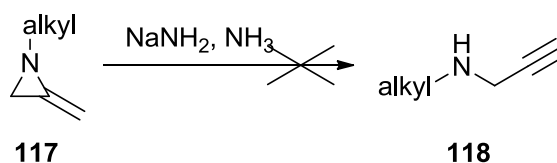


Entry	Scale (mmol)	[113] (M)	t (min)	113 : 114 : 115 <sup>a</sup>
1	6.64	0.060	25	0 : 78 : 22
2	6.64	0.128	25	0 : 87 : 13
3	3.32	0.060	30	51 : 22 : 27
4	6.64	0.266	20	7 : 88 : 5
5	6.64	0.266	30	0 : 96 : 4

**Table 1.6.** All reactions performed using 2 equiv. of NaNH<sub>2</sub> at –33 °C. <sup>a</sup> ratio determined by <sup>1</sup>H NMR spectroscopy

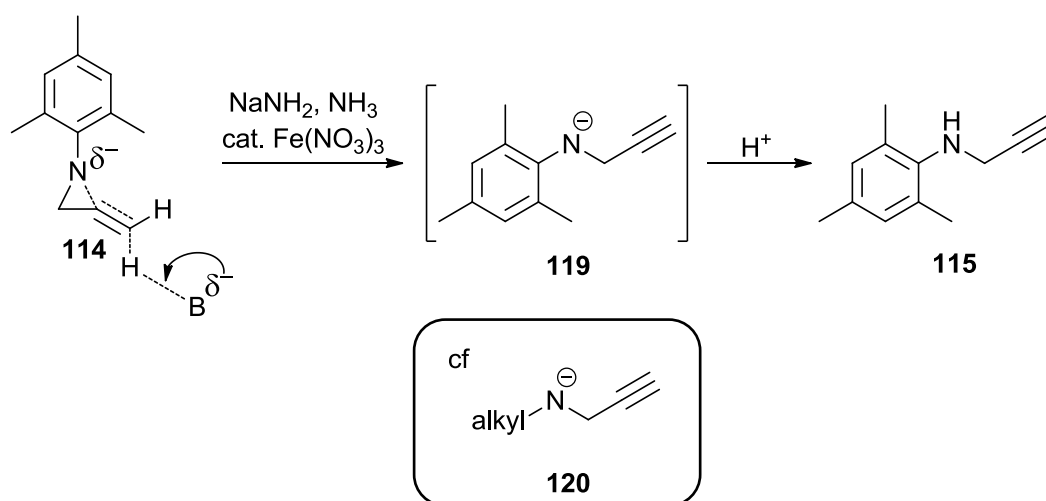
The optimised conditions for this reaction involve treatment with NaNH<sub>2</sub> (2 eq.) for 0.5 h at –33 °C. However, for preparative scales (>6.64 mmol), 1 h was the preferred length of time to consistently achieve high yields. Gratifyingly, with careful control of the reaction conditions, clean reactions with high yields (>85 %) can be realised.

It is known that alkyne **118** is not formed from the corresponding N-alkyl methyleneaziridine **117** (Scheme 1.42).



Scheme 1.42.

The early inconsistent results in the optimisation study (Table 1.5) led us to postulate that this was not the case for *N*-mesityl methyleneaziridine **114**. A sample of **114** was re-subjected to the cyclisation conditions; where it could be seen after work-up that more alkyne was present. This suggests that E2-elimination via removal of the hydrogen antiperiplanar to the C-N bond, leads to the formation of the stable anion, which is protonated during work-up (Scheme 1.43). The greater stability of anion **119** relative to **120**, and the transition state leading to it, perhaps explains why this process is favoured.



Scheme 1.43.

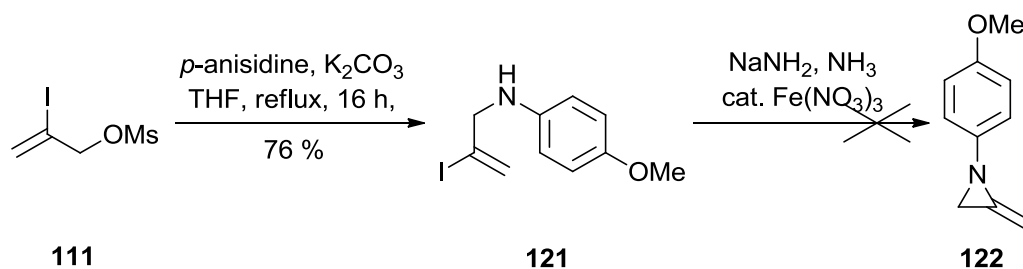
We also confirmed that the reverse reaction does not take place. When alkyne **115** was re-subjected to the cyclisation conditions methyleneaziridine **114** was not formed (Scheme 1.44).



Scheme 1.44.

The inclusion of the two methyl groups in the *ortho* positions on the benzene ring had successfully solved the problem of the formation of side products under the reaction conditions. Next, we briefly explored whether other aryl substituents could be tolerated. As *p*-anisidine was readily available in our laboratory we explored the synthesis of methyleneaziridine **122**.

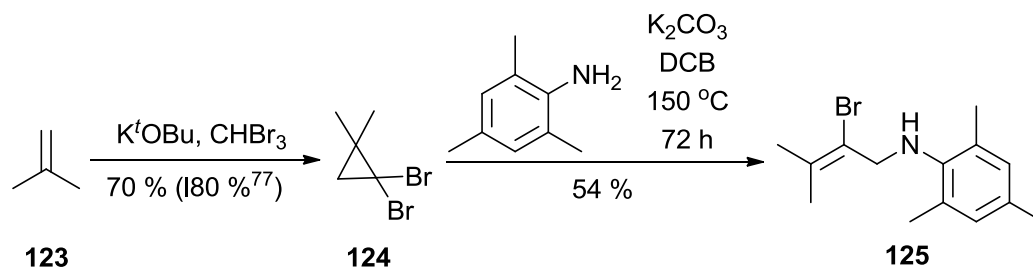
Precursor **121** was synthesised from mesylate **111** in 76% yield. Amino iodide **121**, was then subjected to the optimised cyclisation conditions with a view to forming **122** (Scheme 1.45). Unfortunately, the <sup>1</sup>H NMR spectra showed that, although there was some evidence for cyclisation there was considerable over integration in the aromatic region, suggesting benzyne formation may still be occurring. No further investigations of substrates devoid of *o*-substituents were pursued.



Scheme 1.45.

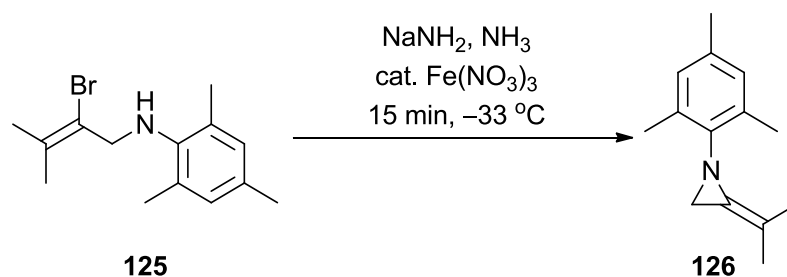
### 1.5.2.1. Synthesis of Substituted N-Mesityl-2-methyleneaziridines

The synthesis of the *gem*-dimethyl substituted methyleneaziridine **126** was also investigated, in collaboration with an MChem project student, Alyn Davies.<sup>76</sup> As the formation of the alkyne by-product is not possible in this system it was not necessary to have the iodide precursor for facile cyclisation. Therefore bromide **125** was synthesised in the same manner as related *gem*-dimethyl methyleneaziridines.<sup>19</sup> The first step was addition of dibromocarbene, generated from bromoform and potassium *t*-butoxide to isopropylene, which proceeded in 70% yield (Scheme 1.46).<sup>77</sup> The second step involved opening the cyclopropane **124** with 2,4,6-trimethylaniline. The initial yield was very poor, however, after some optimisation and changing the reaction vessel to a sealed tube, the yield was improved to 54% yield (Scheme 1.46).<sup>76</sup>



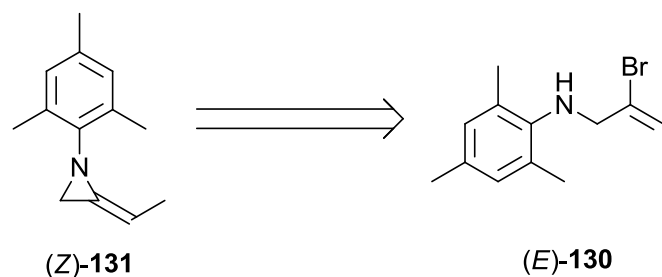
Scheme 1.46.

The cyclisation was best performed at  $-33^\circ\text{C}$  for 15 minutes (Scheme 1.47). Somewhat surprisingly, this indicates that the cyclisation is taking place more quickly than it does with no substitution on the double bond (cf. Table 1.6, Entry 5). Unfortunately, unlike *N*-alkyl methyleneaziridines, the inclusion of substitution on the double bond did not make methyleneaziridine **126** stable to column chromatography. Characterisation of methyleneaziridine **126** proved challenging as the crude  $^1\text{H}$  NMR consisted of a large number of non-coupling hydrogens. The high resolution mass spectrum was consistent with the required mass,  $m/z$  202.1589 (calc. 202.1590 for  $\text{C}_{14}\text{H}_{20}\text{N}$ ). Moreover, the IR spectrum for methyleneaziridines is very distinctive with the  $\text{C}=\text{C}$  alkene stretches at 1770–1730  $\text{cm}^{-1}$ , the IR spectrum of **126** had a distinct peak at 1774  $\text{cm}^{-1}$ .



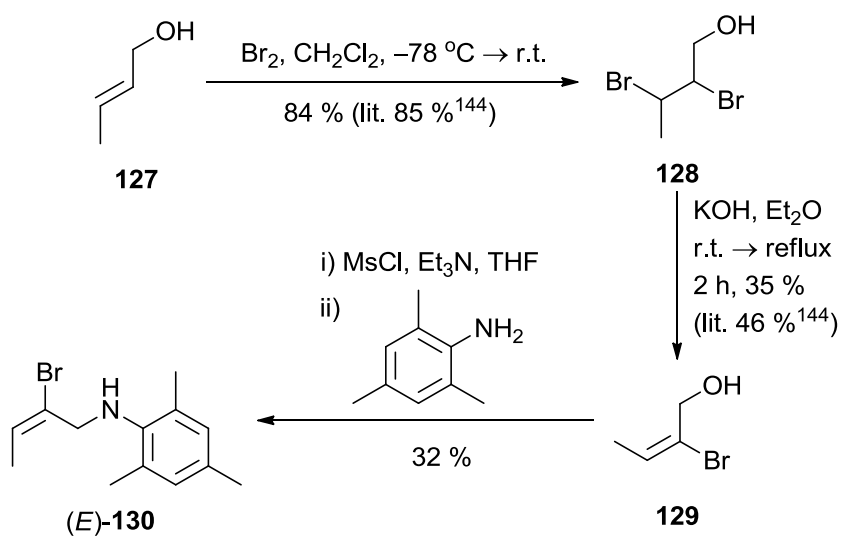
Scheme 1.47.

Next, mono-substituted methyleneaziridine (**(Z)**-**131**) was targeted. We chose the *trans*-bromide precursor (**(E)**-**130** as the antiperiplanar methyl group should prevent the competing E2-elimination reaction, favouring cyclisation (Scheme 1.48).



Scheme 1.48.

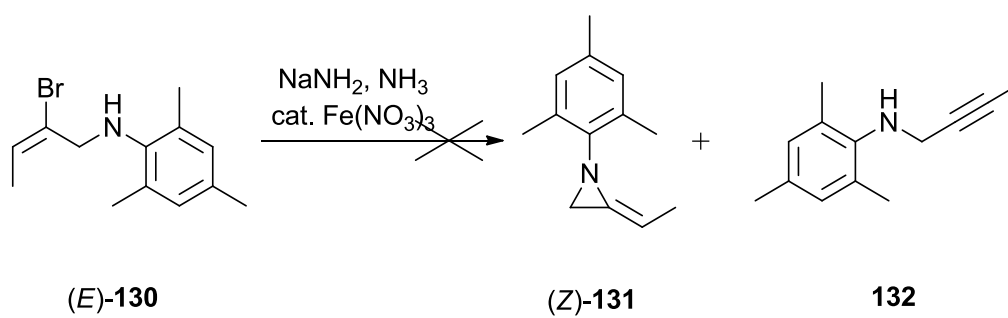
Bromination of crotyl alcohol (**127**), base induced elimination, mesylation, and further alkylation with 2,4,6-trimethylaniline gave (**(E)**-**130** in 9% yield over four steps (Scheme 1.49).



Scheme 1.49.



The cyclisation was first attempted using the previously optimised conditions for the cyclisation of iodo precursor **113** (2 equiv. sodium amide at  $-33\text{ }^{\circ}\text{C}$  for 60 minutes), but no product was observed. The reaction did not proceed cleanly as judged by  $^1\text{H}$  NMR and it was not possible to identify any peaks that could be attributed to alkyne **132**. Reducing the reaction time to 10 or 30 minutes and lowering the reaction temperature to  $-78\text{ }^{\circ}\text{C}$  did not improve the cyclisation (Scheme 1.50).



Scheme 1.50.

Undeterred, we decided to explore the use of the corresponding iodide based precursors (Z)-133 and (E)-133. Ideally, (E)-133 would be preferred as it should make alkyne formation more difficult. However, there is no simple method for installing the iodine with this stereochemistry (Figure 1.4.). Thus we targeted the synthesis of iodide (Z)-133. Hashmi *et al.* have reported the preparation of alcohol **135**<sup>78</sup> which potentially could be mesylated, then alkylated along similar lines to that used in Scheme 1.38. Starting from alkyne **134**, this sequence was successfully employed to make amine (Z)-133 (Scheme 1.51).

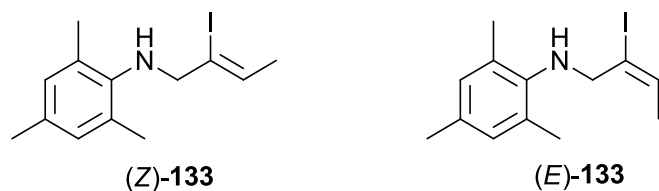
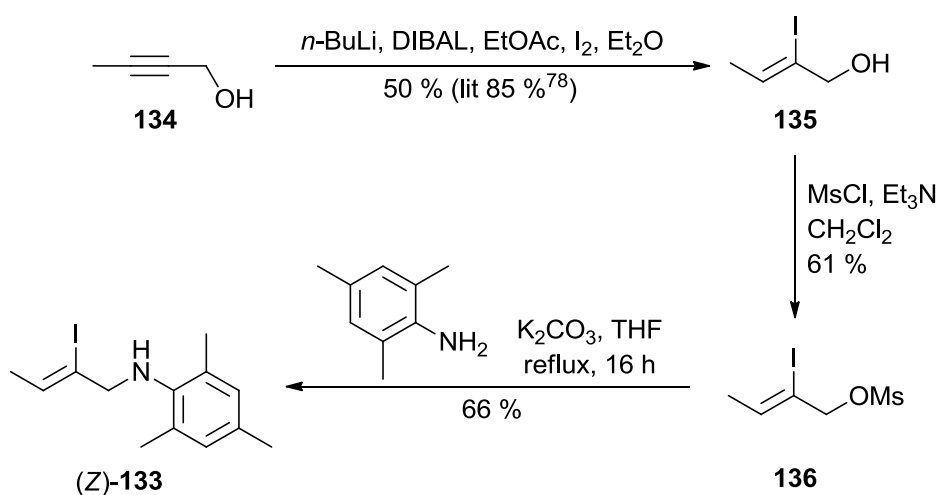
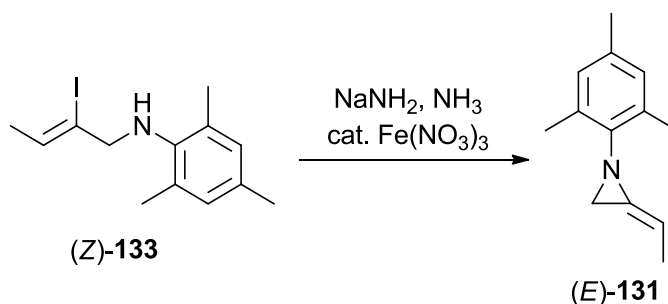


Figure 1.4.



Scheme 1.51.

Cyclisation of **(Z)-133** was attempted at  $-33\text{ }^{\circ}\text{C}$  for 30 minutes (Scheme 1.52). This time the reaction was much cleaner than for iodide **130**, however no methyleneaziridine was apparent by  $^1\text{H}$  NMR analysis. Considerable amounts of starting material were present, so the reaction was repeated for a longer duration (60 min). Again the reaction had not gone to completion but this time a new quartet at 5.45 ppm was visible by  $^1\text{H}$  NMR spectroscopy that might be associated with methyleneaziridine **(E)-131**. Unfortunately the sample was not stable so characterisation was not possible. As the reaction was still messy, further optimisation of this cyclisation was not attempted.

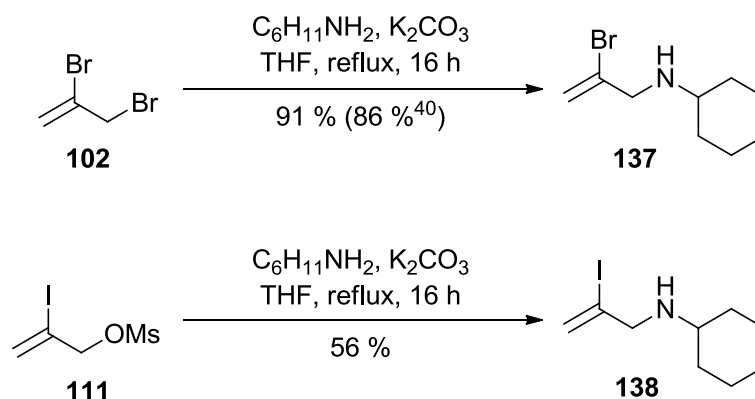


Scheme 1.52.

## 1.6. Methyleneaziridine Formation: Effect of the Leaving Group

### 1.6.1. Cyclisation of Bromide 137 and Iodide 138

It was clear that changing bromide for iodide had benefited the cyclisation forming methyleneaziridines **104** and **114**. We wanted to try and quantify and understand these effects in greater detail. To do this we needed to compare the cyclisations of bromide and iodide precursors. We needed a cyclisation that is known to be quite slow for the bromide and where the yield is often relatively low. This might allow for practical improvements in the reaction to be achieved. One candidate is *N*-cyclohexyl methyleneaziridine **48**, which is often produced in low yield, from bromide **137** (30-50%).<sup>40</sup> The two precursors required; bromide **137** and iodide **138** were synthesised using conventional methods (Scheme 1.53).



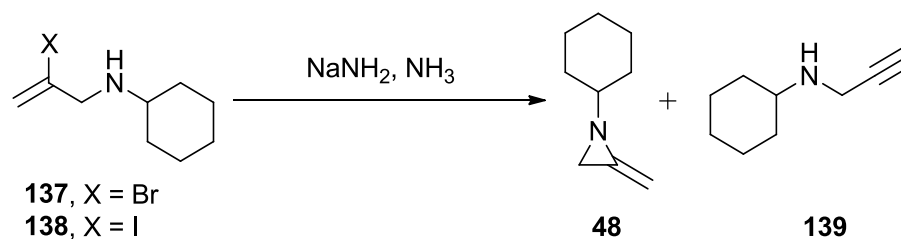
Scheme 1.53.

As reproducibility had proven to be an issue with our earlier work, we ran all the cyclisations in duplicate and in parallel, taking care to minimise any practical differences (i.e. identical flasks, cold finger condensers, stirrer bars and similar stirring rates).

It is possible to identify precursors **137/138**, methyleneaziridine **48** and alkyne **139** by  $^1\text{H}$  NMR spectroscopy of the crude product, and so this method of analysis was chosen. All the cyclisations were run with 2 equiv. sodium amide in 12 mL of ammonia.

Usually for these types of cyclisation, iron(III) nitrate nonahydrate is used to generate the  $\text{NaNH}_2$ , however, due to it being very hygroscopic it is difficult to weigh out accurately. An alternative catalyst is iron(III) chloride.<sup>15</sup> This is much easier to weigh out so we switched to this for the rest of the study. Runs performed using this catalyst are presented (Table 1.7). Although the conditions used in entry 2 (Table 1.7) were encouraging when they were attempted with iodide **138** (Entry 5) we were surprised to see that the reaction had gone almost to

completion, a finding that suggested little difference in the relative rates of the cyclisations.



Entry	X	Time (min)	Catalyst (mg)	138 : 48 : 139
1	I	10	2	18.5 $\pm$ 5.5 : 43.5 $\pm$ 5.5 : 38 $\pm$ 0
2	I	10	10	10 $\pm$ 3 : 69.5 $\pm$ 3.5 : 20.5 $\pm$ 0.5
3	I	10	15	4 $\pm$ 4 : 80 $\pm$ 10 : 16 $\pm$ 6
4	I	20	10	0 $\pm$ 0 : 79.5 $\pm$ 20.5 : 20.5 $\pm$ 20.5
5 <sup>a</sup>	Br	10	10	1.5 $\pm$ 1.5 : 79.5 $\pm$ 9.5 : 19 $\pm$ 8

**Table 1.7.** All reactions performed in 50 mL flasks and 2 equiv.  $\text{NaNH}_2$  made using  $\text{FeCl}_3$ .

Errors calculated from the mean. <sup>a</sup> 137 : 48 : 139.

However, we were still concerned about the reproducibility of the reaction. Ideally, the two precursors **137** and **138** need to be in the same reaction vessel in a genuine competition experiment.

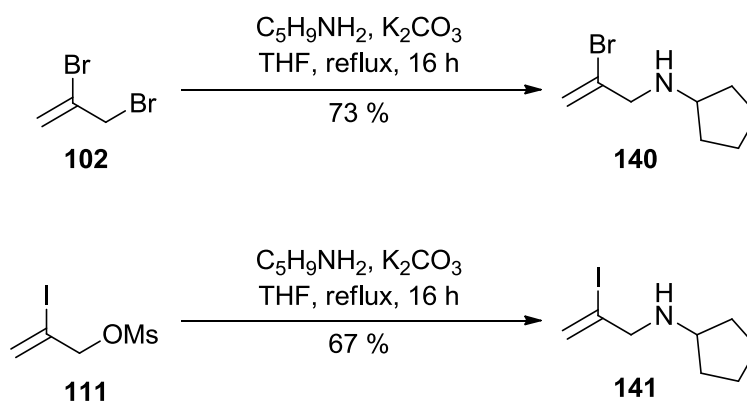
### 1.6.2. Direct Competition Experiments

By using precursors with similar but different substituents on the nitrogen atom, it should be possible to identify the different reaction components by a suitable analytical technique such as GC–MS. Of course, changing the substituent on the nitrogen could affect the cyclisation rate. As we were working with cyclohexyl

methyleneaziridine **48** we thought it may be possible to compare this with the closely related cyclopentyl methyleneaziridine **142**, as such a small variation should make little difference to the cyclisation rate, but change the product masses by 14 Daltons.

The plan was to cyclise cyclohexyl iodide **138** and cyclopentyl bromide **140** in the same vessel, each would give their respective methyleneaziridine and alkyne. This strategy requires the identification of six different compounds in the reaction mixture. We were confident that GC–MS analysis might be suitable for this challenging analytical task.

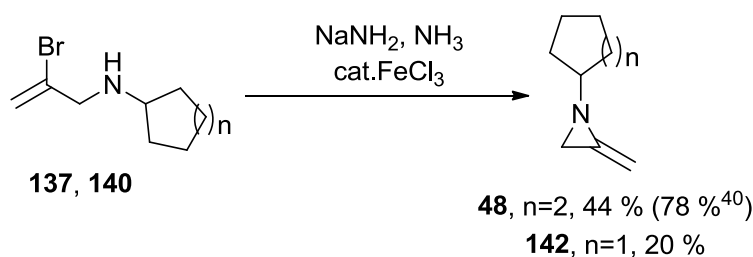
Two new cyclisation precursors **140** and **141** were synthesised in 73% and 67% yield respectively (Scheme 1.54).



Scheme 1.54.

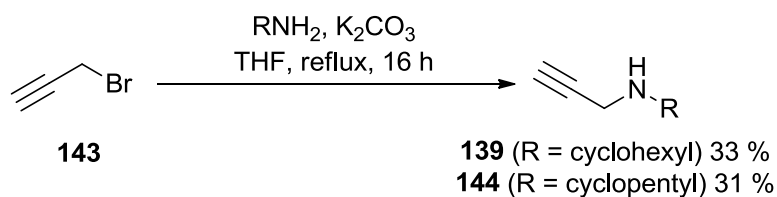
All four precursors, namely **137**, **138**, **140** and **141**, could be separated by GC–MS analysis (Table 1.8). Methyleneaziridine **142** is not known so the cyclisation was tested. Methyleneaziridine **142** proved more volatile than methyleneaziridine **48**

which made isolation more difficult. Only a small sample of methyleneaziridine **142** was isolated in low yield, but sufficient to characterise and analyse by GC–MS (Scheme 1.55).



Scheme 1.55.

Next, we turned our attention to the final two products required; alkynes **139** and **144**. Starting with propargyl bromide, these were readily made in 33% and 31% yield respectively (Scheme 1.56).



Scheme 1.56.

Comparing the retention times of all eight compounds showed that bromide **137** and iodide **141** were running very close together. Unfortunately this meant that when they were analysed together they essentially co-eluted. All the other compounds were fully resolved (Table 1.8 and Appendix 2). We now had all eight compounds required for the cyclisation study to hand, and a method to separate them (Figure 1.5.).

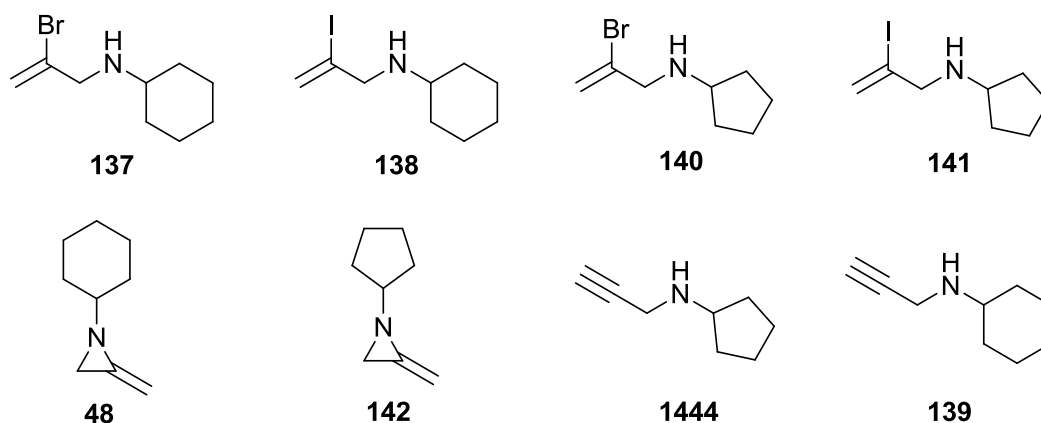


Figure 1.5.

Compound	Retention time (min)	Correction factor
138	7.6	1
137	6.9	2.24
141	7.0	1.04
140	6.4	1.88
139	5.5	3.02
144	4.9	8.14
48	5.3	10.37
142	4.6	10.12

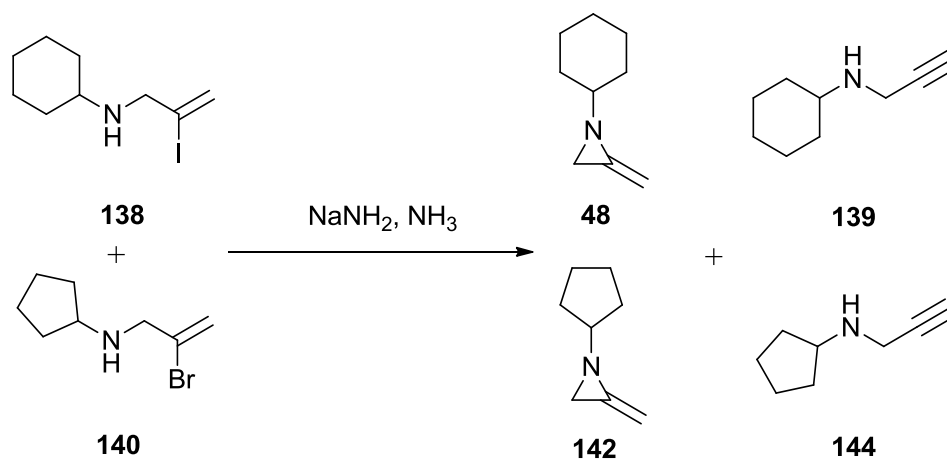
Table 1.8. GC–MS analysis using a factorfour capillary column, with flow rate 1 mL min<sup>-1</sup>, injection volume = 2 µL, injection temperature = 240 °C – splitless. The temperature was held at 50 °C for 1 min, increased at 25 °C/min for 9 min and held at 300 °C for 9 min.

A further consideration was to quantify the amounts of compounds accurately as their ionisation potential in the mass detector of the GC–MS might be different. To compensate for this, each compound needed to have a correction factor calculated. To determine this correction, each compound was run alongside every



other one in a 1:1 molar ratio. The calculated correction factors were affirmed by re-running mixtures of compounds at varying concentrations and combinations.

With all the expected products to hand, and a good analytical method established, we were well placed to undertake the competition experiments. Initially, the conditions for the competition reaction were optimised. Using iodide **138** and bromide **140** a variety of conditions were investigated (Table 1.9). It is clear that only one set of conditions showed acceptable reproducibility and tantalisingly suggests that the iodine is indeed cyclising faster (Table 1.9, Entry 4). Entry 2 demonstrates the need for two equivalents of sodium amide and entry 3 indicated we needed to cool the reaction to slow the cyclisation rate.



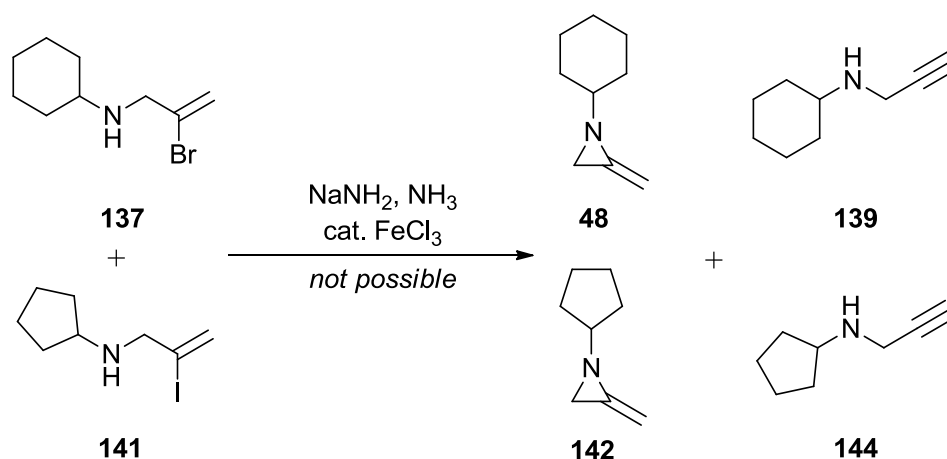
Entry	Equiv. $\text{NaNH}_2$	t (min)	T ( $^{\circ}\text{C}$ )	138 : 48 : 139 140 : 142 : 144
1	2	10	-33	1 $\pm$ 1 : 88 $\pm$ 7 : 11 $\pm$ 6 19 $\pm$ 19 : 49 $\pm$ 37 : 32 $\pm$ 18
2	1	10	-33	39 $\pm$ 3 : 31 $\pm$ 3 : 16 $\pm$ 14 100 $\pm$ 0 : 0 : tr
3	2	5	-33	tr : 97 $\pm$ 1 : 3 $\pm$ 1 tr : 90 $\pm$ 3 : 10 $\pm$ 3
4	2	10	-78	14 $\pm$ 1 : 86 $\pm$ 1 : tr 54 $\pm$ 1 : 46 $\pm$ 1 : tr
5	2	30	-78	24 $\pm$ 18 : 75 $\pm$ 17 : 1 $\pm$ 1 79 $\pm$ 21 : 21 $\pm$ 21 : tr
6	2	10	-78	6.5 $\pm$ 3.5 : 90 $\pm$ 4 : 3.5 $\pm$ 0.5 36.5 $\pm$ 1.5 : 63.5 $\pm$ 1.5 : tr

**Table 1.9.** All results performed in duplicate.  $\text{NaNH}_2$  made using  $\text{FeCl}_3$  and the errors calculated from the mean. tr = compound present but peak too small to integrate.

We started by repeating the cyclisations with cyclohexyl iodide **138** and cyclopentyl bromide **140** using the optimised conditions ( $-78\text{ }^{\circ}\text{C}$ , 10 min, 2 equiv.  $\text{NaNH}_2$ , 12 mL  $\text{NH}_3$  and  $\text{FeCl}_3$ ). Satisfyingly the results of the two runs were reasonably consistent (Table 1.9, Entry 6). It is clear from the results that the

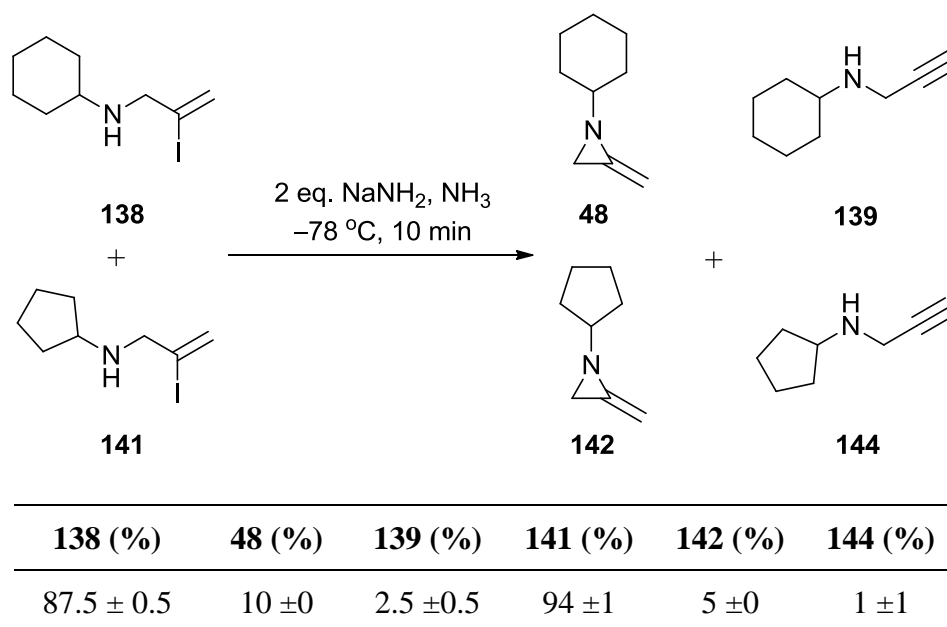
cyclisation of iodide **138** is quicker than that of bromide **140**. Also, in both cases the amount of alkyne formed is minimal.

The proposed study involved cyclisation of bromide **140** and iodide **138** in a series of experiments, and bromide **137** and iodide **141** in another. If the results were consistent, it would confirm that the substituents on the nitrogen atom are not influencing the cyclisation rate. Unfortunately, as the retention time of bromide **137** and iodide **141** on GC–MS are very similar, the second of the proposed reactions could not provide quantitative data. To circumvent this problem, the same data could be obtained by comparing the rates of cyclisation of either the iodide **138** and **141** or bromide **137** and **140** precursors.



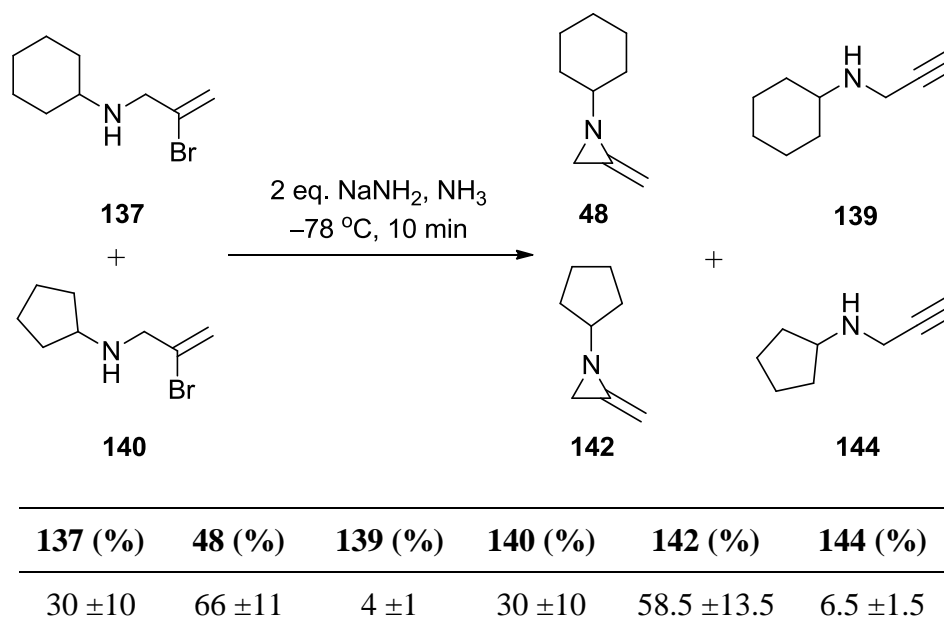
Scheme 1.57.

The reaction comparing both the iodide precursors **138** and **141** showed that the different groups on the nitrogen atom were not having an effect on the rate of cyclisation (Table 1.10).



**Table 1.10.** All reactions performed in duplicate and NaNH<sub>2</sub> made using FeCl<sub>3</sub>. The errors calculated from the mean.

However, the extent of methyleneaziridine formation in all these reactions was lower than expected, highlighting the difficulties in reproducibility in the reactions and reaffirming the importance of completing such reactions in competition. Better results were seen with bromides **137** and **140** which again appear to cyclise at similar rates (Table 1.11). These data indicate that it is only the halogen that is affecting the rate of the cyclisation in Table 1.9 and not the substituent on the nitrogen atom. Taken together, we have been able to provide good evidence that iodide substrates cyclise faster in these reactions.



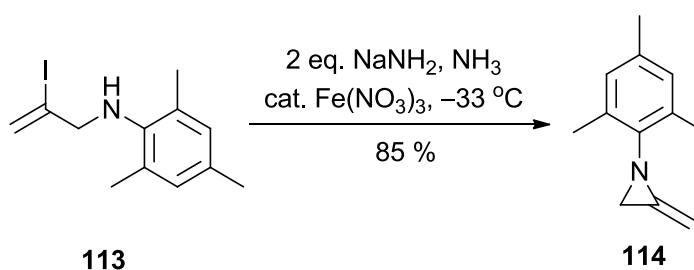
**Table 1.11.** All results performed in duplicate with  $\text{NaNH}_2$  made using  $\text{FeCl}_3$ . The errors calculated from the mean.

## 1.7. Conclusions

The attempted synthesis of methyleneaziridines **88** and **89** from allene (**74**) using modern catalysed aziridination methods met with no success. The reactions only produced expected by-products (tosylamide and iodobenzene) and unidentifiable products. One possible explanation is that the products are not stable enough for isolation, a hypothesis supported by the observations made by Bingham and Gilbert in their work on reaction of carbethoxynitrene with allenes.<sup>79</sup>

The first route to *N*-aryl methyleneaziridines has been developed. Success was achieved using the sodium amide ring closure method of Pollard and Parcell.<sup>14</sup> By replacing the bromide leaving group with an iodide, blocking the *o*-hydrogens of the aromatic ring, and careful reaction optimisation. In this way, *N*-mesityl

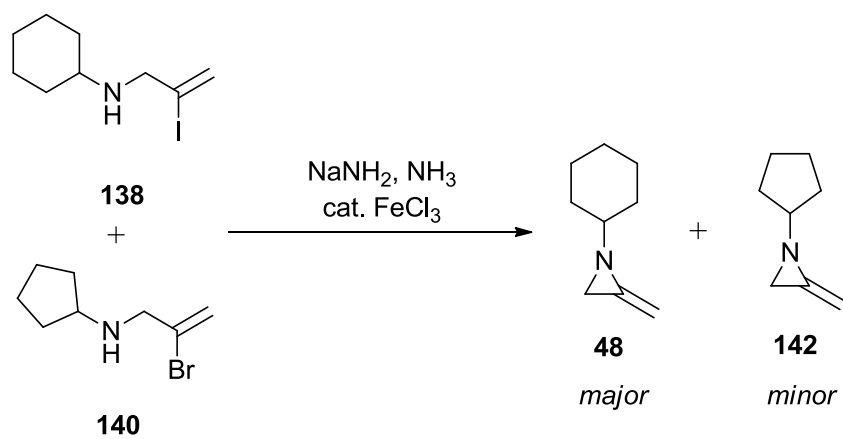
substituted methyleneaziridine **114** could be made in 85 % yield (*ca.* 95 % purity) (Scheme 1.58). The reactivity of this new class of methyleneaziridines is described in Chapter 2.



Scheme 1.58.

Efforts to extend this chemistry to the synthesis of related methyleneaziridines through variation in the alkene substituents, or aryl group met with limited success.

These discoveries led us to investigate the impact of the leaving group on the cyclisation of *N*-cyclo-alkyl methyleneaziridines. Encouraging computational studies by Ando<sup>73</sup> have been supported by the experimental data showing that iodide precursor **138** cyclises faster than bromide **140** (Scheme 1.59). The data was obtained by conducting a series of internal competition reactions at (-78 °C for 10 min). Further data confirmed that the small changes in the *N*-substituent do not markedly alter the cyclisation rates. These data suggest that for the synthesis of difficult methyleneaziridines, the use of iodide precursors should be investigated.



Scheme 1.59.

# **Chapter 2:**

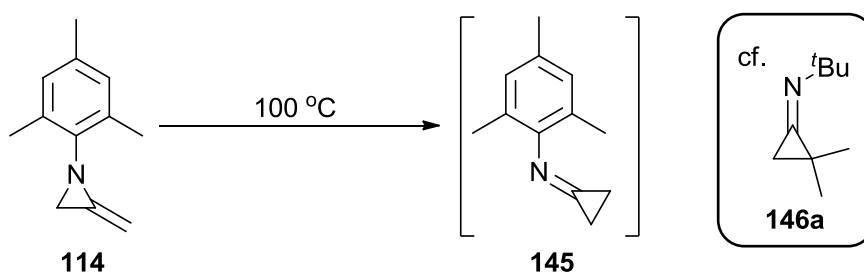
## **Rearrangement Reactions of *N*-Aryl- 2-methyleneaziridines**



In Chapter One, the first *N*-aryl methyleneaziridines were produced. Before exploring new transition metal catalysed chemistry of these methyleneaziridines, we set about exploring some of their simple chemistry, to understand more about their reactivity.

### 2.1. Thermal Rearrangement of *N*-Mesityl-2-methyleneaziridine (**114**)

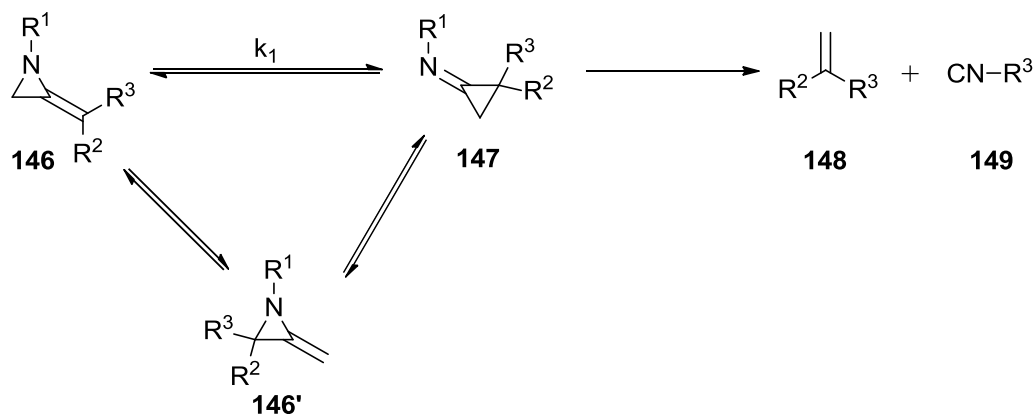
Methyleneaziridine **114** cannot be purified by distillation, due to low thermal stability (Chapter 1.5.2). The product obtained after distillation at 100 °C can be assigned as imine **145** (Scheme 2.1). Evidence for this is provided by <sup>1</sup>H NMR spectroscopy. The two 1H singlets at 4.94 and 4.79 ppm and the 2H singlet at 2.6 ppm are lost, being replaced by two 2H multiplets at 1.65 and 1.29 ppm (cf. 1.3 and 1.1 ppm for **146a**<sup>80</sup>).



Scheme 2.1.

This type of rearrangement is already known for *N*-alkyl methyleneaziridines (Scheme 2.2).<sup>80</sup> Quast and Risler demonstrated methyleneaziridine **146** decomposes quantitatively; slowly at 120 °C and rapidly above 190 °C to give ethylene **148** and isocyanide **149** quantitatively. They speculated that to form **148** and **149**, methyleneaziridine **146** must first rearrange to cyclopropanimine **147**.

This hypothesis is strengthened by reports that methyleneaziridine **146b** also converts quantitatively above 140 °C to ethylene **148b** and isocyanide **149b**.<sup>81</sup> By following the thermolysis of methyleneaziridine **146a** by <sup>1</sup>H NMR spectroscopy, transient signals attributed to both **146'a** and **147a** were observed.



<b>146</b>	<b>R<sup>1</sup></b>	<b>R<sup>2</sup></b>	<b>R<sup>3</sup></b>
<b>a</b>	<i>t</i> Bu	Me	Me
<b>b</b>	<i>i</i> PrCH <sub>2</sub>	<i>t</i> Bu	H
<b>c</b>	Me	H	H
<b>d</b>	Et	H	H
<b>e</b>	<i>t</i> Bu	H	H

Scheme 2.2.

In the cases of methyleneaziridines **146c-e**, **146** → **147** is a valence topomerisation and so simplifies the <sup>1</sup>H NMR; making it possible to follow the rearrangement by observing the decrease in the intensity of the olefinic signals. It was shown that the reaction was first order with respect to **146** (Equation 2.1). The values for *k*<sub>1</sub> at 150 °C, 170 °C and 190 °C were extrapolated and

subsequently the enthalpy and entropy of activation values were deduced (Table 2.1).

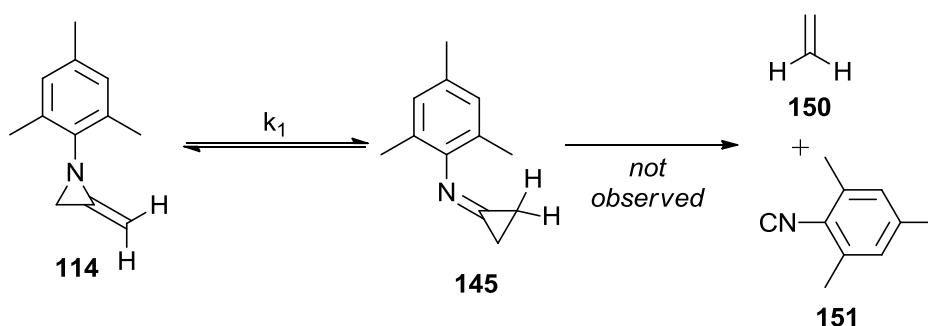
$$[\mathbf{146}] = [\mathbf{146}]_0 \exp[-k_1 t]$$

**Equation 2.1.** Where  $k$  = rate constant ( $\text{s}^{-1}$ ) and  $t$  = time (s).

<b>146</b>	<b><math>10^5 \times k_1 [\text{s}^{-1}]</math></b>			<b><math>\Delta H^\ddagger</math></b>	<b><math>\Delta S^\ddagger</math></b>
	<b>150.0 °C</b>	<b>170.0 °C</b>	<b>190.0 °C</b>	<b>[kJ mol<sup>-1</sup>]</b>	<b>[J K<sup>-1</sup> mol<sup>-1</sup>]</b>
<b>c</b>	3.50 ± 0.03	21.4 ± 0.1	127.5 ± 0.8	142.8 ± 3.3	4.2 ± 4.2
<b>d</b>	1.561 ± 0.008	—	—	—	—
<b>e</b>	0.085 ± 0.002	0.510 ± 0.04	3.29 ± 0.04	145.7 ± 0.8	-20.1 ± 2.1

**Table 2.1.**

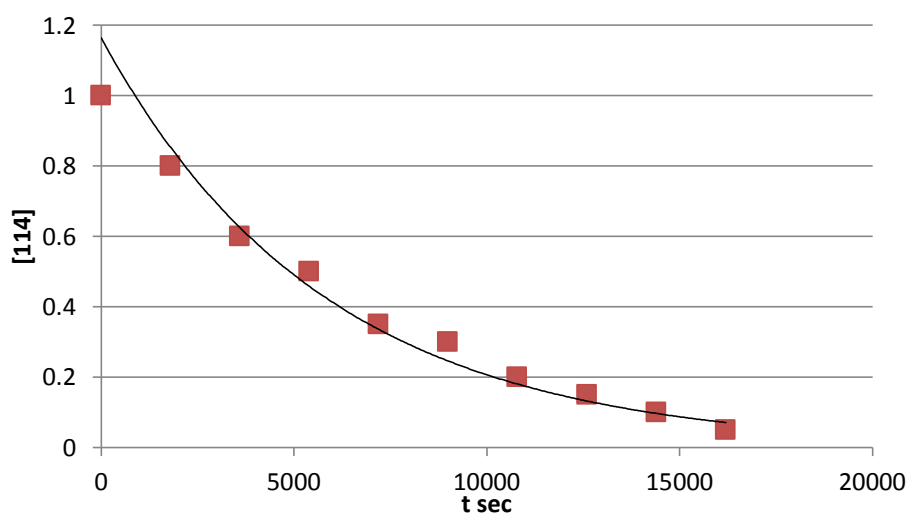
In methyleneaziridine **114**, it was apparent that the rearrangement was taking place at a lower temperature and that we did not observe any formation of isocyanide **151** (Scheme 2.3). This suggests that the rearrangement was faster. We sought to quantify this increase in rate by a similar method to that used by Quast and Reisler.<sup>80</sup>



**Scheme 2.3.**

### 2.1.1. Kinetic Study

With knowledge that the rearrangement of methyleneaziridine **114** to imine **145** occurs at 100 °C we sought to investigate whether it would proceed at an appreciable rate at lower temperatures. Indeed in THF, only imine **145** was present after 18 h. The reaction was expected to be first order. To demonstrate this, we heated methyleneaziridine **114** at reflux, in THF, and sampled it every 30 minutes. The samples were rapidly cooled to –78 °C to stop further reaction, and the solvent removed. The extent of reaction was analysed by  $^1\text{H}$  NMR. To aid analysis, an internal standard of 1,3,5-trimethoxybenzene was included in the reaction. The extent of conversion could be deduced by integration of the alkene hydrogens with the standard. An exponential curve was seen, as expected for a 1<sup>st</sup> order reaction (Graph 2.1).

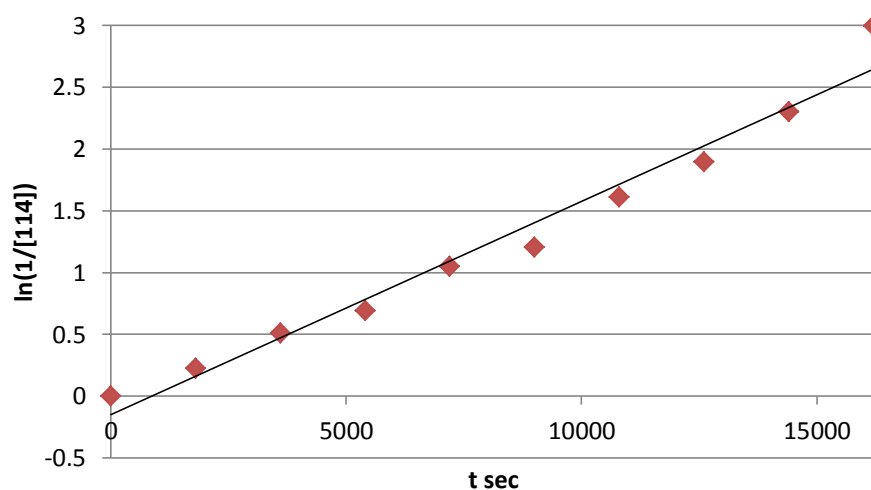


Graph 2.1.

With  $\ln(1/[114])$  plotted against time (Equation 2.2) an approximately straight line was obtained, from which a rate constant of  $k = 2.0 \pm 0.1 \times 10^{-4} \text{ s}^{-1}$  was extrapolated (Graph 2.2).

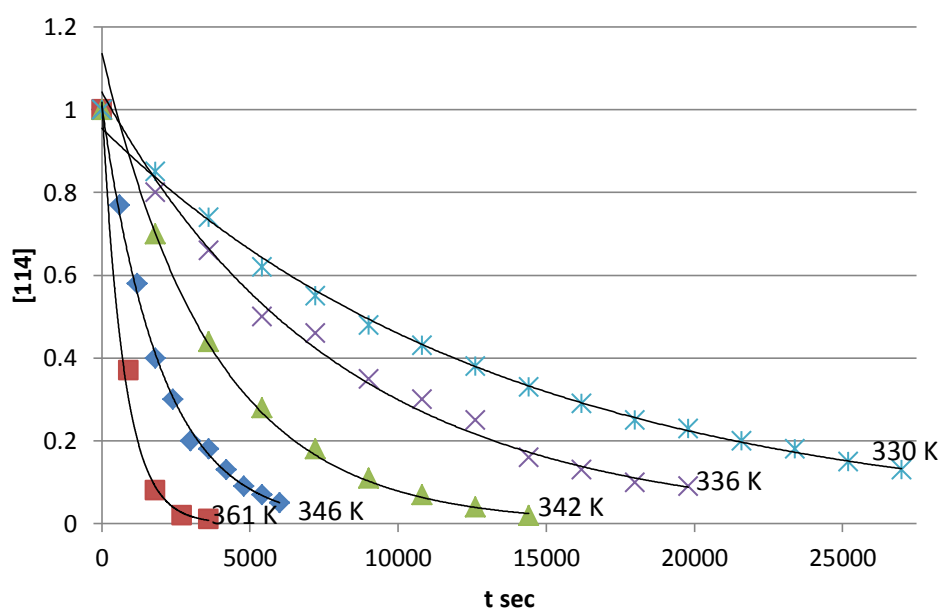
$$\ln\left(\frac{1}{[114]}\right) = kt$$

**Equation 2.2.** Where  $k$  = rate constant ( $\text{s}^{-1}$ ) and  $t$  = time (s)



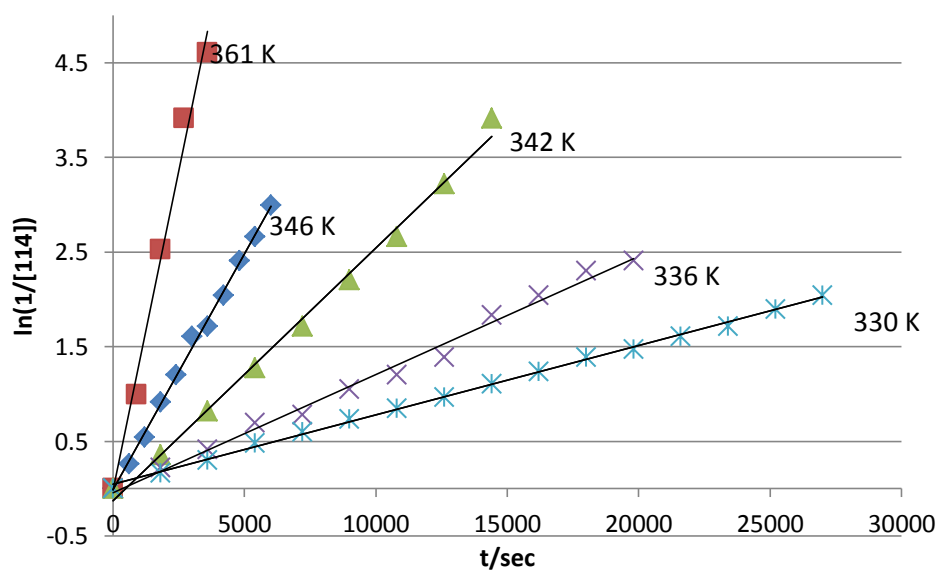
**Graph 2.2.**

To calculate the  $\Delta G^\ddagger$ ,  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  values for the rearrangement, this isomerisation needed to be studied over a range of temperatures. For these experiments, toluene was chosen. Five different temperatures were investigated; 361, 346, 342, 336 and 330 K (Graph 2.3) which all gave the expected exponential curves.



Graph 2.3.

By plotting  $\ln(1/[114])$ , all the reactions gave straight lines consistent with 1<sup>st</sup> order reactions (Graph 2.4). The rate constants for each reaction are summarised in Table 2.2.



Graph 2.4.

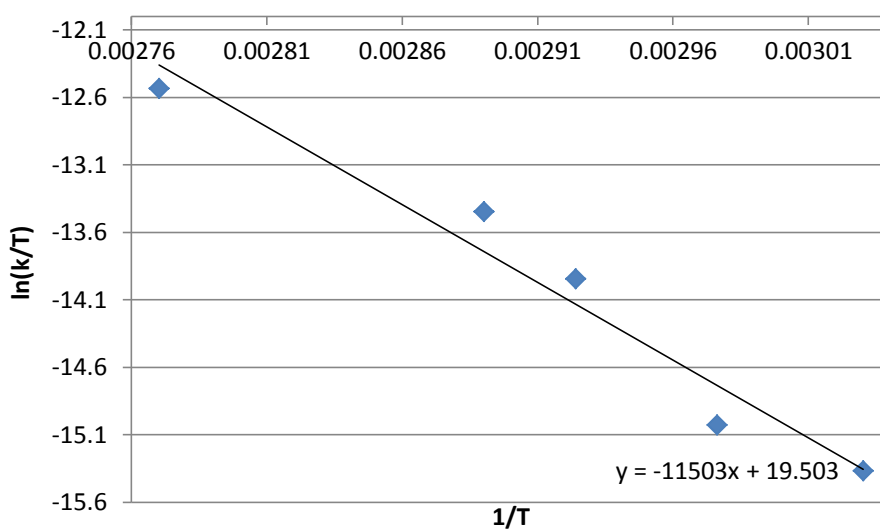
By plotting  $\ln(k/T)$  against  $1/T$  (Graph 2.5) from the Eyring equation (Equation 2.3), the enthalpy and entropy of activation for the isomerisation and subsequently, using Equation 2.4, the Gibbs Free energy for the isomerisation at each temperature were calculated (Table 2.2).

$$\ln\left(\frac{k}{T}\right) = \frac{-\Delta H}{R} \frac{1}{T} + \ln \frac{k_b}{h} + \frac{\Delta S}{R}$$

**Equation 2.3.** Where;  $k$  = rate constant ( $\text{s}^{-1}$ ),  $T$  = temperature (K),  $\Delta H$  = enthalpy ( $\text{kJ mol}^{-1}$ ),  $R$  = Gas constant ( $\text{J K}^{-1} \text{mol}^{-1}$ ),  $k_b$  = Boltzmann's constant ( $\text{J K}^{-1}$ ),  $h$  = Planck's constant ( $\text{J s}^{-1}$ ) and  $\Delta S$  = entropy ( $\text{J K}^{-1} \text{mol}^{-1}$ ).

<b>T (K)</b>	<b><i>k</i> (<math>\text{s}^{-1}</math>)</b>
361	$1.3 \times 10^{-3}$
346	$5.0 \times 10^{-4}$
342	$2.7 \times 10^{-4}$
336	$1.3 \times 10^{-4}$
330	$7.3 \times 10^{-5}$

**Table 2.2.**



Graph 2.5.

$$\Delta G = \Delta H - T\Delta S$$

**Equation 2.4.** Where  $\Delta G$  = Gibbs free energy ( $\text{kJ mol}^{-1}$ ),  $\Delta H$  = enthalpy ( $\text{kJ mol}^{-1}$ ),  $T$  = temperature (K) and  $\Delta S$  = entropy ( $\text{J K}^{-1} \text{mol}^{-1}$ ).

$$\Delta H^\ddagger = 99.9 \pm 11.9 \text{ kJ mol}^{-1}$$

$$\Delta S^\ddagger = -35.5 \pm 34.8 \text{ J K}^{-1} \text{mol}^{-1}$$

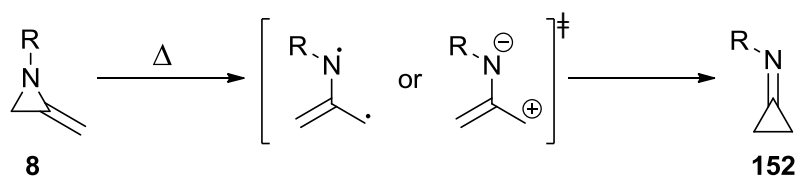
$$\Delta G_{298}^\ddagger = 110.5 \pm 22.3 \text{ kJ mol}^{-1}$$

Estimated errors calculated using the 'Least Squares' method.<sup>82,83</sup>

The errors are presumed to be random and are calculated from the uncertainty in the straight line (Graph 2.5). This has given relatively large estimated errors, especially for  $\Delta S^\ddagger$ . Comparing the enthalpy value to those calculated by Quast *et al.* for the *N*-alkyl methyleneaziridines **146a-e**<sup>80</sup> it can be seen that the value for



*N*-mesityl methyleneaziridine **114** is significantly lower (cf. **146c** =  $142.8 \pm 3.3$  and **146e** =  $145.7 \pm 0.05$  kJ mol<sup>-1</sup>, Table 2.1), showing it has a lower energy barrier to rearrange. If the mechanism is not concerted either a radical or zwitterionic intermediate may be formed (Scheme 2.4). When R = Ar, stabilisation of these intermediates is possible, leading to a lowering of the transition state barrier. The entropy value is also interesting. It is larger than the values reported by Quast *et al.* (cf. **146c** =  $4.2 \pm 4.2$  and **146e** =  $20.1 \pm 2.0$  J K<sup>-1</sup> mol<sup>-1</sup>, Table 2.1). The negative value suggests that the system is becoming more ordered in the transition state; however as the error for this value is large it is not possible to know how significant the change in entropy is. It would be unusual for a unimolecular process to have a largely negative value for  $\Delta S^\ddagger$  however the change in conformation may account for a small change.



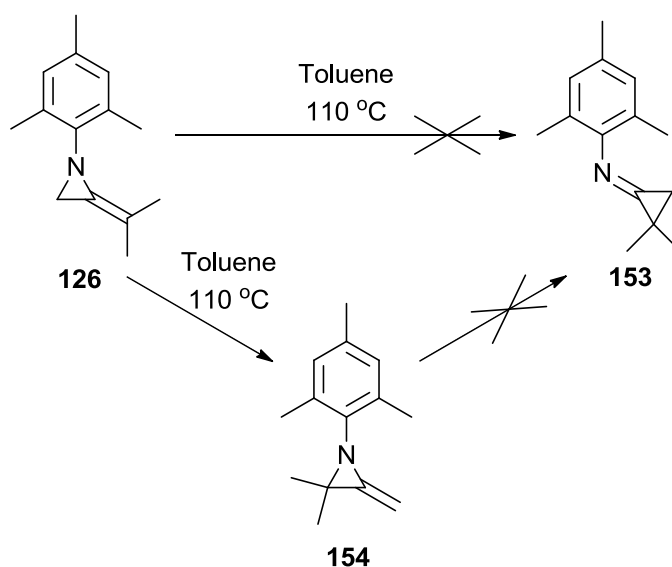
Scheme 2.4.

## 2.2. Rearrangement of Substituted *N*-Mesityl-2-methyleneaziridines

### 2.2.1. *N*-Mesityl-2-isopropylideneaziridine (**126**)

From Quast and Risler's work<sup>80</sup> it was expected that when heated, methyleneaziridine **126** would rearrange to both methyleneaziridine **154** and imine **153**. However when methyleneaziridine **126** was heated to reflux (110 °C)

in toluene only the isomeric methyleneaziridine **154** was observed (Scheme 2.5).<sup>76</sup> We did not observe any evidence for this rearrangement at temperatures below 30 °C over short periods of time, or during storage for several weeks at –18 °C.



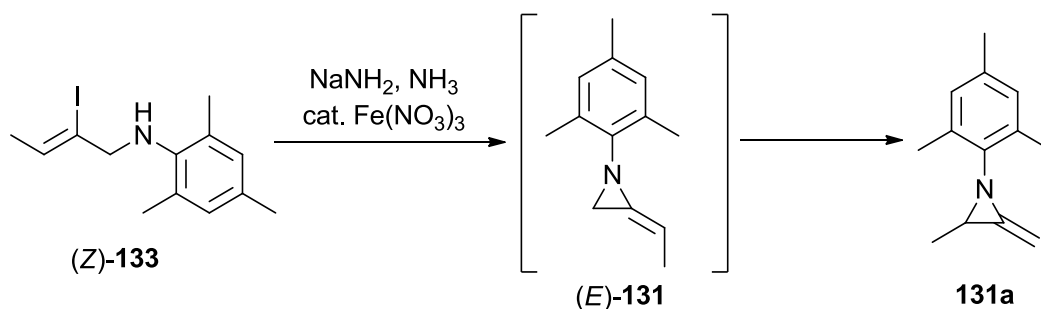
Scheme 2.5.

On further inspection of the <sup>1</sup>H NMR spectrum of methyleneaziridine **126** after it had been subjected to silica gel column chromatography, it was clear that in addition to degradation some of the signals could be assigned to **154**. The acidity of the silica gel was evidently also catalysing the rearrangement.

### 2.2.2. *N*-Mesityl-2-ethyleneaziridine (**131**)

As discussed in Chapter 1.5.2.1, methyleneaziridine (*E*)-**131** was possibly observed in the crude <sup>1</sup>H NMR; however, due to poor stability the product could not be fully assigned. On close inspection two singlet peaks just below 5.0 ppm were visible in the crude <sup>1</sup>H NMR of the cyclisations from both the bromide and

iodide starting materials (*E*)-**130** and (*Z*)-**133**. These singlets looked like the very distinct olefinic peaks of an unsubstituted methyleneaziridine. Hence, we postulate that methyleneaziridine **131a** is being formed by rapid rearrangement (Scheme 2.6). A <sup>1</sup>H quartet at 2.65 ppm coupled to a 3H doublet at 1.48 ppm strengthens this postulation as they are consistent with substitution at the C-3 of the methyleneaziridine ring. It is clear that this rearrangement is taking place at much lower temperatures than those required by methyleneaziridines **114** and **126**.

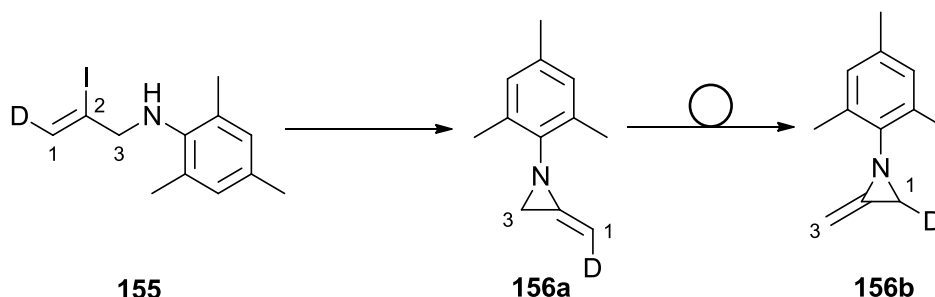


Scheme 2.6.

### 2.2.3. Deuterium Labelling Studies

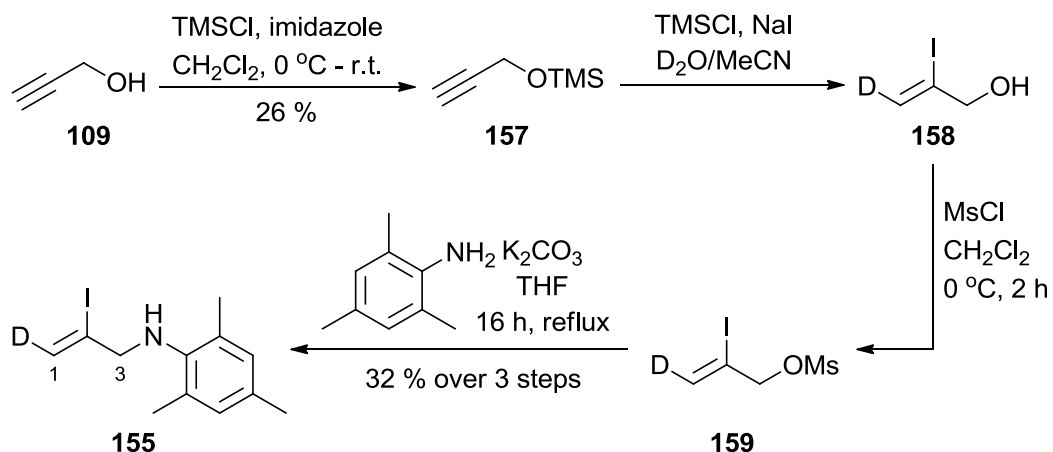
Methyleneaziridine **114** rearranges to imine **145** when heated above 57 °C, but it is not possible to know if the methyleneaziridine backbone is interconverting at this or lower temperatures. The data presented above suggested that this might be feasible. By including a deuterium label on carbon 1 in precursor **155** it may be possible to visualise which carbon is which in the product (Scheme 2.7). To test

these ideas, we decided to deuterate C-1 of precursor **155**, and examine where the label ends up in methyleneaziridine **156** after aziridination.



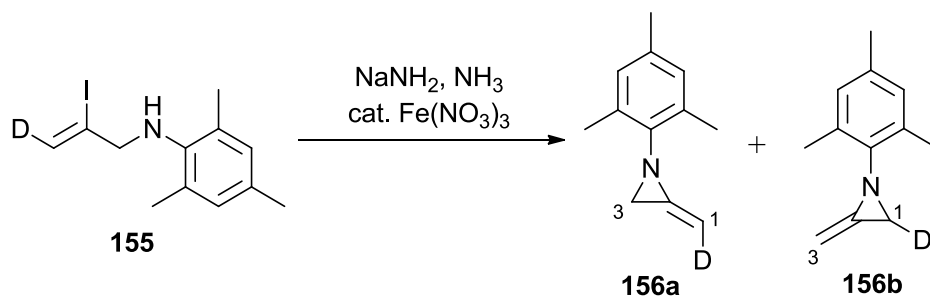
Scheme 2.7.

The formation of iodide **155** from propargyl alcohol lends itself to the inclusion of a deuterium atom. By substituting  $\text{H}_2\text{O}$  for  $\text{D}_2\text{O}$ , a deuterium can be incorporated into alcohol **158** (Scheme 2.8).<sup>74</sup> As the starting material contains an alcohol, this needs to be masked, to prevent proton/deuterium exchange. The first step therefore involved protection of propargyl alcohol with TMS-Cl. Next, deuteration was conducted to give alcohol **158** after concomitant loss of the silyl protecting group. Mesylation of the alcohol gave **159** which was alkylated with 2,4,6-trimethylaniline to give iodide **155** in 32 % yield over 3 steps (Scheme 2.8). The extent of deuterium incorporation was ca. 70 % as judged by  $^1\text{H}$  NMR and HRMS analysis. Mass spectrometry confirmed a single deuterium was contained within each molecule. The majority of the deuterium atoms were located at C-1 (75 %) with the remainder located at C-3 (25 %). Presumably, the latter product arises from partial  $\text{S}_{\text{N}}2'$  displacement of mesylate **159**.



Scheme 2.8.

With only a limited amount of iodide **155** available, it was only possible to run the cyclisation once on a relatively small scale (1.44 mmol). If the rearrangement is not taking place we would expect to see no change in the amount of deuterium located at C-1 and C-3. The ratio of **156a** : **156b** is 2 : 1 (cf. to 3 : 1 in **155**) which would suggest that rearrangement is taking place. However, due to the complexity of the system; the possibility of alkyne formation from iodide **155** and methyleneaziridine **156**, it is not possible to draw a firm conclusion from this small change in ratio. If deuterium was only located at the C-1 position in iodide **155** it would be possible to ascertain whether the rearrangement was occurring. Due to time constraints this chemistry was not explored further.



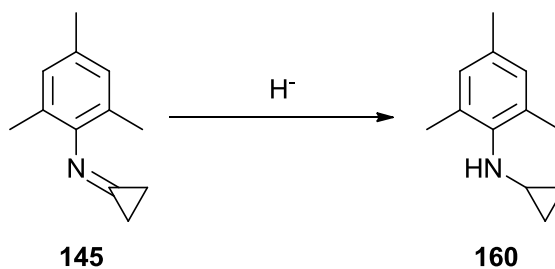
Scheme 2.9.

### 2.3. Cyclopropylamines

Cyclopropylamines are well known within medicine<sup>84,85,86</sup> and nature<sup>87,88</sup> and have been widely studied over the past few years. Moreover, they are versatile intermediates and building blocks in organic synthesis<sup>89,90,91</sup> and are found in a number of biologically active natural compounds including coronatine and (+)-(*E*)-2,3-methano-*m*-tyrosine.<sup>87,88</sup>

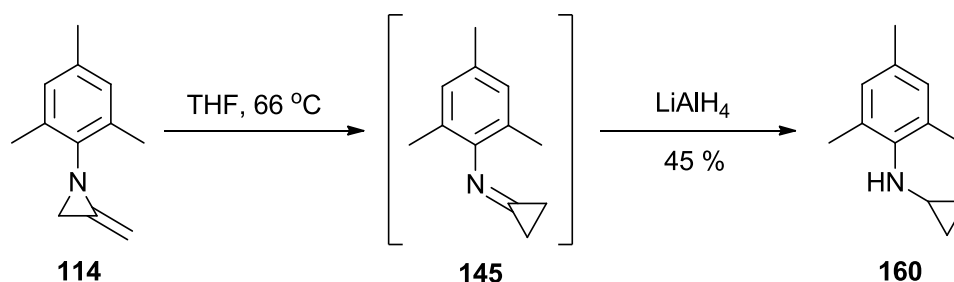
Kishner reported the first synthesis of cyclopropylamines in 1901<sup>92</sup> utilising a Hoffmann rearrangement. There are now several methods for the preparation of cyclopropylamines including; cyclopropanation of enamines and aminonitriles,<sup>88,93,94</sup> amidocyclopropanation of alkenes,<sup>95</sup> rearrangements,<sup>96</sup> and reductive amination reactions.<sup>97</sup>

Earlier in this Chapter, imine **145** had been produced by the thermal rearrangement of methyleneaziridine **114**. This suggested that *N*-aryl methyleneaziridines could provide a new method for the production of cyclopropylamines (Scheme 2.10).



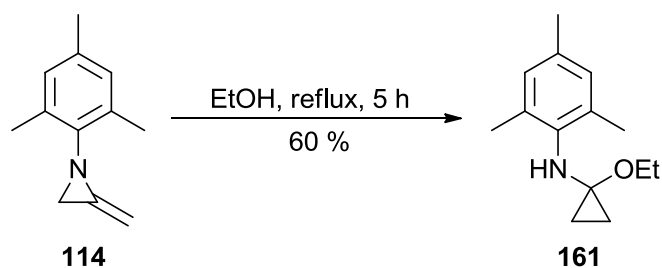
Scheme 2.10.

Initial attempts to thermally rearrange methyleneaziridine **114** then reduce the resulting imine **145** using lithium aluminium hydride in THF led to amine **160** in 45% yield (Scheme 2.11). Thermal rearrangement to imine **145** must be realised before addition of the lithium aluminium hydride to achieve acceptable yields. Attempts to use sodium cyanoborohydride or triacetoxyborohydride to reduce imine **145** were not successful. Although, in both cases amine **160** was present in the crude  $^1H$  NMR spectra, the reaction had not run cleanly with poor mass recovery so the products were not isolated.



Scheme 2.11.

Next, attempts were made to capture imine **145** with other nucleophiles. By heating methyleneaziridine **114** in ethanol at reflux, rearrangement and addition of ethanol led to cyclopropane **161** in 60 % yield (Scheme 2.12). The reaction did not work well using just 5 equivalents of ethanol in THF as solvent.

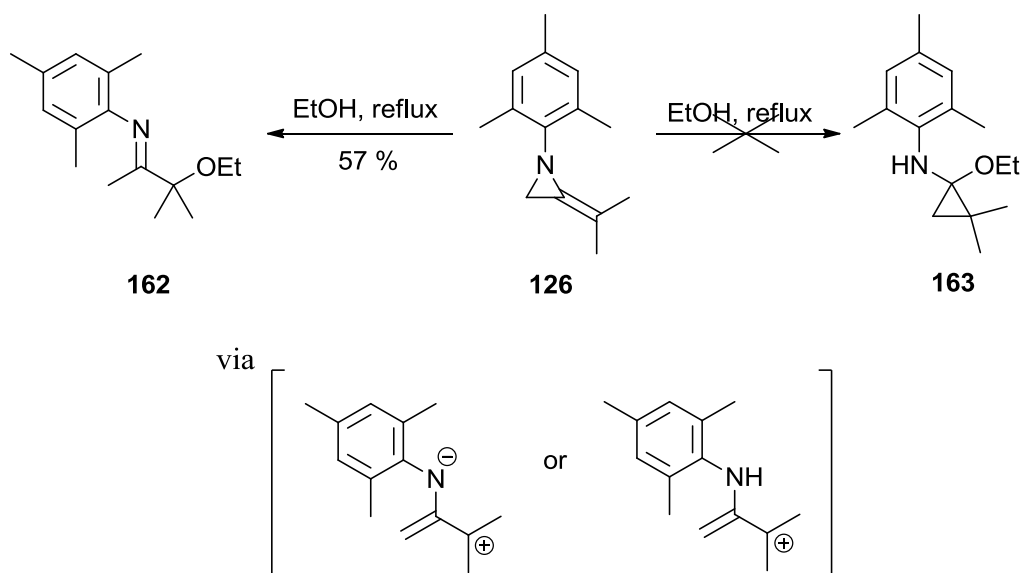


Scheme 2.12.

Attempts to capture the imine with other powerful nucleophiles (pyrrolidine; vinylmagnesium bromide; ethylmagnesium chloride; benzoic acid; diethyl phosphonate; 5 eq.) in THF were unsuccessful.

Interestingly, when methyleneaziridine **126** was heated, in ethanol, at reflux, cyclopropane **163** was not observed.<sup>76</sup> Instead imine **162** was isolated (Scheme 2.13). Similar products have been reported by Steinberg *et al.* during a detailed study into this kind of rearrangement.<sup>98</sup> Imine **162** might arise from attack of ethanol on the zwitterionic intermediate involved in the rearrangement reaction. The additional methyl groups presumably stabilise it to such an extent that it is sufficiently long-lived to be directly captured by ethanol.





Scheme 2.13.

## 2.4. Conclusions

The rearrangement of methyleneaziridine **114** has been carefully studied and the activation parameters ( $\Delta H^\ddagger$ ,  $\Delta S^\ddagger$  and  $\Delta G^\ddagger$ ) deduced for this process. The data shows that methyleneaziridine **114** has a significantly lower enthalpy of activation than alkyl methyleneaziridines studied by Quast *et al.*<sup>80</sup> The ability of methyleneaziridine **114** to better stabilise charge separation in this isomerisation reaction explains these differences.

This rearrangement has practical value in that it can be used to make cyclopropylamines. Reduction with lithium aluminium hydride produces amine **160**, whilst capture with EtOH gives hemiaminal **161**.

Different behaviour is observed using substituted derivatives **126** and **131**. Compound **126** also undergoes a thermal rearrangement however in the presence of ethanol cyclopropane **163** was not observed but the ring opened product **162** was obtained in 57 % yield.<sup>76</sup> We also noted that methyleneaziridine **131** appears to undergo the rearrangement to **131a** at much lower temperatures than those required for methyleneaziridines **114** and **126**. The origins of these differences cannot be fully rationalised at this point in time.

Future work, including molecular modelling of the isomerisation reaction would allow us to more fully understand these subtle differences in behaviour.

# **Chapter 3:**

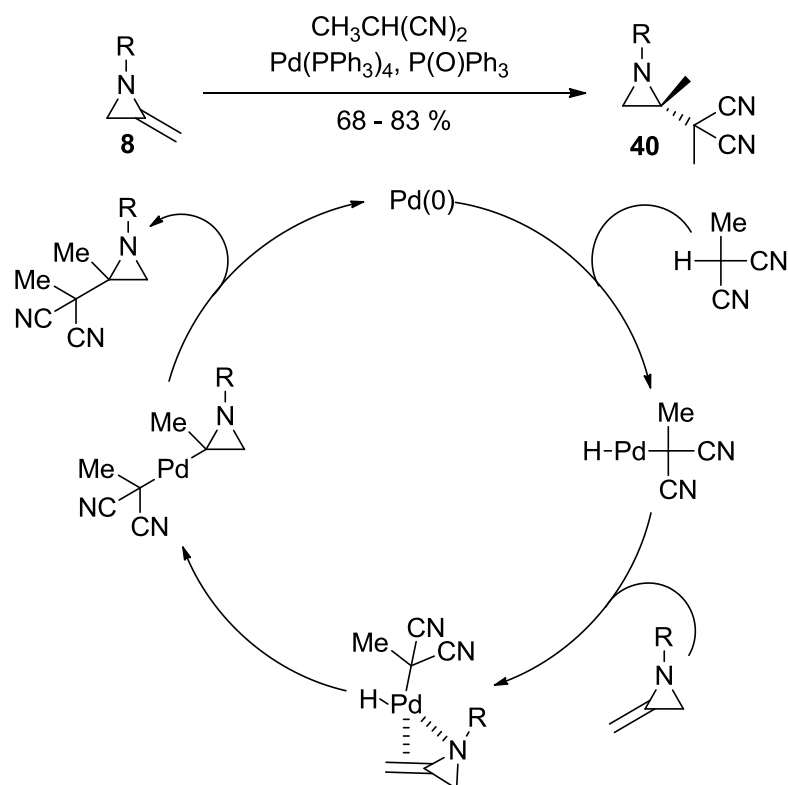
## **Metal Catalysed Reactions of**

### **Methyleneaziridines**

In Chapter 2 we showed that *N*-aryl methyleneaziridines have a higher propensity to rearrange than *N*-alkyl methyleneaziridines. This indicates that they have a greater ability to stabilise zwitterionic intermediates. As proposed in Chapter 1 (Scheme 1.1), this may be beneficial for metal catalysed reactions. In this chapter we show that *N*-mesityl methyleneaziridine **114** can indeed participate in palladium-catalysed reactions. The palladium-catalysed carbonylation of methyleneaziridines as reported by Alper<sup>1</sup> is explored, as is the use of methyleneaziridines in Pauson-Khand reactions.

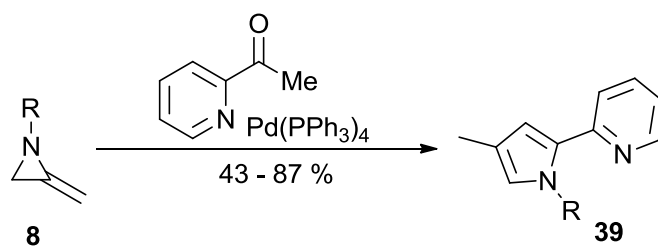
### 3.1. Palladium Catalysed Additions to Methyleneaziridines.

The simplest palladium catalysed reaction of methyleneaziridines involves the addition of carbon pronucleophiles such as methylmalononitrile across the double bond (Scheme 3.1).<sup>36</sup> Nakamura *et al.* showed that regiocontrolled additions to methyleneaziridine **8** can be realised leading to aziridine **40**. The regioselectivity was rationalised by suggesting that there was an interaction between the palladium and the nitrogen prior to the addition step (Scheme 3.1).



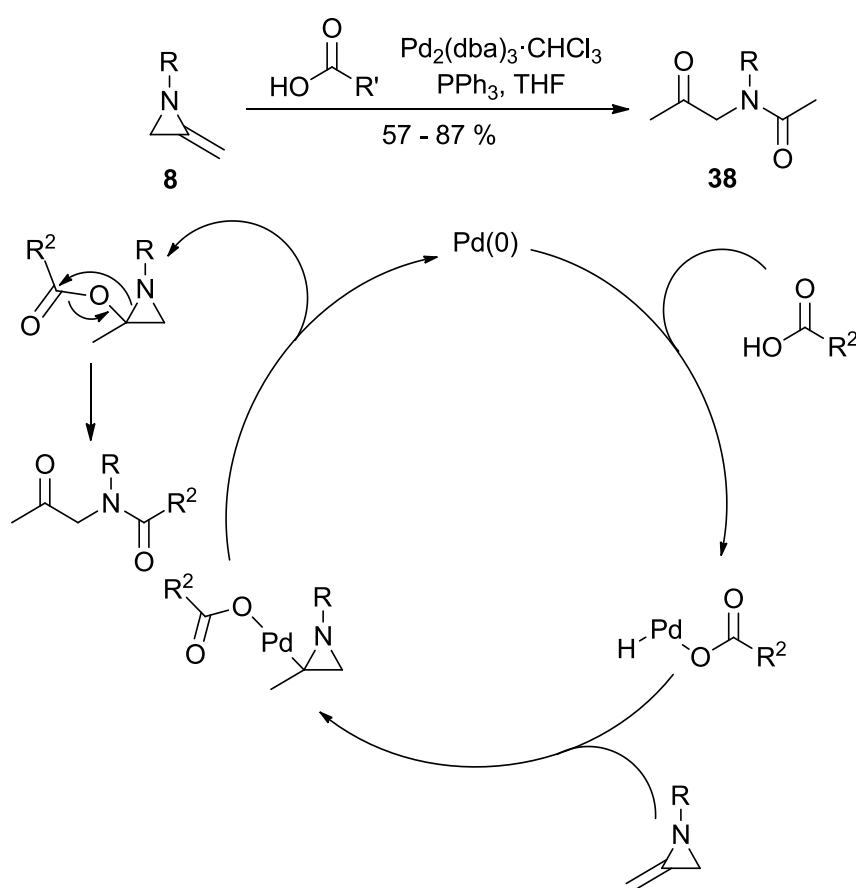
Scheme 3.1.

Siriwardana *et al.* extended this chemistry to the synthesis of pyridinylpyrroles by palladium catalysed reaction of methyleneaziridines with acetylpyridines (Scheme 3.2).<sup>34,35</sup> A similar mechanism was proposed with a rearrangement occurring to form the pyrrole ring **39**.



Scheme 3.2.

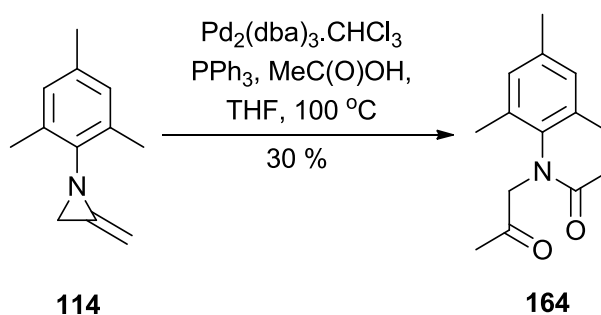
Nakamura *et al.* have also shown that methyleneaziridines will react with carboxylic acids in the presence of palladium to give amido ketones.<sup>37</sup> The mechanism, like the one suggested by Siriwardana *et al.*, involves the insertion of the palladium into the H-O bond of the acid before adding across the double bond of the methyleneaziridine. Again, after reductive elimination, the product undergoes a rearrangement to give amido ketone **38** (Scheme 3.3).



Scheme 3.3.

Initially, we explored the palladium catalysed ring opening reaction of methyleneaziridine **114** with acetic acid as reported by Nakamura.<sup>37</sup> Taking **114** with palladium(0), triphenyl phosphine and acetic acid in THF gave  $\alpha$ -amido-

ketone **164** in approximately 30% yield (Scheme 3.4). Purification was challenging due to suspected degradation of the product or another component of the crude reaction mixture was taking place on the silica gel. This yield is lower than the reported literature examples using  $\text{CH}_2\text{R}$  groups on the nitrogen atom.<sup>37</sup> Several explanations for the lower yield are apparent. Alongside the purification, the proposed mechanism for the reaction suggests an interaction between the nitrogen atom and the palladium (Scheme 3.3). The incorporation of an aromatic ring may have reduced the coordinating ability of the nitrogen atom. Alternatively, steric hindrance caused by the mesityl group may have inhibited the interaction. It is also conceivable that at these elevated temperatures, rearrangement to the cyclopropylamine is competitive.

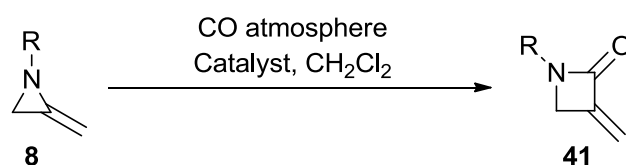


Scheme 3.4.

Nevertheless, encouraged that *N*-mesityl methyleneaziridine **114** could participate in palladium-catalysed processes we decided to explore other palladium catalysed reactions of this substrate.

### 3.2. Carbonylation of Methyleneaziridines

Methyleneaziridines are known to undergo expansion to  $\alpha$ -methylene  $\beta$ -lactams by the palladium-catalysed insertion of carbon monoxide into the N–C bond. Alper *et al.* first reported this method and synthesised a variety of  $\beta$ -lactams from methyleneaziridines (Table 3.1).<sup>1</sup>

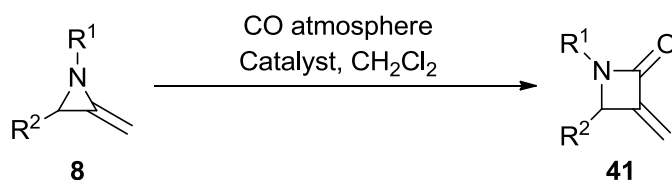


R	t (h)	Catalyst	Yield (%)
<i>n</i> -C <sub>4</sub> H <sub>9</sub>	40	Pd(PPh <sub>3</sub> ) <sub>4</sub>	79
<i>n</i> -C <sub>6</sub> H <sub>16</sub>	21	Pd(OAc) <sub>2</sub> , 4PPh <sub>3</sub>	72
CH <sub>2</sub> CH(OCH <sub>3</sub> ) <sub>2</sub>	21	Pd(OAc) <sub>2</sub> , 4PPh <sub>3</sub>	83

**Table 3.1.**

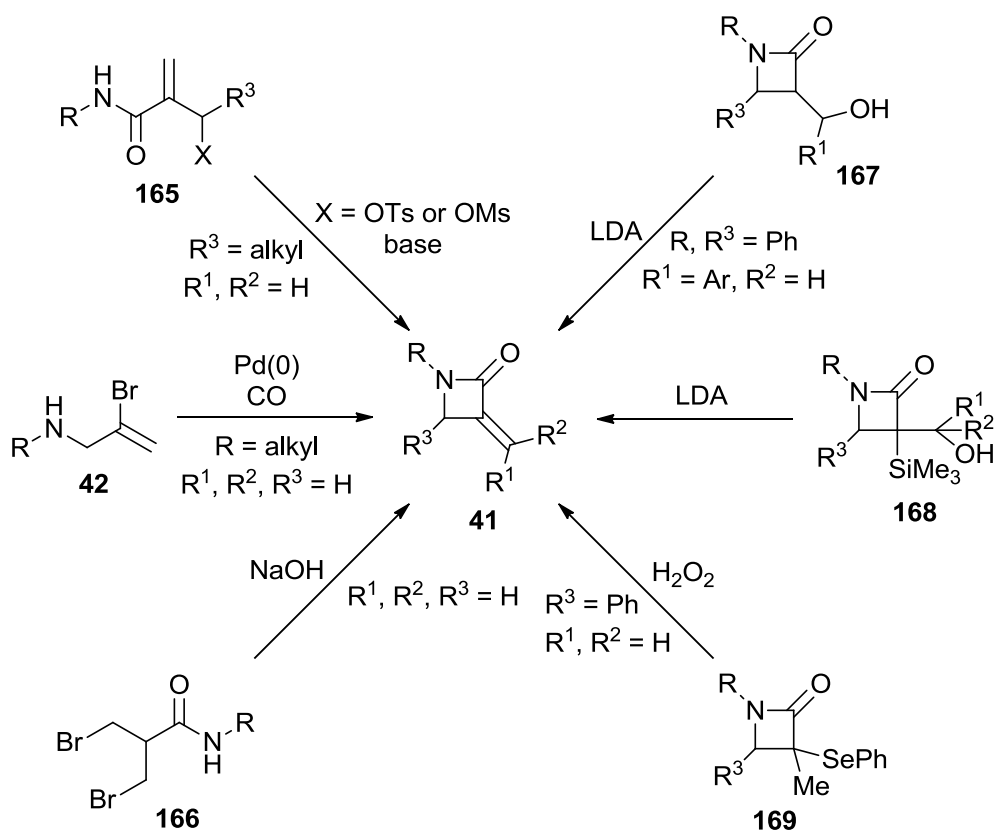
We felt there were opportunities to further extend the scope of this reaction, specifically through use of *N*-aryl methyleneaziridines and derivatives substituted at C-3. The latter chemistry allows for the functionalisation on  $\alpha$ -methylene  $\beta$ -lactams in a position that is relatively difficult to achieve using traditional methods (Scheme 3.5). By including a chiral, non-racemic group such as  $\alpha$ -methylbenzyl on the nitrogen atom ( $R^1 = \text{CHMePh}$ ), it may also be possible to develop a route to chiral, non-racemic  $\alpha$ -methylene  $\beta$ -lactams.





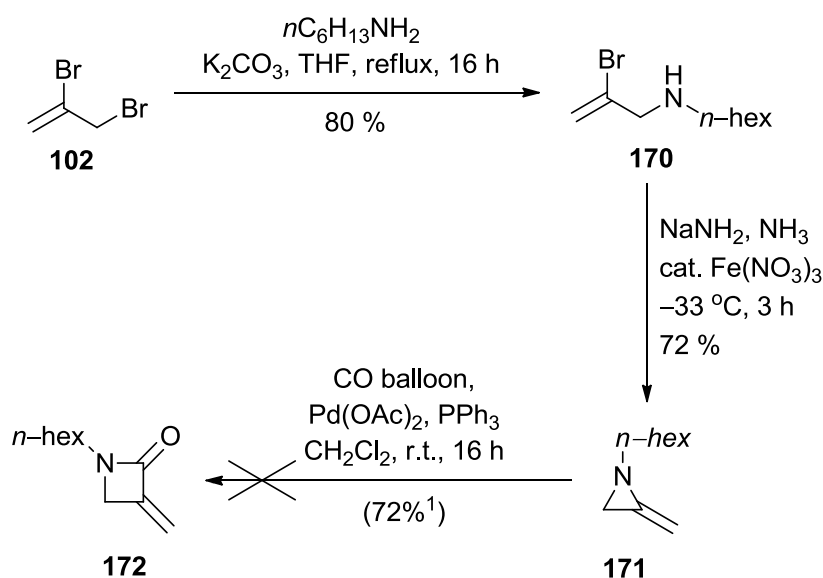
Scheme 3.5.

Existing methods for the synthesis of  $\alpha$ -methylene  $\beta$ -lactams are relatively rare and include (i) the introduction of double bond into preformed  $\beta$ -lactams;<sup>99,100,101</sup> (ii) ring closure of  $\alpha,\beta$ -unsaturated amides,<sup>102,103,104</sup> and (iii) carbonylation of vinyl bromides (Scheme 3.6).<sup>105</sup>



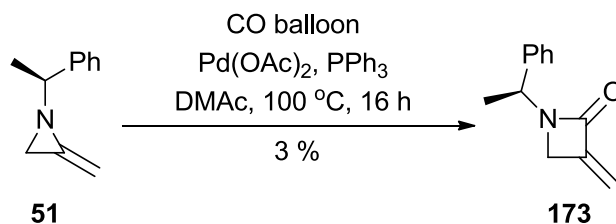
Scheme 3.6.

To familiarise ourselves with this chemistry, we chose to re-examine one of the reactions reported by Alper.<sup>1</sup> The carbonylation of *N*-*n*-hexyl-methyleneaziridine (**171**) was selected, for which a 72% yield had been reported. Methyleneaziridine **171** was synthesised in two steps in 57% yield and then subjected to Alper's reported conditions (Scheme 3.7). Unfortunately, in our hands, no reaction took place.



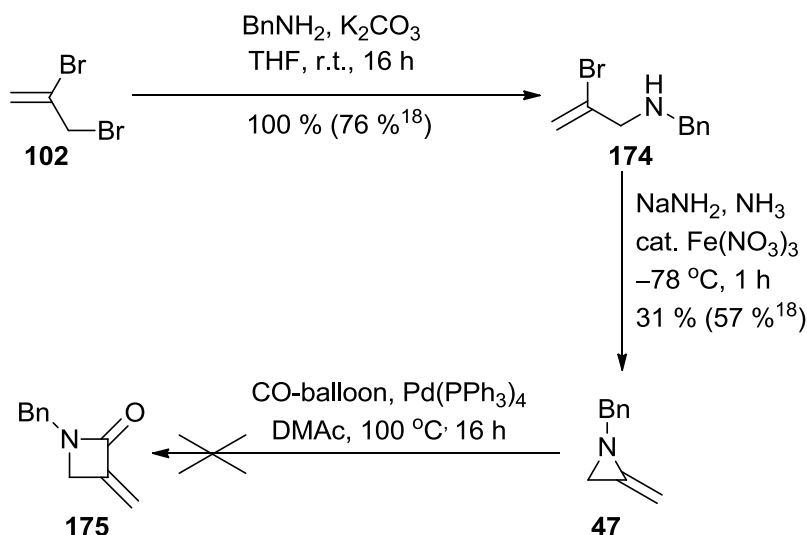
Scheme 3.7.

Samuel Coe in the Shipman group has also experienced difficulty reproducing Alper's work.<sup>106</sup> He examined the carbonylation of methyleneaziridine **51**. The reaction, following Alper's conditions, again only gave starting material; however when the solvent was changed to DMAc and the temperature raised to  $100\text{ }^\circ\text{C}$ , **173** was isolated in 3% yield (Scheme 3.8).



Scheme 3.8.

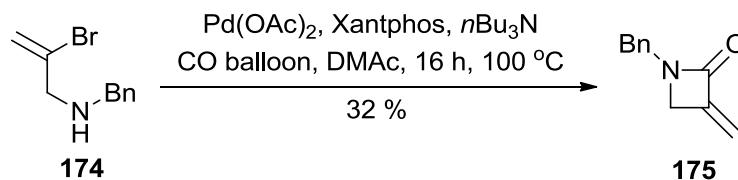
Wondering whether branching in methyleneaziridine **51** could be slowing the carbonylation, we decided to explore the reaction using *N*-benzyl methyleneaziridine. This substrate was not included in the original Alper study. *N*-Benzyl methyleneaziridine (**47**) was synthesised using standard methods (Scheme 3.9).<sup>18</sup> Using  $\text{Pd}(\text{PPh}_3)_4$  as catalyst, initial attempts to carbonylate methyleneaziridine **47** under Alper's conditions met with failure (Scheme 3.9).



Scheme 3.9.

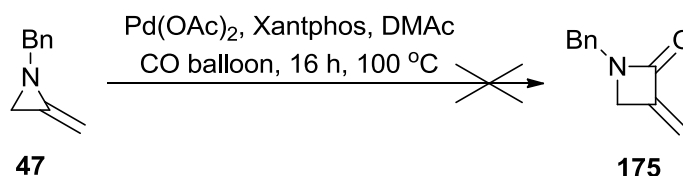
To make identifying the products easier, we synthesised an authentic sample of  $\beta$ -lactam **175**. Taking bromide **174** and using conditions developed within the

Shipman group<sup>106</sup>  $\alpha$ -methylene  $\beta$ -lactam **175** was successfully synthesised in an unoptimised 32% yield (Scheme 3.10).



Scheme 3.10.

When methyleneaziridine **47** was also subjected to these conditions (Scheme 3.11), no product was observed.



Scheme 3.11.

Carbonylations of epoxides<sup>107</sup> and aziridines<sup>108,109</sup> frequently use high pressures of CO (up to 62 bar). Consequently, we decided to examine if higher pressures might lead to improvements. By employing an autoclave, we were able to increase the pressure to 4–5 bar.

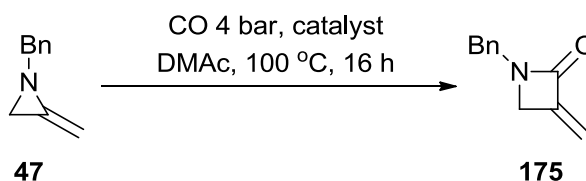
### 3.2.1. Pressurised Carbonylations of Methyleneaziridines

The autoclave allowed for multiple reactions to be carried out concurrently; however they all had to be run at the same temperature and for the same length of

time. It also meant that the reactions had to be run on a very small scale (~60 mg).

The crude reactions were analysed by  $^1\text{H}$  NMR spectroscopy.

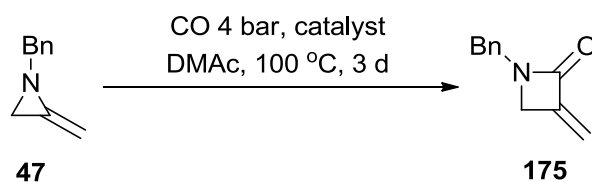
Entry 1 (Table 3.2) confirmed that increasing the pressure of the CO did have a positive effect on the reaction however the amount of **175** produced was very modest (4%) at best.



Entry	Catalyst	Ligand	47 : 175 (%)
1	$\text{Pd}(\text{PPh}_3)_4$	—	94 : 4 <sup>a</sup>
2	$\text{Pd}_2(\text{dba})_3$	$\text{PPh}_3$ (2 equiv per Pd)	76 : 0 <sup>a</sup>
3	$\text{Pd}_2(\text{dba})_3$	$\text{PPh}_3$ (4 equiv per Pd)	65 : 4 <sup>a</sup>
4	$\text{Pd}(\text{OAc})_2$	Xantphos	100 : 0
5	$\text{Pd}(\text{OAc})_2$	Xphos	100 : 0

**Table 3.2.** <sup>a</sup>1,3,5-Trimethoxybenzene standard used to calculate ratio, the remaining % was unaccounted for.

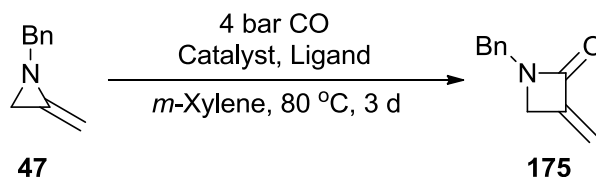
Next, we increased the duration of the reaction (Table 3.3, Entries 3-6). This improved the extent of conversion (Table 3.3, Entries 3 and 5), however, lowering the temperature reduced the extent of conversion (Table 3.3, Entry 4).  $\text{Pd}(\text{PPh}_3)_4$  was the best of the palladium catalysts investigated.



Entry	Catalyst	Ligand	T (°C)	t	47 : 175 (%) <sup>a</sup>
1	Pd(OAc) <sub>2</sub>	Xantphos	100	16 h	S.M
2	Pd(PPh <sub>3</sub> ) <sub>4</sub>	n/a	100	16 h	94:4
3	Pd(PPh <sub>3</sub> ) <sub>4</sub>	n/a	100	3 d	27:12
4	Pd(PPh <sub>3</sub> ) <sub>4</sub>	n/a	80	3 d	66:1
5	Pd <sub>2</sub> (dba) <sub>3</sub>	PPh <sub>3</sub>	100	3 d	39:8
6	Pd(P <sup>t</sup> Bu) <sub>3</sub> ) <sub>2</sub>	n/a	100	3 d	48:1

**Table 3.3.** <sup>a</sup>1,3,5-Trimethoxybenzene standard used to calculate ratio, the remaining % was unaccounted for.

Since Rh,<sup>110,111</sup> and Co<sup>109,112,107</sup> catalysts have been used in CO insertion reactions of strained heterocycles, and Ir catalysts have been shown to catalyse cycloadditions and carbonylations,<sup>113,114</sup> we decided to explore if they might prove more effective. Changing the solvent to *m*-xylene and lowering the temperature to 80 °C did not improve the conversion (Table 3.4, Entry 1). Using a range of other metal catalysts offered no improvement and indeed no product was detected in any case (Table 3.4, Entries 2-6) with [Rh(COD)Cl]<sub>2</sub> causing degradation (Table 3.4, Entry 2).



Entry	Catalyst	Ligand	47 : 172 (%) <sup>a</sup>
1	Pd(PPh <sub>3</sub> ) <sub>4</sub>	n/a	42:3
2	[Rh(COD)Cl] <sub>2</sub>	n/a	Degradation
3	[Rh(COD)Cl] <sub>2</sub>	dppp	54:0
4	[Ir(COD)Cl] <sub>2</sub>	n/a	20:0
5	[Ir(COD)Cl] <sub>2</sub>	dppp	90:0
6	[Co(CO) <sub>8</sub> ] <sub>2</sub>	n/a	S.M.

**Table 3.4.** <sup>a</sup>1,3,5-Trimethoxybenzene standard used to calculate ratio, the remaining % was unaccounted for.

As palladium appeared to be the only catalyst suitable for this reaction, we screened a variety of other ligands; monodentate Xphos **176**, bidentate Xantphos **177**, dppp **178** and dppe **179**, dppf **180** and CataCXium<sup>®</sup> A (**181**)<sup>115,116,117</sup> (Figure 3.1). The reactions were run with Pd<sub>2</sub>(dba)<sub>3</sub> in DMAc (4 bar CO, 100 °C, 3 d). Unfortunately, none of these commercially available ligands gave any conversion.

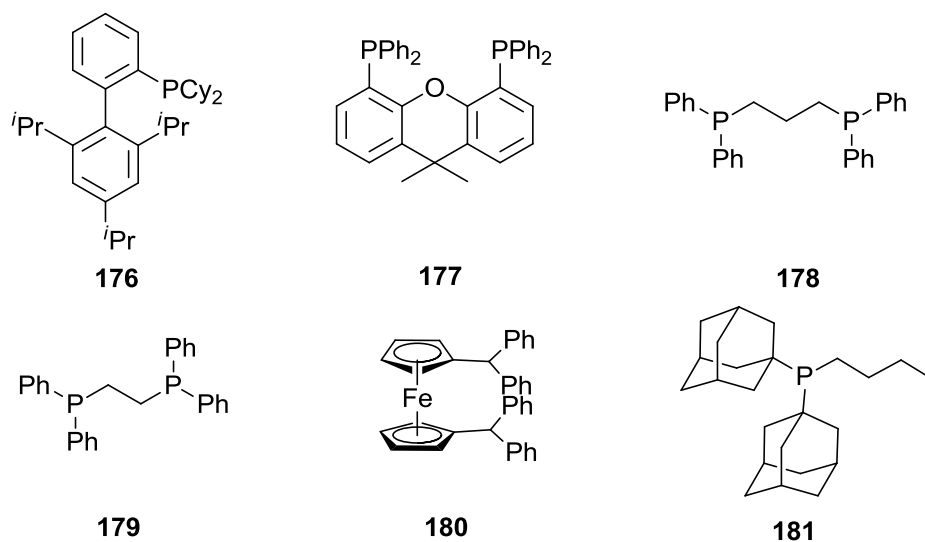
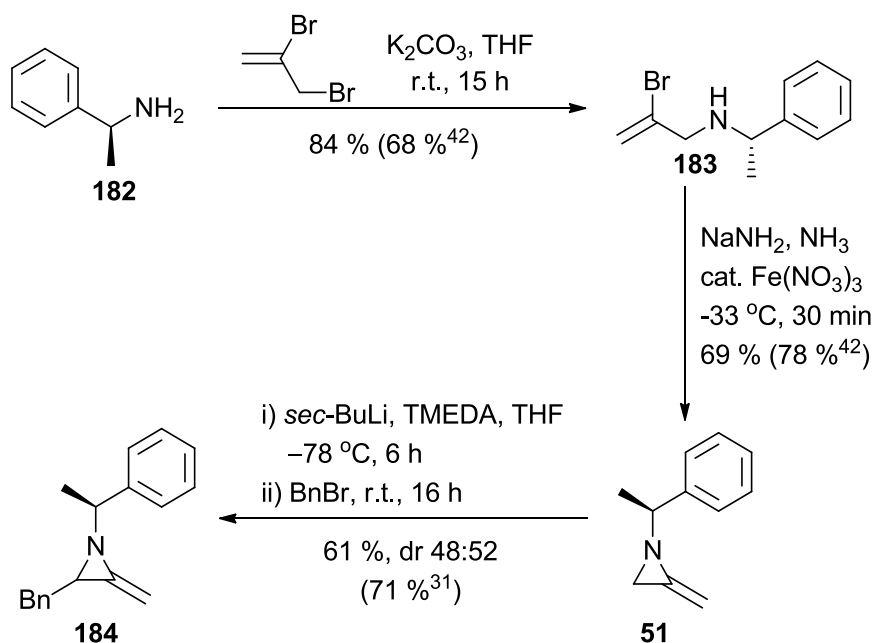


Figure 3.1.

A possible cause of the very low yields could be debenzylation of methyleneaziridine **47** or lactam **175**. By changing the group to a less labile one, for example *N*- $\alpha$ -methylbenzyl **51** or cyclohexyl **48** it was thought the yield may be increased. We also wanted to explore if the reaction might proceed with a C-3 substituent. The required compounds, **48**, **51** and **184** were synthesised following the literature procedures (Scheme 3.12, Scheme 1.53).<sup>44</sup>

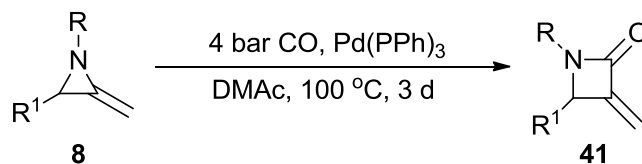




Scheme 3.12.

Taking the best conditions for the ring expansion ( $\text{Pd(PPh}_3)_4$ , DMAc,  $100\text{ }^\circ\text{C}$ , 3 d) the three methyleneaziridines were subjected to carbonylation (Table 3.5). Although some product was observed with methyleneaziridine **51** (Table 3.5, Entry 1), it was not an improvement on the result obtained with **47** (Table 3.3). Disappointingly, the carbonylation of alkylated methyleneaziridine **184** led to degradation.

Finally, we looked at the carbonylation of methyleneaziridine **114**. The reaction was run under the most favourable conditions (Table 3.5, Entry 4) however this led only to degradation. By reducing the temperature to room temperature only methyleneaziridine **114** was seen after 3 days.



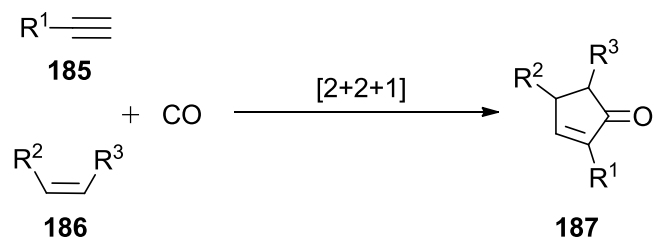
Entry	R	R <sup>1</sup>	8 : 41 (%) <sup>a</sup>
1	$\alpha$ -Methyl benzyl	H	38 : 4
2	<i>c</i> -Hexyl	H	60 : 0
3	$\alpha$ -Methyl benzyl	Bn	Degradation
4	Mesityl	H	Degradation
5 <sup>b</sup>	Mesityl	H	100 : 0

**Table 3.5.** <sup>a</sup>1,3,5-Trimethoxybenzene standard used to calculate ratio, the remaining % was unaccounted for. <sup>b</sup> reaction ran at room temperature.

One possible way of solving these problems and making the reaction more successful would be the use of even higher pressures of carbon monoxide. Unfortunately, this is currently not possible within our research group at Warwick. As to why Alper was able to achieve the reaction using just a balloon of CO remains unclear to us at this point in time.

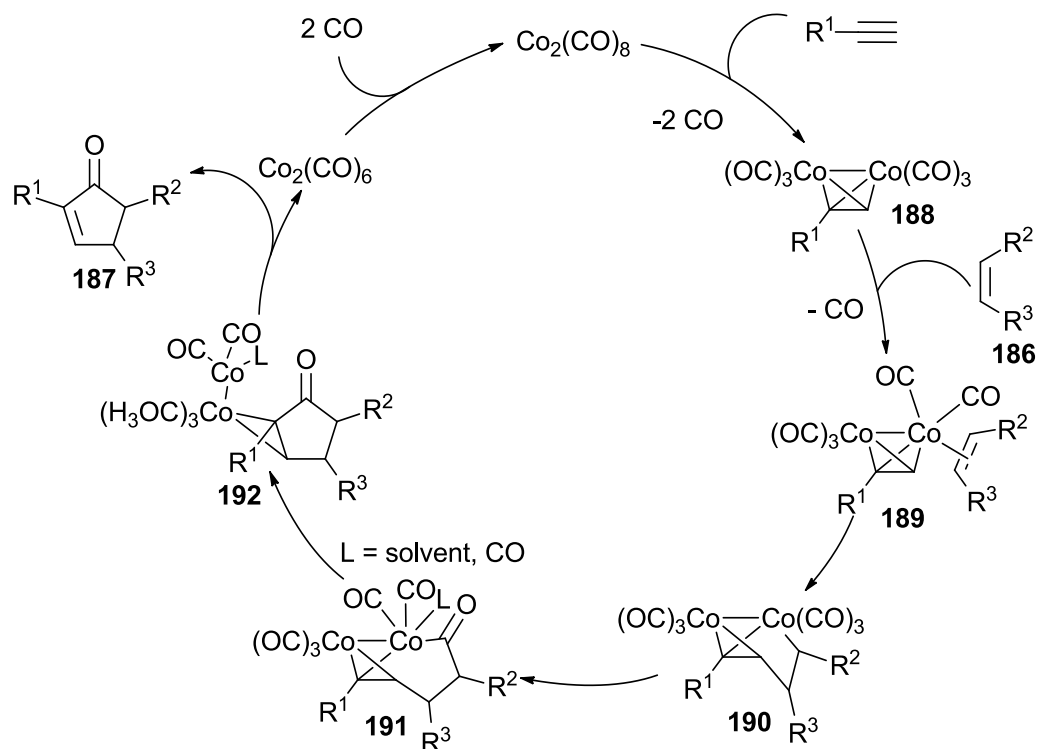
### 3.3. The Pauson-Khand Reaction

The Pauson-Khand reaction is an important tool in synthetic organic chemistry, including natural product synthesis. First discovered in 1973, the reaction involves a formal [2+2+1] cycloaddition of an alkene **186**, alkyne **185** and carbon monoxide (Scheme 3.13).<sup>118</sup> In 1981, Schore *et al.* developed the first intramolecular Pauson-Khand reaction whereby R<sup>1</sup> and R<sup>2</sup> were tethered together.<sup>119</sup>



Scheme 3.13.

The mechanism for the Pauson-Khand reaction was first proposed by Magnus and Principe in 1985.<sup>120</sup> More recent negative-ion electrospray experiments provide support for this mechanism which is now widely accepted (Scheme 3.14).<sup>121</sup> The reaction is initiated by addition of cobalt across the alkyne to form complex **188**. Olefin **186** coordinates and then inserts at the least hindered end of the alkyne to give complex **190**. This then undergoes rapid CO insertion followed by reductive elimination to afford the cyclopentenone **187**. The catalytic cycle is completed by the oxidation of the 16 electron species  $\text{Co}_2(\text{CO})_6$  to the 18 electron species  $\text{Co}_2(\text{CO})_8$  by the addition of two carbon monoxide molecules. Interestingly all the bond-forming processes occur on one cobalt atom. The second cobalt atom is presumed to be acting as an anchor, and supports the observed reactions through the metal-metal bond.



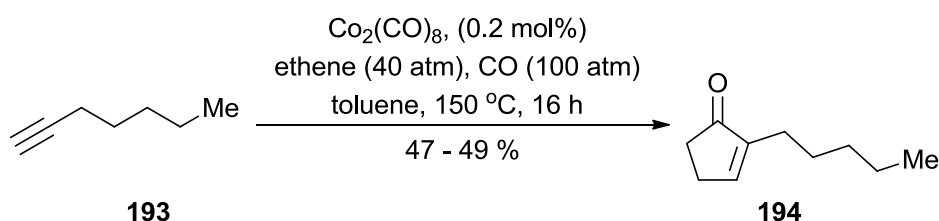
Scheme 3.14.

A number of other metal complexes have been shown to facilitate the Pauson-Khand reaction; these include iron pentacarbonyl,<sup>122,123</sup> molybdenum hexacarbonyl,<sup>124</sup> zirconium<sup>125</sup> and tungsten pentacarbonyl.<sup>126</sup> However, due to its ability to tolerate a broad range of functional groups, activity towards both terminal and internal alkynes and its relatively low cost,  $\text{Co}_2(\text{CO})_8$  is still often the catalyst of choice for these reactions.<sup>127</sup>

By the addition of *N*-methymorpholine *N*-oxide<sup>128</sup> or trimethylamine *N*-oxide,<sup>129</sup> formation of cyclopentenones can be achieved in good yields at temperatures as low as room temperature. The addition of *N*-oxides accelerates the rate-determining step, the oxidative addition of the alkene, by assisting the liberation of the CO ligand. Other reagents that have also been shown to help accelerate the

reaction include molecular sieves,<sup>130</sup> alkyl methyl sulphides,<sup>131</sup> and silica gel,<sup>132</sup> but they appear less versatile than *N*-oxides.

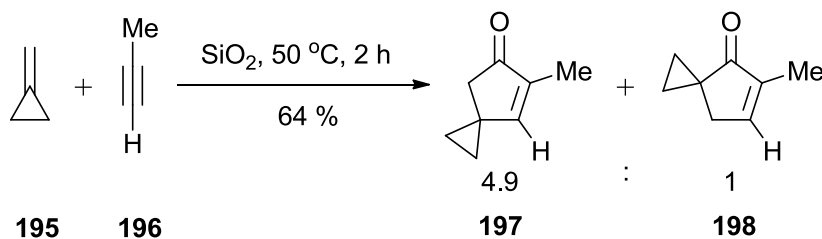
The first catalytic Pauson-Khand reaction was reported by Rautenstrauch *et al.* in 1990 (Scheme 3.15).<sup>133</sup> They employed 0.2 mol%  $\text{Co}_2(\text{CO})_8$  to successfully synthesise cyclopentenone **194**. To operate with such low metal loadings harsh reaction conditions were required; 100 atm carbon monoxide at 150 °C. More recently, Jeong *et al.* reported milder catalytic conditions through application of triphenylphosphite ligands.<sup>134</sup>



Scheme 3.15.

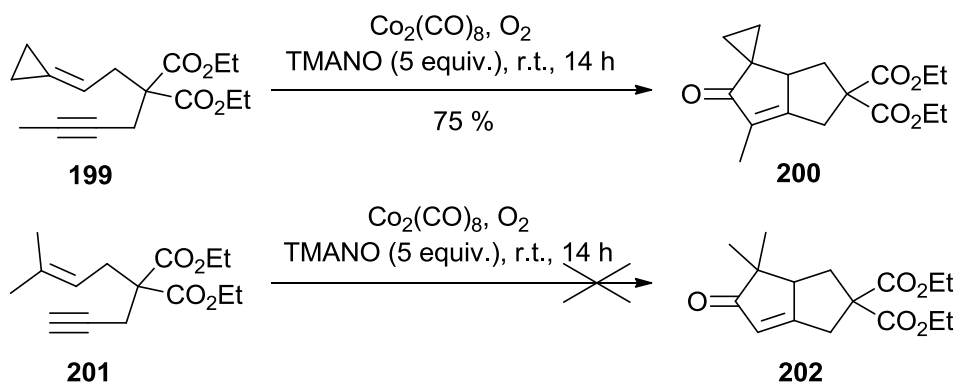
### 3.3.1. Pauson-Khand Reaction of 3-Membered Ring Containing Substrates

As the original conditions for the Pauson-Khand reaction required the use of a strained alkene component it is unsurprising that methylenecyclopropane has been investigated for its use in this type of reaction. The first example was reported by Tarasov *et al.* in 1989.<sup>135</sup> They were surprised to discover that the reaction did not proceed very well under standard conditions (10-15% yields) however when **195** was absorbed onto  $\text{SiO}_2$  and heated to 50 °C for 2 hours, the reaction proceeded in an improved 64% yield (Scheme 3.16).



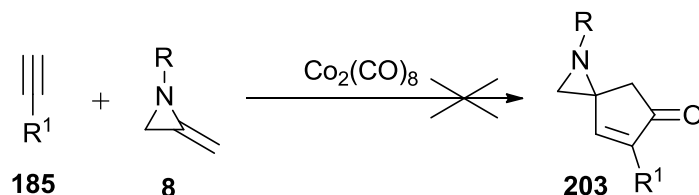
Scheme 3.16.

The intramolecular Pauson-Khand reaction of methylenecyclopropanes is also known.<sup>136</sup> Methylene cyclopropane **199** was successfully cyclised using trimethylamine *N*-oxide (TMANO),  $\text{Co}_2(\text{CO})_8$  and  $\text{O}_2$  to give **200** in 75% yield (Scheme 3.27). Interestingly, when the cyclopropane was replaced with *gem*-dimethyl groups, no product was observed (Scheme 3.17).



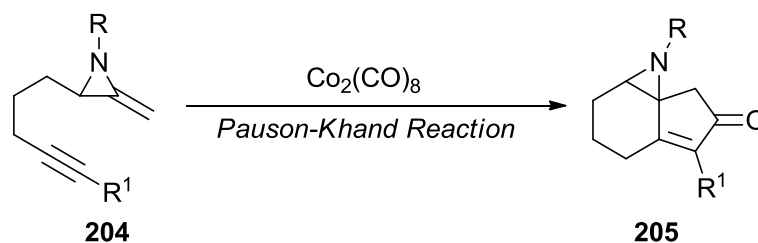
Scheme 3.17.

With these examples it seemed reasonable to expect methyleneaziridines might participate in Pauson-Khand type reactions. Previous work within the Shipman group has looked at the suitability of methyleneaziridines for intermolecular Pauson-Khand cyclisations, but these studies had not proven fruitful (Scheme 3.18).<sup>137</sup>



Scheme 3.18.

No attempt, however, had been made to look at intramolecular reactions of methyleneaziridines where the alkyne was tethered through the C-3 position (Scheme 3.19). The starting materials were expected to be readily accessible,<sup>33,138</sup> and so this process appeared to merit investigation.



Scheme 3.19.

### 3.3.1.1. Synthesis of Alkyne Tethered-Methyleneaziridines.

As alkyne tethered methyleneaziridines have been previously synthesised, we anticipated that the formation of the Pauson-Khand precursors would be relatively straightforward. The simplest of the methyleneaziridines that would be suitable for a Pauson-Khand cyclisation was terminal alkyne **206** (Figure 3.2). This is not previously known but we anticipated that it could be made either by direct alkylation with an appropriate terminal alkyne electrophile or by the desilylation

of **207** (Figure 3.2). A third target was the phenyl substituted alkyne **208**, a substrate made previously for [3+2] cycloaddition reactions.<sup>33</sup>

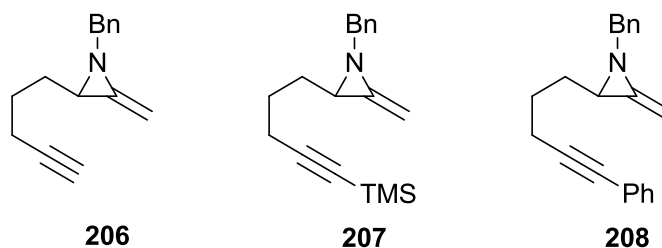
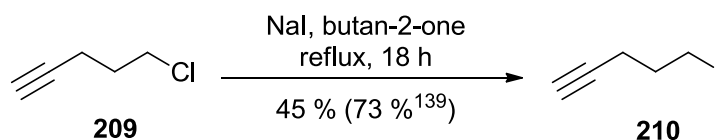


Figure 3.2.

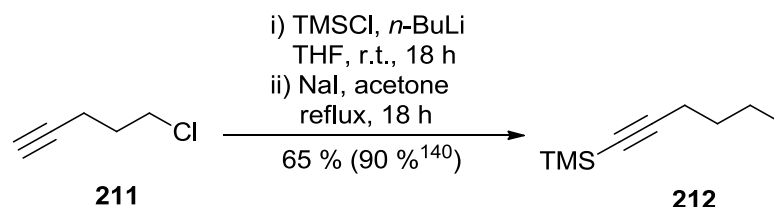
Alkyne **210** was made by Finkelstein reaction of commercially available chloride **209** in 45% yield (Scheme 3.20).<sup>139</sup> With sufficient quantities of **210** in hand, no attempts were made to improve this yield.



Scheme 3.20.

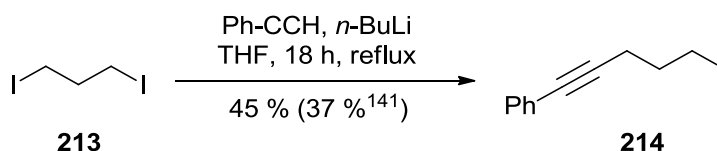
Alkyne **212** was made from 5-chloropent-1-yne (**211**) by first reacting it with TMS-Cl in the presence of *n*-butyllithium. The product was then subjected to the Finkelstein conditions to give **212** in 65% yield (Scheme 3.21).<sup>140</sup>





Scheme 3.21.

Finally **214** was synthesised by reacting phenyl acetylene with 1,3-diiodo propane (**213**), which proceeded in 45% yield (Scheme 3.22).<sup>141</sup> Although all the products were clean by TLC analysis, each product was purified by column chromatography to ensure removal of any trace of HI which would hamper the subsequent alkylation reactions.



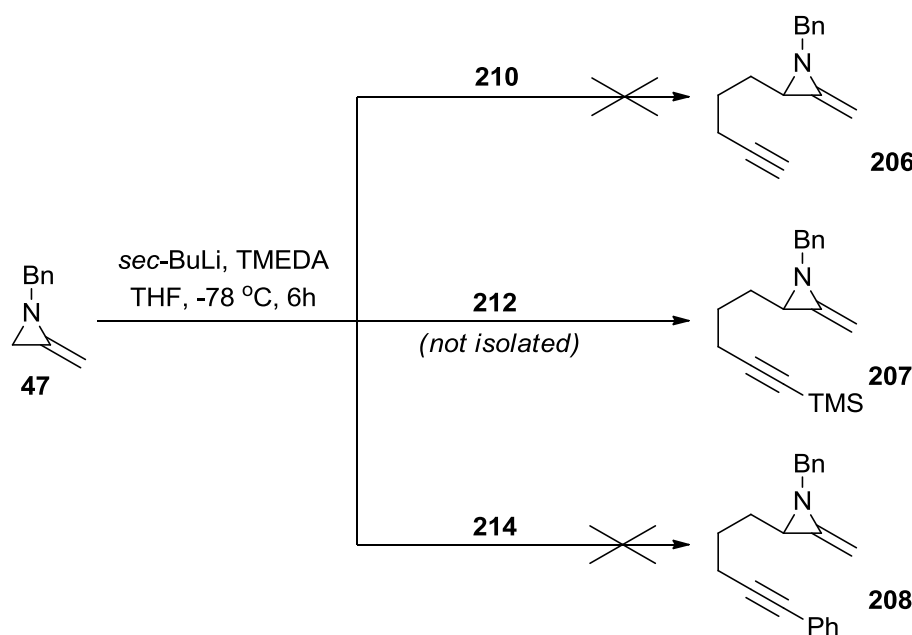
Scheme 3.22.

The lithiation reactions were carried out under the standard conditions; *sec*-butyllithium, TMEDA,  $-78\text{ }^{\circ}\text{C}$ , 6 h whereupon the lithiated aziridines were quenched with the appropriate electrophile and allowed to warm to room temperature overnight (Scheme 3.23).<sup>31,142</sup>

Unsubstituted methyleneaziridines are generally not stable to column chromatography.<sup>15</sup> Hence, they are typically purified by distillation. The high molecular weights of methyleneaziridnes **206–208** makes distillation impractical. By using an excess of methyleneaziridine **47**, we planned to remove unreacted **47**

by distillation and leave the tethered methyleneaziridine in a good state of purity. Therefore all the reactions were run with an excess of methyleneaziridine **47**.

Using alkyne **210**, no trace of methyleneaziridine **206** was observed (Scheme 3.23). Presumably, deprotonation of the alkyne by the aziridine anion was competing with the required iodine displacement.



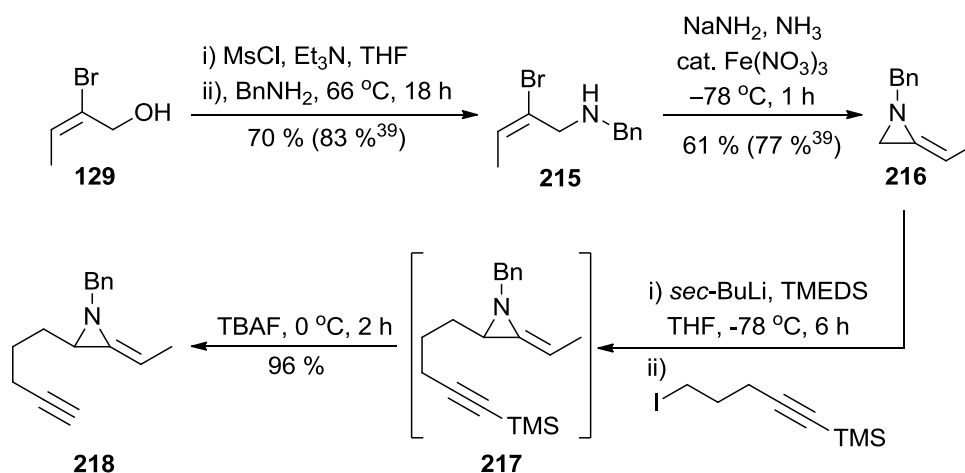
Scheme 3.23.

The reaction to form phenyl alkyne **208** was unsuccessful. Although it had been synthesised successfully within the Shipman group previously (in 35% yield),<sup>33</sup> I was unable to reliably reproduce this reaction. On one occasion the product was visible in the crude <sup>1</sup>H NMR spectrum however the reaction had not run cleanly and the product was a minor component which could not be isolated.

The synthesis of tethered methyleneaziridine **207** was also not very successful. Lithiation of methyleneaziridine **47** followed by quenching with alkyne **212** gave low yields of methyleneaziridine **207**. It was a capricious reaction and gave varied results (Scheme 3.23). Again it was not possible to isolate the product.

As purification was going to be necessary, we decided to synthesise related substrate **218**. Substitution on the olefin was expected to make the product stable to column chromatography.<sup>39</sup> Methyleneaziridine (Z)-**218** was chosen as we expected it might cause less steric hindrance in the Pauson-Khand cyclisation.

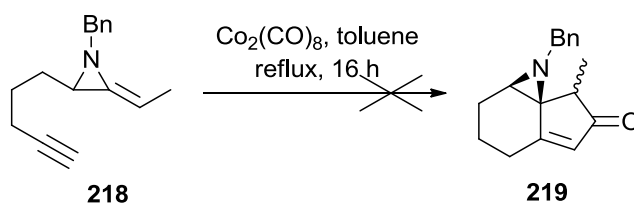
Using the same procedure, methyleneaziridine (Z)-**216** was lithiated and quenched with alkyne **212** to give **217** (Scheme 3.24). Gratifyingly, the removal of the TMS group from the crude product using TBAF provided **218** in 96% yield over two steps after column chromatography (Scheme 3.24).



Scheme 3.24.

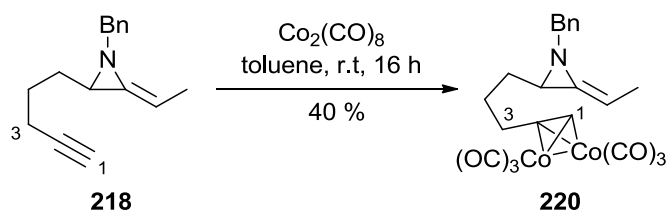
### 3.3.1.2. Attempted Pauson-Khand Reaction of Alkyne Tethered-Methyleneaziridine **218**

With quantities of methyleneaziridine **218** in hand, it was possible to investigate conditions for the Pauson-Khand cyclisation. Using stoichiometric amounts of  $\text{Co}_2(\text{CO})_8$  in refluxing toluene, no cyclopentenone products were observed (Scheme 3.25). The reaction was messy and no starting material was recovered.



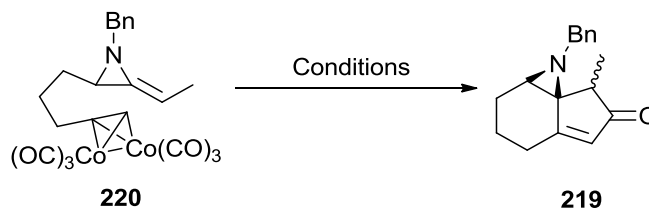
Scheme 3.25.

Next, we attempted to pre-form the cobalt/alkyne complex. By mixing methyleneaziridine **218** with  $\text{Co}_2(\text{CO})_8$  in toluene at room temperature for 16 h, a red oil was isolated after column chromatography (Scheme 3.26). This was confirmed to be complex **220**. The  $^1\text{H}$  NMR spectra showed the alkyne hydrogen (C1) at 1.9 ppm had disappeared and a signal at 5.95 ppm had appeared. The signals assigned to H-3 were also affected, shifting from 2.09 ppm to 2.78 ppm. The IR spectra also provided evidence for the loss of the alkyne and the gain of CO with the absence of the absorption at  $3297\text{ cm}^{-1}$  and the appearance of a strong absorption at  $2090\text{ cm}^{-1}$  and a very strong absorption at  $1993\text{ cm}^{-1}$ . This constitutes the first methyleneaziridine containing cobalt/alkyne complex.



Scheme 3.26.

The successful formation of complex **220** was a positive step forward. The next step, the insertion of the alkene, is often rate limiting. A variety of conditions were used to try and encourage the cyclisation (Table 3.6). Unfortunately, the addition of carbon monoxide or NMO at a variety of temperatures did not promote the cyclisation (Table 3.6).



Entry	Solvent	Additive	T (°C)	t (h)	Result
1	Toluene	–	40	96	No reaction
2	Toluene	CO	25	16	No reaction
3	Toluene	NMO	–10	16	No reaction
4	Toluene	NMO	25	16	No reaction
5	Benzene	NMO	reflux	1	Decomplexation <sup>a</sup>
6	Toluene	NMO/4Å ms	–10	18	No reaction

**Table 3.6.** <sup>a</sup> an insoluble brown solid was separated from the reaction solution which contained **218** (by <sup>1</sup>H NMR analysis)

At this juncture, further efforts to effect the cyclisation were abandoned.

### 3.4. Conclusions

Preliminary investigations into palladium catalysed reactions of methyleneaziridine **114** have shown that it can be converted into amide **164** in 30 % yield (Scheme 3.4). The propensity of methyleneaziridine **114** to thermally rearrange to cyclopropane imine **145** may make it difficult to employ it more generally in transition metal-catalysed reactions that involve heating.

We have confirmed that  $\alpha$ -methylene  $\beta$ -lactams can be synthesised from methyleneaziridines using 4 bar CO, Pd(PPh<sub>3</sub>)<sub>4</sub>, DMAc at 100 °C for 3 d. Although we were unable to reproduce Alper's results, we have shown that the use of an increased pressure of CO has a positive effect on the reaction. Further increases in CO pressure may lead to greater success.

Investigations into the use of methyleneaziridines in intramolecular Pauson-Khand reactions met with only limited success. Alkyne tethered methyleneaziridine **218** was successfully produced and converted into the corresponding cobalt complex **220**. However, we were unable to trigger cyclisation to the corresponding cyclopentanone under a variety of conditions. It is conceivable that the basic nitrogen in the labile aziridine ring makes the substrate/product too sensitive to achieve control in the process. However, further studies may be merited using alternative catalysts/conditions.<sup>122,123, 124,125,126</sup>

# **Chapter 4:**

# **Experimental**

#### 4.1. General Remarks

Anhydrous solvents were purchased in Sure/Seal<sup>TM</sup> 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<sub>2</sub>) 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<sub>254</sub>) and developed using UV fluorescence (254 nm) and/or an appropriate developing agent, 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.

<sup>1</sup>H and <sup>13</sup>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 <sup>1</sup>H and <sup>13</sup>C spectra are reported as singlets (s), doublets (d), triplets (t), quartets (q) etc, which refer to the observed spin-spin coupling patterns. Chemical shifts (δ) are quoted in parts per million (ppm)



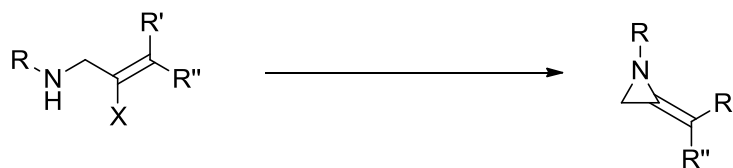
relative to TMS ( $\delta = 0$  ppm), with the residual solvent as the internal standard. Coupling constants ( $J$ ) are reported in Hertz. Ambiguous signals were assigned using COSY, HMQC, HMBC and NOE correlation spectroscopy.

Low resolution mass spectra were recorded on an Esquire 200 platform with electrospray ionisation. High resolution spectra were obtained using a Bruker MicroTOF instrument.

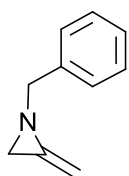
GC–MS spectra were recorded on a Varian 4000 GC–MS spectrometer using a Factorfour Capillary Column VF-5MS 30MX0.25mm, ID DF = 0.25 with helium as the delivery gas.

## 4.2. Preparations

### General Method 1: Synthesis of Methyleneaziridines

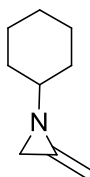


A multi-necked flask was fitted with a cold-finger condenser and a gas inlet. Iron (III) nitrate nonahydrate (0.2-0.5 mol%) was added and the system flushed with anhydrous ammonia. A dry ice/acetone mixture was added to the condenser and ammonia condensed into the flask. The addition of freshly cut sodium (2.0 – 2.5 M equiv.) initially resulted in a deep blue colouration, which over time, faded to afford a grey suspension of sodium amide. The mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  or maintained at  $-33\text{ }^{\circ}\text{C}$ , whereupon a solution of allylamine (1.0 M equiv) in  $\text{Et}_2\text{O}$  (1:1 w/v) was added slowly. After 10 - 180 minutes, the mixture was diluted with  $\text{Et}_2\text{O}$  and quenched by the cautious addition of  $\text{H}_2\text{O}$ . After the ammonia had been allowed to evaporate, the mixture was partitioned between  $\text{Et}_2\text{O}$ , and 10 % NaOH solution. The phases were separated and the organic phase washed with either 1. 0.1 M acetic acid followed by 10 % NaOH solution and brine or 2. 10 % NaOH solution and brine. The organic phase was dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give the crude product. Where possible, purification by column chromatography or bulb-to-bulb distillation afforded the title compound.

**1-Benzyl-2-methyleneaziridine **47****<sup>18</sup>

Following General Method 1, iron(III) nitrate nonahydrate, sodium (840 mg, 36.44 mmol) and *N*-benzyl-2-bromoprop-2-en-1-amine **174** (3.30 g, 14.57 mmol) were reacted in ammonia (100 mL) at -78 °C for 2.5 h. Following work-up 1, purification by bulb-to-bulb distillation (50 °C, 1 mbar) afforded 1-benzyl-2-methyleneaziridine **47** (654 mg, 31 %) as a colourless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.10 – 7.28 (5H, m, 5 x CH, Ph), 4.60 (2H, s, =CH<sub>2</sub>), 3.56 (2H, s, CH<sub>2</sub>), 2.00 (2H, s, CH<sub>2</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 138.3 (C, Ph), 137.0 (C=CH<sub>2</sub>), 128.5 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.4 (CH, Ph), 83.7 (=CH<sub>2</sub>), 62.8 (CH<sub>2</sub>), 30.7 (CH<sub>2</sub>) ppm; MS (ES<sup>+</sup>) *m/z* 146 [MH<sup>+</sup>]. Data is in accordance with literature values.<sup>18</sup>

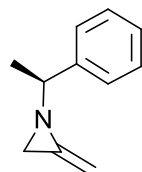
**1-Cyclohexyl-2-methyleneaziridine **48****<sup>40</sup>

Following General Method 1, iron(III) nitrate nonahydrate), sodium (1.80 g, 80.25 mmol) and *N*-(2-bromoprop-2-en-1-yl)cyclohexanamine **137** (7.00 g, 32.10 mmol) were reacted in ammonia (150 mL) at -33 °C for 4 h. After work-up, purification by column chromatography (1 % Et<sub>3</sub>N and 10 % EtOAc in petroleum ether) afforded 1-cyclohexyl-2-methyleneaziridine **48** (1.94 g, 44%) as a colourless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 4.69 (1H, br d, =CHH), 4.58 (1H, br d, CHH) 1.96 (2H, s, CH<sub>2</sub>), 1.91 – 1.07 (11H, m, CH, 5 x CH<sub>2</sub>, Cy) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 136.7 (C=CH<sub>2</sub>), 82.4 (=CH<sub>2</sub>), 67.3 (CH), 32.5 (CH<sub>2</sub>, Cy), 28.9

(CH<sub>2</sub>), 25.7 (2 x CH<sub>2</sub>, Cy), 24.4 (2 x CH<sub>2</sub>, Cy) ppm. GCMS (CI<sup>+</sup>) m/z: 138 [MH<sup>+</sup>]. Data is in accordance with literature values.<sup>40</sup>

### 2-Methylene-1-[(*S*)-1-phenylethyl]aziridine **51**<sup>41</sup>



Following General Method 1, iron(III) nitrate nonahydrate, sodium (930 mg, 40.37 mmol) and 2-bromo-*N*-[(1*S*)-1-phenylethyl]prop-2-en-1-amine **183** (3.83 g, 16.15 mmol) were reacted in ammonia (100 mL) at -33 °C for 30 min. Following work-up 1, purification by bulb-to-bulb distillation (70 °C, 1 mbar) afforded 2-methylene-1-[(*S*)-1-phenylethyl]aziridine **51** (1.78 g, 69 %) as a colourless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.12 – 7.27 (5H, m, 5 x CH, Ph), 4.50 – 4.54 (2H, m, =CH<sub>2</sub>), 2.51 (1H, q, *J* = 6.6 Hz, CH), 1.98 (1H, s, CHH), 1.89 (1H, s, CHH), 1.40 (3H, d, *J* = 6.6, CH<sub>3</sub>) ppm. (75 MHz, CDCl<sub>3</sub>) δ = 143.9 (C, Ph), 137.1 (C=CH<sub>2</sub>), 128.4 (2 x CH, Ph), 127.6 (CH, Ph), 126.8 (2 x CH<sub>2</sub>, Ph), 83.2 (=CH<sub>2</sub>), 68.5 (CH), 29.9 (CH<sub>2</sub>) 23.6 (CH<sub>3</sub>) ppm. GCMS (CI<sup>+</sup>) m/z: 160 [MH<sup>+</sup>]. Data is in accordance with literature values.<sup>41</sup>

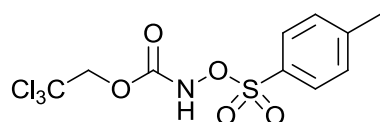
### Allene **74**<sup>66</sup>

H<sub>2</sub>C=•=CH<sub>2</sub> A 2-neck 50 mL flask was fitted with a coil condenser and a pressure equalizing dropping funnel. The exit to the coil condenser was connected to a calcium chloride trap and a cold finger condenser, filled with dry ice/acetone, with a 25 mL 3-neck round bottom flask in a dry ice/acetone bath. Zinc dust (12.8 g, 0.195 mol) was placed in the 50 mL flask with EtOH (17 mL) and H<sub>2</sub>O (3.5 mL) and heated to reflux. 2,3-Dichloropropene **95** (9.2 mL, 0.1 mol) was added

dropwise at a rate that permitted mild reflux without external heating. After all the 2,3-dichloropropene was added, the reaction mixture was heated to reflux for 1 h. The resulting allene **74** condensed and collected in the 25 mL flask as a colourless liquid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 4.69 (4H, s,  $\text{CH}_2$ ) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 212.5 ( $=\text{C}=\text{C}$ ) 73.8 (2 x  $\text{CH}_2$ ) ppm. Data is in accordance with literature values.<sup>67</sup>

### 2,2,2-Trichloroethyl *N*-4-tosyloxycarbamate **85**<sup>143</sup>



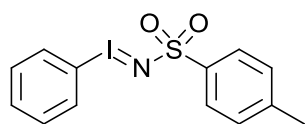
To a solution of NaOH (1.5 M, 80 mL) and hydroxylamine hydrochloride (6.9 g, 100 mmol) cooled to 0 °C, was added 2,2,2-trichloroethyl chloroformate **93** (4.08 g, 19.25 mmol) dropwise. The reaction mixture was stirred at room temperature for 1 h and then acidified to pH 5 using conc. HCl. The acidified solution was extracted with  $\text{Et}_2\text{O}$  (10 x 100 mL) and the combined organic phases were washed with brine (200 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give 2,2,2-trichloroethyl *N*-hydroxycarbamate **94** as a pale yellow oil, which slowly solidified on standing at room temperature to give a pale yellow solid (1.99 g).

To a solution of 2,2,2-trichloroethyl *N*-hydroxycarbamate **94** (1.99 g, 9.57 mmol), in  $\text{Et}_2\text{O}$  (100 mL) at 0 °C, was added dropwise *p*-toluenesulfonyl chloride (2.01 g, 10.54 mmol) followed by  $\text{Et}_3\text{N}$  (1.32 mL, 9.57 mmol). The resulting suspension was stirred at room temperature for 16 h whereupon the reaction was quenched with  $\text{H}_2\text{O}$  (10 mL). The phases were separated and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  (2 x 10 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in*

*vacuo* to give the crude product as a viscous yellow oil. The product was purified by column chromatography (10 – 30 % EtOAc in hexane) and recrystallised from hexane and chloroform, to give 2,2,2-trichloroethyl *N*-4-tosyloxycarbamate **85** (814 mg, 11% over 2 steps) as a white solid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.20 (1H, br s, NH), 7.88 (2H, d  $J$  = 7.9 Hz, 2 x CH, Ph), 7.34 (2H, d,  $J$  = 7.9 Hz, 2 x CH, Ph), 4.62 (2H, s,  $\text{CH}_2$ ), 2.44 (3H, s,  $\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 151.1 (C=O), 146.9 ( $\text{CSO}_3$ ), 130.4 ( $\text{CCH}_3$ ), 129.9 (2 x CH, Ph), 129.4 (2 x CH, Ph), 93.4 ( $\text{CCl}_3$ ), 76.2 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_3$ ) ppm; MS ( $\text{ES}^+$ )  $m/z$  363 [ $\text{MH}^+$ ]. Data is in accordance with literature values.<sup>143</sup>

#### ***N*-Tosyliminobenzylidiodinane **91**<sup>63</sup>**

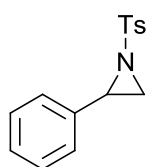


A solution of *p*-toluenesulfonamide (2.01 g, 11.77 mmol) and KOH (1.69 g, 30.07 mmol) in MeOH (50 ml) was cooled to below 10 °C whereupon iodobenzene diacetate **90** (3.79 g, 11.77 mmol) was added. The resulting yellow solution was stirred for 4 h at room temperature before being poured onto iced water (300 mL). The resulting suspension was stirred for a further 1 h before being left to stand for 16 h. The pale yellow solid was filtered and the precipitate was washed with  $\text{Et}_2\text{O}$  and then recrystallised from MeOH to give *N*-tosyliminobenzylidiodinane **91** (1.56 g, 35 %) as a yellow solid.

$^1\text{H}$  NMR (300 MHz, DMSO)  $\delta$  = 7.73 – 7.65 (2H, m, 2 x CH, Ph), 7.49 – 7.39 (3H, m, 3 x CH, Ph), 7.34 – 7.25 (2H, m, 2 x CH, Ph), 7.10 – 7.02 (2H, m, 2 x CH, Ph), 2.27 (3H, s,  $\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR 75 MHz, DMSO)  $\delta$  = 142.5 (C, Ts),

142.2 (C, Ts), 137.46 (Ph), 131.0 (2 x CH, Ph), 129.6 (2 x CH, Ts), 128.1 (2 x CH, Ph), 126.1 (CH, Ts), 126.0 (CH, Ts), 95.23 (CH, Ph), 21.29 (CH<sub>3</sub>) ppm. MS (ES<sup>+</sup>)  $m/z$  374 [MH<sup>+</sup>]. Data is in accordance with literature values.<sup>63</sup>

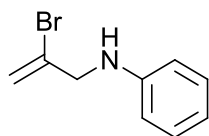
### 2-Phenyl-1-tosylaziridine **92**<sup>64</sup>



To a stirred solution of *N*-tosyliminobenzylidiodinane **91** (400 mg, 1.07 mmol) and styrene (556 mg, 3.35 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added Cu(acac)<sub>2</sub> (28 mg, 10 mol%) and the mixture was stirred for 2 h at room temperature. The reaction mixture was then filtered through celite<sup>®</sup> and washed through with CH<sub>2</sub>Cl<sub>2</sub>. The solvent was removed *in vacuo*. The crude product was purified by column chromatography (10 % EtOAc in petroleum ether) which afforded 2-phenyl-1-tosylaziridine **92** (226 mg, 77 %) as a white solid.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.80 (2H, d,  $J$  = 8.3 Hz, 2 x CH, Ph), 7.12 – 7.29 (7H, m, 7 x CH, Ph), 3.71 (1H, dd,  $J$  = 7.3, 4.5 Hz, CH), 2.92 (1H, d,  $J$  = 7.3 Hz, CHH), 2.37 (3H, s, CH<sub>3</sub>), 2.32 (1H, d,  $J$  = 4.5 Hz, CHH) ppm. Data is in accordance with literature values.<sup>64</sup>

### *N*-(2-Bromoprop-2-en-1-yl)aniline **103**<sup>71</sup>

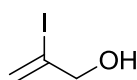


To a solution of aniline (9.1 mL, 100 mmol) in H<sub>2</sub>O (20 mL) at 60 °C was added 2,3-dibromopropene **102** (5.2 mL, 50 mmol) dropwise. The reaction mixture was stirred for 4 h before being cooled to 10 °C whereupon NaOH (5 g, 125 mmol) was added and the reaction stirred for a further 1 h while gradually warming to 20 °C. The reaction was then extracted with Et<sub>2</sub>O

(2 x 30 mL). The organic fractions were combined and washed with brine (50 mL), dried over  $\text{MgSO}_2$  and filtered. The solvent was removed *in vacuo* and the resulting crude product was purified by bulb-to-bulb distillation affording *N*-(2-bromoprop-2-en-1-yl)aniline **103** (8.60 g, 80 %) a yellow oil.

$\nu_{\text{max}}$  (neat) 3417, 2359, 1601, 1504, 1261, 747  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.13 – 7.23 (2H, m, 2 x CH, Ph), 6.74 (1H, t,  $J$  = 1.0 Hz, CH, Ph), 6.45 – 6.56 (2H, m, 2 x CH, Ph), 5.85 (1H, s, =CHH), 5.55 (1H, s, =CHH), 4.18 (1H, br s, NH), 3.99 (2H, m,  $\text{CH}_2$ ) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 146.1 (CBr), 130.5 (C, Ph), 128.7 (2 x CH, Ph), 117.6 (CH, Ph), 116.1 (=CH<sub>2</sub>), 112.4 (2 x CH, Ph), 51.5 ( $\text{CH}_2$ ) ppm; MS ( $\text{ES}^+$ )  $m/z$  214 [ $\text{MH}^+$ ,  $^{81}\text{Br}$ ], 212 [ $\text{MH}^+$ ,  $^{79}\text{Br}$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_9\text{H}_{11}\text{BrN}$  [ $\text{MH}^+$ ,  $^{81}\text{Br}$ ]: 214.0049; found: 214.0050; calcd for  $\text{C}_9\text{H}_{11}\text{BrN}$  [ $\text{MH}^+$ ,  $^{79}\text{Br}$ ]: 212.0069, found: 212.0068.

### 2-Iodoprop-2-en-1-ol **110**<sup>74</sup>

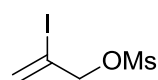


To a solution of sodium iodide (18.54 g, 124.00 mmol) and  $\text{TMSCl}$  (15.70 mL, 124 mmol) in  $\text{MeCN}$  (45 mL) at 0  $^\circ\text{C}$  was added propargyl alcohol **109** (6 mL, 103 mmol) and  $\text{H}_2\text{O}$  (1.1 mL). The reaction mixture was then stirred for 4 h at room temperature before being quenched with sat.  $\text{NaHCO}_3$  (50 mL). The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (2 x 50 mL). The combined organic fractions were washed with  $\text{Na}_2\text{S}_2\text{O}_3$  (60 mL), dried over  $\text{MgSO}_4$  and the solvent was removed *in vacuo* to give 2-iodoprop-2-en-1-ol **110** as a dark orange oil. The product was used in the following step without further purification.



$\nu_{\max}$  (neat) 3290, 1626, 1397, 1226, 1027, 899  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.41 (1H, s, =CHH), 5.87 (1H, s, =CHH), 4.17 (2H, s,  $\text{CH}_2$ ), 2.52 (1H, OH) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 123.8 (=CH<sub>2</sub>), 109.8 (CI), 70.1 ( $\text{CH}_2$ ) ppm.

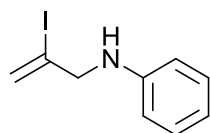
### 2-Iodoprop-2-en-1-yl methanesulfonate **111**<sup>75</sup>



To a stirred solution of 2-iodoprop-2-en-1-ol **110** (4 g, 21.76 mmol) in  $\text{CH}_2\text{Cl}_2$  (80 mL) was added  $\text{MsCl}$  (2.00 mL, 26.11 mmol). The mixture was cooled to 0 °C,  $\text{Et}_3\text{N}$  (3.64 mL, 26.11 mmol) was added. After 2 h the solvent was removed *in vacuo* and the resulting crude product was diluted with  $\text{Et}_2\text{O}$  (50 mL) and washed with  $\text{H}_2\text{O}$  (50 mL), sat.  $\text{NH}_4\text{Cl}$  (50 mL) and brine (50 mL). The organic phase was dried over  $\text{MgSO}_4$ , filtered and the solvent removed *in vacuo* which afforded 2-iodoprop-2-en-1-yl methanesulfonate **111** as a brown oil. The product was used directly without further purification.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.53 (1H, s, =CHH), 6.06 (1H, s, =CHH), 4.79 (2H, s,  $\text{CH}_2$ ), 3.09 (3H, s,  $\text{CH}_3$ ) ppm.

### N-(2-Iodoprop-2-en-1-yl)aniline **112**

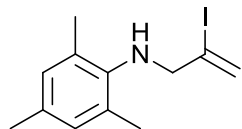


To a solution of aniline (3.9 mL, 42.6 mmol) in  $\text{H}_2\text{O}$  (9 mL) at 60 °C was added 2-iodoprop-2-en-1-yl methanesulfonate **111** (5.58 g, 21.3 mmol) dropwise. The reaction mixture was stirred for 4 h before being cooled to 10 °C whereupon  $\text{NaOH}$  (2.1 g, 53.2 mmol) was added and the reaction stirred for a further 1 h while gradually warming to 20 °C. The reaction was then extracted with  $\text{Et}_2\text{O}$  (2 x 30 mL). The organic fractions were combined and washed with brine (60 mL), dried over  $\text{MgSO}_2$  and filtered. The solvent was

removed *in vacuo* and the resulting crude product was purified by column chromatography (0-1% EtOAc in petroleum ether) affording *N*-(2-iodoprop-2-en-1-yl)aniline **112** (3.74 g, 67 %) as a dark orange oil.

$\nu_{\text{max}}$  (neat) 3412, 3050, 1600, 1503, 1262, 747  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.22 – 7.13 (2H, m, 2 x CH, Ph), 6.79 – 6.70 (1H, m, CH, Ph), 6.64 – 6.55 (2H, m, 2 x CH, Ph), 6.32 (1H, dt,  $J$  = 1.6 Hz,  $J$  = 1.6 Hz, =CHH), 5.83 (1H, dt,  $J$  = 1.6 Hz,  $J$  = 1.6 Hz, =CHH), 3.96 (2H, t,  $J$  = 1.6 Hz,  $\text{CH}_2$ ) ppm; NH not visible.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 146.6 (C, Ph), 129.4 (2 x CH, Ph), 125.2 (=CH<sub>2</sub>), 118.7 (CH, Ph), 112.2 (2 x CH, Ph), 109.9 (CI), 55.8 ( $\text{CH}_2$ ) ppm; MS ( $\text{ES}^+$ )  $m/z$  260 [ $\text{MH}^+$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_9\text{H}_{10}\text{IN}$  [ $\text{MH}^+$ ] 259.9931; found 259.9931.

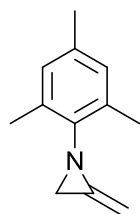
### *N*-(2-Iodoprop-2-en-1-yl)-2,4,6-trimethylaniline **113**



To a stirred suspension of  $\text{K}_2\text{CO}_3$  (4.80 g, 35.4 mmol) in THF (100 mL) was added 2,4,6-trimethylaniline (9.00 mL, 64.4 mmol) and 2-iodoprop-2-en-1-yl methanesulfonate **111** (8.43 g, 32.2 mmol). The reaction mixture was stirred at reflux for 18 h and then partitioned between 10 % NaOH solution (200 mL) and  $\text{Et}_2\text{O}$  (200 mL). The organic phase was washed with  $\text{H}_2\text{O}$  (200 mL), brine (200 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (0 – 20 %  $\text{CH}_2\text{Cl}_2$  in petroleum ether) afforded *N*-(2-iodoprop-2-en-1-yl)-2,4,6-trimethylaniline **113** (7.06 g, 72 %) as a dark, orange oil.

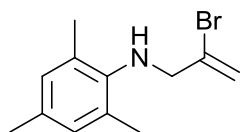
$\nu_{\max}$  (neat) 2920, 2357, 1614, 1482, 1218, 899, 852  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.80 (2H, s, 2 x CH, Ph), 6.33 (1H, s, =CHH), 5.83 (1H, s, =CHH), 3.74 (2H, s,  $\text{CH}_2$ ), 2.27 (6H, s, 2 x  $\text{CH}_3$ ), 2.21 (3H, s,  $\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 141.0 (C, Ph), 131.3 ( $\text{CH}_3\text{C}$ , Ph), 129.0 (2 x  $\text{CH}_3\text{C}$ , Ph), 129.0 (2 x CH, Ph), 125.9 ( $=\text{CH}_2$ ), 108.8 (CI), 59.6 ( $\text{CH}_2$ ), 19.9 (2 x  $\text{CH}_3$ ), 17.97 ( $\text{CH}_3$ ) ppm; MS ( $\text{ES}^+$ )  $m/z$  302 [ $\text{MH}^+$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{12}\text{H}_{17}\text{IN}$  [ $\text{MH}^+$ ] 302.0400; found 302.0398.

## 2-Methyldene-1-(2,4,6-trimethylphenyl)aziridine **114**



Following General Method 1, iron(III) nitrate nonahydrate, sodium (0.3 g, 13.28 mmol) and *N*-(2-iodoprop-2-en-1-yl)-2,4,6-trimethylaniline **113** (2.00 g, 6.6 mmol) were reacted in ammonia (25 mL) at -33 °C for 1 h. Following work-up 2, 2-methyldene-1-(2,4,6-trimethylphenyl)-aziridine **114** (970 mg, 85 %) was afforded as a dark brown oil.

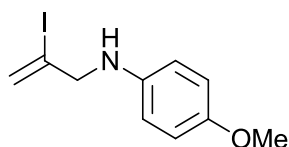
$\nu_{\max}$  (neat) 2920, 1758, 1482, 1248, 852, 639  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.72 (2H, s, 2 x CH, Ph) 4.94 (1H, s, =CHH), 4.79 (1H, s, =CHH), 2.60 (2H, s,  $\text{CH}_2$ ), 2.43 (6H, s, 2 x  $\text{CH}_3$ ) 2.20 (3H, s,  $\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 142.9 (NC, Ph), 132.6 ( $\text{C}=\text{CH}_2$ ), 131.8 ( $\text{CH}_3\text{C}$ , Ph), 129.7 (2 x CH, Ph), 128.8 (2 x  $\text{CH}_3\text{C}$ , Ph), 83.6 ( $=\text{CH}_2$ ), 31.2 ( $\text{CH}_2$ ), 19.8 ( $\text{CH}_3$ ), 18.9 (2 x  $\text{CH}_3$ ) ppm; MS ( $\text{ES}^+$ )  $m/z$  174 [ $\text{MH}^+$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{12}\text{H}_{16}\text{N}$  [ $\text{MH}^+$ ] 174.1277; found 174.1276.

***N*-(2-Bromoprop-2-en-1-yl)-2,4,6-trimethylaniline **116****

To a stirred suspension of  $\text{K}_2\text{CO}_3$  (3.6 g, 26.4 mmol) in THF (50 mL) was added 2,4,6-trimethylaniline (6.7 mL, 48.0 mmol) and 2,3-dibromopropene **102** (2.5 mL, 24.0 mmol).

The reaction mixture was stirred at reflux for 16 h, allowed to cool and then partitioned between 10 % NaOH solution (100 mL) and  $\text{Et}_2\text{O}$  (100 mL). The organic phase was washed with  $\text{H}_2\text{O}$  (100 mL), brine (100 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (0 – 30 %  $\text{CH}_2\text{Cl}_2$  in petroleum ether) afforded *N*-(2-bromoprop-2-en-1-yl)-2,4,6-trimethylaniline **116** (2.7 g, 45 %) as an orange oil.

$\nu_{\text{max}}$  (neat) 2914, 1626, 1484, 1220, 892, 853, 733  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.82 (2H, s, 2 x CH, Ph), 5.86 (1H, d,  $J$  = 1.67 Hz, =CHH), 5.54 (1H, d,  $J$  = 1.67 Hz, =CHH), 3.79 (2H, s,  $\text{CH}_2$ ), 3.37 (1H, br s, NH), 2.29 (6H, s, 2 x  $\text{CH}_3$ ), 2.23 (3H, s,  $\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 141.9 (C, Ph), 132.2 (CBr), 131.7 ( $\text{CH}_3\text{C}$ , Ph), 129.7 (2 x  $\text{CH}_3\text{C}$ , Ph), 129.6 (2 x CH, Ph), 117.7 (=CH<sub>2</sub>), 56.7 ( $\text{CH}_2$ ), 20.6 ( $\text{CH}_3$ ), 18.4 (2 x  $\text{CH}_3$ ) ppm; MS ( $\text{ES}^+$ )  $m/z$  256 [ $\text{MH}^+$ ,  $^{81}\text{Br}$ ], 254 [ $\text{MH}^+$ ,  $^{79}\text{Br}$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{12}\text{H}_{17}\text{BrN}$  [ $\text{MH}^+$ ,  $^{81}\text{Br}$ ]: 256.0518; found: 256.0524; calcd for  $\text{C}_{12}\text{H}_{17}\text{BrN}$  [ $\text{MH}^+$ ,  $^{79}\text{Br}$ ]: 254.0539; found: 254.0545.

***N*-(2-Iodoprop-2-en-1-yl)-4-methoxyaniline **121****

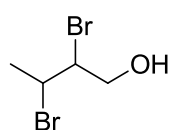
To a stirred suspension of  $\text{K}_2\text{CO}_3$  (3.38 g, 24.8 mmol) in THF (50 mL) was added *p*-anisidine (5.6 g, 45.2 mmol) and 2-iodoprop-2-en-1-yl methanesulfonate **111** (5.9 mL,

22.6 mmol). The reaction mixture was stirred at reflux for 16 h and then

partitioned between Et<sub>2</sub>O (100 mL) and 10 % NaOH solution (100 mL). The organic phase was washed with H<sub>2</sub>O (100 mL), brine (100 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (10 % EtOAc in petroleum ether) afforded *N*-(2-iodoprop-2-en-1-yl)-4-methoxyaniline **121** (4.9 g, 76 %) as an orange oil.

$\nu_{\text{max}}$  (neat) 3409, 2902, 1621, 1508, 1230, 1033, 816 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.79 – 6.75 (2H, m, 2 x CH, Ph), 6.59 – 6.54 (2H, m, 2 x CH, Ph), 6.33 – 6.39 (1H, m, =CHH), 5.85 – 5.82 (1H, m, =CHH), 3.92 (2H, s, CH<sub>2</sub>), 3.74 (3H, s, CH<sub>3</sub>) ppm; NH not visible. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 152.6 (OC, Ph), 140.6 (NC, Ph), 125.2 (=CH<sub>2</sub>), 114.9 (2 x CH, Ph), 114.4 (2 x CH, Ph), 110.6 (CI), 56.7 (CH<sub>2</sub>), 55.7 (CH<sub>3</sub>) ppm; MS (ES<sup>+</sup>) *m/z* 290 [MH<sup>+</sup>]; HRMS (ES<sup>+</sup>) calcd for C<sub>10</sub>H<sub>12</sub>INO [MH<sup>+</sup>] 290.0036; found 290.0042.

### 2,3-Dibromobutan-1-ol **128**<sup>144</sup>

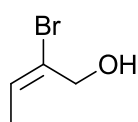


To a vigorously stirred solution of crotyl alcohol **127** (20 mL, 330 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) at -78 °C, was added dropwise a solution of bromine (12.2 mL, 473 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The solution was allowed to warm slowly to room temperature whereupon it was washed with Na<sub>2</sub>SO<sub>4</sub> solution (200 mL) and brine (200 mL), dried over MgSO<sub>4</sub>, filtered and the solvent removed *in vacuo* affording 2,3-dibromobutan-1-ol **128** (50.3 g, 72 %) as a pale purple oil.

$\nu_{\text{max}}$  (neat) 3356, 2930, 1379, 1153, 1062, 840 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.43 – 4.32 (1H, m, CHCH<sub>3</sub>), 4.28 – 4.21 (1H, m, CHCH<sub>2</sub>), 4.11 – 4.06 (2H, m, CH<sub>2</sub>), 1.97 – 1.87 (4H, m, OH, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  =

66.1 (CH<sub>2</sub>), 62.3 (CHCH<sub>2</sub>), 47.6 (CHCH<sub>3</sub>), 25.5 (CH<sub>3</sub>) ppm. Data is in accordance with literature values.<sup>144</sup>

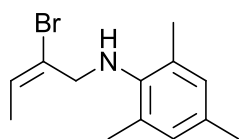
**(*E*)-2-Bromobut-2-en-1-ol **129****<sup>144</sup>



To a vigorously stirred suspension of powdered potassium hydroxide (34 g, 607 mmol) in Et<sub>2</sub>O (130 mL) was added a solution of 2,3-dibromobutan-1-ol **128** (50.3 g, 216 mmol) in Et<sub>2</sub>O (60 mL) at a rate that permitted the reaction mixture to mildly reflux. The resulting mixture was subsequently heated to reflux for 2 h. After cooling to room temperature the mixture was washed with H<sub>2</sub>O (2 x 150 mL), brine (150 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (5 – 10 % EtOAc in petroleum ether) to afford (*E*)-2-bromobut-2-en-1-ol **129** (11.5 g, 35 %) as a colourless oil.

$\nu_{\text{max}}$  (neat) 3282, 1637, 1457, 1260, 1091, 1043 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.04 (1H, q, *J* = 7.33 Hz, CH), 4.29 (2H, s, CH<sub>2</sub>), 2.11 (1H, br s, OH), 1.70 (3H, d, *J* = 7.33 Hz, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 129.1 (=CH), 124.2 (CBr), 62.2 (CH<sub>2</sub>), 15.1 (CH<sub>3</sub>) ppm. Data is in accordance with literature values.<sup>144</sup>

***N*-[(2*E*)-2-Bromobut-2-en-1-yl]-2,4,6-trimethylaniline (*E*)-**130****

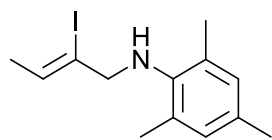


To a stirred solution of (*E*)-2-bromobut-2-en-1-ol **129** (11.5 g, 76.2 mmol) in THF (160 mL) at – 30 °C was added triethylamine (25.0 mL, 173.3 mmol). Methanesulfonyl chloride (6.0 mL, 78.6 mmol) was added to the mixture followed by 2,4,6-

trimethylaniline (22.0 mL, 156.4 mmol). The mixture was heated to reflux for 18 h, allowed to cooled and then partitioned between Et<sub>2</sub>O (200 mL) and 10 % NaOH solution (200 mL). The organic phase was washed with 10 % NaOH solution (200 mL), brine (200 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (0 – 20 % CH<sub>2</sub>Cl<sub>2</sub> in petroleum ether) afforded *N*-[(2*E*)-2-bromobut-2-en-1-yl]-2,4,6-trimethylaniline (*E*)-**130** (6.6 g, 32 %) as an orange oil.

$\nu_{\max}$  (neat) 2916, 1482, 1217, 1008, 852 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.83 (2H, s, 2 x CH, Ph), 6.03 (1H, q, *J* = 7.14 Hz, CH), 3.79 (2H, s, CH<sub>2</sub>), 2.81 (1H, br s, NH), 2.32 (6H, s, 2 x CH<sub>3</sub>), 2.22 (3H, s, CH<sub>3</sub>), 1.55 (3H, d, *J* = 7.14 Hz, CHCH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 142.2 (C, Ph), 132.1 (CH<sub>3</sub>C, Ph), 130.4 (2 x CH<sub>3</sub>C, Ph), 129.7 (CH), 129.5 (2 x CH, Ph), 123.6 (CBr), 51.4 (CH<sub>2</sub>), 20.6 (CH<sub>3</sub>), 18.4 (2 x CH<sub>3</sub>), 14.9 (CH<sub>3</sub>) ppm; MS (ES<sup>+</sup>) *m/z* 270 [MH<sup>+</sup>, <sup>81</sup>Br], 268 [MH<sup>+</sup>, <sup>79</sup>Br]; HRMS (ES<sup>+</sup>) calcd for C<sub>13</sub>H<sub>19</sub>BrN [MH<sup>+</sup>, <sup>81</sup>Br]: 270.0675; found: 270.0676; calcd for C<sub>13</sub>H<sub>19</sub>BrN [MH<sup>+</sup>, <sup>79</sup>Br]: 268.0695; found: 268.0695.

#### *N*-[(2*Z*)-2-iodobut-2-en-1-yl]-2,4,6-trimethylaniline (*Z*)-**133**

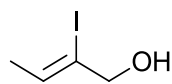


To a stirred suspension of K<sub>2</sub>CO<sub>3</sub> (550 mg, 3.98 mmol) in THF (10 mL) was added 2,4,6-trimethylaniline (600  $\mu$ L, 4.26 mmol) and (2*Z*)-2-iodobut-2-en-1-yl methane-sulfonate **136** (640 mg, 2.31 mmol). The reaction mixture was stirred at reflux for 48 h, allowed to cool and then partitioned between 10 % NaOH solution (20 mL) and Et<sub>2</sub>O (20 mL). The organic phase was washed with H<sub>2</sub>O (20 mL), brine (20 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give the crude

product. Purification by column chromatography (10 % EtOAc in petroleum ether) afforded *N*-[(2*Z*)-2-iodobut-2-en-1-yl]-2,4,6-trimethylaniline (*Z*)-**133** (488 mg, 67 %) as an orange oil.

$\nu_{\text{max}}$  (neat) 2911, 1644, 1483, 1223, 852, 733  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.81 (2H, s, 2 x CH, Ph), 5.86 (1H, q,  $J$  = 6.1 Hz, CH), 3.79 (2H, s,  $\text{CH}_2$ ), 3.25 (1H, br s, NH), 2.29 (6H, s, 2 x  $\text{CH}_3$ ), 2.22 (3H, s,  $\text{CH}_3$ ), 1.77 (3H, d,  $J$  = 6.1 Hz,  $\text{CHCH}_3$ ) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 142.1 (C, Ph), 131.9 ( $=\text{CH}$ ), 131.7 ( $\text{CH}_3\text{C}$ , Ph), 129.9 (2 x  $\text{CH}_3\text{C}$ , Ph), 129.5 (2 x CH, Ph), 108.3 (CI), 60.7 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_3$ ), 20.6 ( $\text{CH}_3$ ), 18.6 (2 x  $\text{CH}_3$ ) ppm; MS ( $\text{ES}^+$ )  $m/z$  316 [ $\text{MH}^+$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{13}\text{H}_{19}\text{IN}$  [ $\text{MH}^+$ ] 316.0560; found 316.0057.

#### (2*Z*)-2-Iodobut-2-en-1-ol **135**<sup>78</sup>



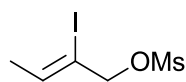
To a solution of but-2-yne-1-ol **134** (0.57 mL, 7.63 mmol) in  $\text{Et}_2\text{O}$  (7.0 mL) at  $-20\text{ }^\circ\text{C}$  was added *n*-butyllithium (2.5 M in hexanes, 3.0 mL, 7.5 mmol) followed by diisobutylaluminium hydride (1 M in THF, 22.8 mL, 22.8 mmol). The resulting mixture was heated to  $35\text{ }^\circ\text{C}$  for 48 h. Excess diisobutylaluminium hydride was decomposed by the addition of EtOAc (1.5 mL) at  $0\text{ }^\circ\text{C}$ . The reaction was cooled to  $-78\text{ }^\circ\text{C}$  and iodine (17.3 g, 136.2 mmol) dissolved in  $\text{Et}_2\text{O}$  (100 mL) was added and the resulting mixture was stirred for 15 min at  $-78\text{ }^\circ\text{C}$ . The reaction mixture was poured into a  $\text{Na}_2\text{S}_2\text{O}_3$  solution and the product extracted with  $\text{Et}_2\text{O}$  (5 x 100 mL). The combined organic fractions were washed with brine (200 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography (16 %



EtOAc in petroleum ether) affording (2Z)-2-iodobut-2-en-1-ol **135** (1.02 g, 68 %) as a pale yellow oil.

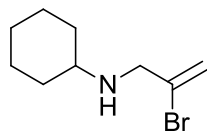
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 5.96 (1H, qt,  $J$  = 1.21 Hz,  $J$  = 6.48 Hz, CH), 4.27 – 4.22 (2H, m,  $\text{CH}_2$ ), 1.95 (1H, br s, OH), 1.79 (3H, dt,  $J$  = 1.21 Hz,  $J$  = 6.48 Hz,  $\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 130.9 (CH), 109.1 (CI), 71.0 ( $\text{CH}_2$ ), 21.4 ( $\text{CH}_3$ ) ppm; MS ( $\text{ES}^+$ )  $m/z$  199 [ $\text{MH}^+$ ]. Data is in accordance with literature values.<sup>78</sup>

#### (2Z)-2-Iodobut-2-en-1-yl methanesulfonate **136**



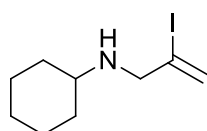
To a solution of (2Z)-2-iodobut-2-en-1-ol **135** (1.65 g, 8.33 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) at 0 °C was added methanesulfonyl chloride (0.77 mL, 9.9 mmol) followed by  $\text{Et}_3\text{N}$  (1.4 mL, 9.9 mmol) and the reaction was stirred for 2 h at 0 °C. The solvent was removed *in vacuo* and the resulting residue was partitioned between  $\text{H}_2\text{O}$  (25 mL) and  $\text{Et}_2\text{O}$  (25 mL). The organic phase was washed with sat.  $\text{NH}_4\text{Cl}$  (25 mL) and brine (25 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* affording (2Z)-2-iodobut-2-en-1-yl methanesulfonate **136** (1.99 g, 86 %) as a brown oil. The product was used directly without further purification.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.20 (1H, q,  $J$  = 6.54 Hz, CH), 4.90 (2H, s,  $\text{CH}_2$ ), 3.06 (3H, s,  $\text{SCH}_3$ ), 1.84 (3H, d,  $J$  = 6.54 Hz,  $\text{CH}_3$ ) ppm.

***N*-(2-Bromoprop-2-en-1-yl)cyclohexanamine **137****<sup>145</sup>

To a stirred suspension of  $\text{K}_2\text{CO}_3$  (7.3 g, 52.83 mmol) in THF (120 mL) was added cyclohexylamine (11.0 mL, 96.06 mmol) and 2,3-dibromopropene **102** (5.0 mL, 48.03 mmol). The reaction mixture was stirred at reflux for 22 h, allowed to cool to room temperature and then partitioned between 10 % NaOH solution (200 mL) and  $\text{Et}_2\text{O}$  (200 mL). The organic phase was washed with  $\text{H}_2\text{O}$  (200 mL), brine (200 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (1 %  $\text{Et}_3\text{N}$  and 10 - 20 %  $\text{EtOAc}$  in petroleum ether) afforded *N*-(2-bromoprop-2-en-1-yl)cyclohexylamine **137** (8.4 g, 91 %) as a dark orange oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 5.74 (1H, d,  $J$  = 1.7 Hz, =CHH). 5.51 (1H, d,  $J$  = 1.7 Hz, =CHH), 3.45 (2H, s,  $\text{CH}_2$ ), 2.47-2.35 (1H, m, CH), 1.85-1.52 (6H, m, 5 x CHH, Cy and NH), 1.27-1.01 (5H, m, 5 x CHH, Cy) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 134.1 (CBr), 117.3 ( $=\text{CH}_2$ ), 54.4 ( $\text{CH}_2\text{NH}$ ), 54.3 (CH, Cy), 33.3 (2 x  $\text{CH}_2$ , Cy), 26.1 ( $\text{CH}_2$ , Cy), 24.9 (2 x  $\text{CH}_2$ , Cy) ppm; MS ( $\text{ES}^+$ )  $m/z$  220 [ $\text{MH}^+$ ,  $^{81}\text{Br}$ ], 218 [ $\text{MH}^+$ ,  $^{79}\text{Br}$ ]. Data is in accordance with literature values.<sup>145</sup>

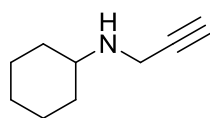
***N*-(2-Iodoprop-2-en-1-yl)hexan-1-amine **138****

To a stirred suspension of  $\text{K}_2\text{CO}_3$  (8 g, 58.30 mmol) in THF (130 mL) was added cyclohexylamine 12.0 mL, 106.0 mmol) and 2-iodoprop-2-en-1-yl methanesulfonate **111** (13.9 g, 53.0 mmol). The reaction mixture was stirred at reflux for 16 h, allowed to cool and then partitioned between 10 % NaOH solution (200 mL) and  $\text{Et}_2\text{O}$  (200 mL). The organic phase was washed with  $\text{H}_2\text{O}$  (200 mL), brine (200 mL), dried over  $\text{MgSO}_4$ , filtered and

concentrated *in vacuo* to give the crude product. Purification by column chromatography (5 – 10 % EtOAc in petroleum ether) afforded *N*-(2-iodoprop-2-en-1-yl)hexan-1-amine **138** (7.94 g, 56 %) as a dark, orange oil.

$\nu_{\text{max}}$  (neat) 2922, 2849, 1616 1447, 1113, 839  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.21 (1H, s, =CHH), 5.82 (1H, s, =CHH), 3.37 (2H, s,  $\text{CH}_2$ ), 2.35 – 2.47 (1H, m, CH) 1.53 – 1.85 (6H, m, 3 x  $\text{CH}_2$ , Cy), 1.03 – 1.27 (5H, m, NH, 2 x  $\text{CH}_2$ , Cy), ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 125.2 ( $=\text{CH}_2$ ), 113.4 (CI), 57.3 ( $\text{CH}_2$ ), 53.4 (CH), 32.6 (2 x  $\text{CH}_2$ , Cy), 25.5 ( $\text{CH}_2$ , Cy), 24.2 (2 x  $\text{CH}_2$ , Cy) ppm; MS ( $\text{ES}^+$ )  $m/z$  266 [ $\text{MH}^+$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_9\text{H}_{17}\text{IN}$  [ $\text{MH}^+$ ] 266.0400; found 266.0403.

#### ***N*-(prop-2-yn-1-yl)cyclohexanamine 139**

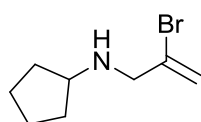


To a stirred suspension of  $\text{K}_2\text{CO}_3$  (1.8 g, 14.7 mmol) in THF (25 mL) was added cyclohexylamine (3 mL, 26.8 mmol) and propargyl bromide **143** (80 % sol. 2 g, 13.4 mmol). The reaction mixture was stirred at reflux for 20 h, allowed to cool and then partitioned between 10 % NaOH solution (50 mL) and  $\text{Et}_2\text{O}$  (50 mL). The organic phase was washed with  $\text{H}_2\text{O}$  (50 mL), brine (50 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (5 – 10 % EtOAc in petroleum ether) *N*-(prop-2-yn-1-yl)cyclohexanamine **139** (525 mg, 28 %) as a pale, yellow oil.

$\nu_{\text{max}}$  (neat) 2924, 2851, 2015, 1448, 1120, 908  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.42 (2H, d,  $J$  = 2.5 Hz,  $\text{CH}_2$ ), 2.54 – 2.67 (1H, m, CH, Cy), 2.15 (1H, t,  $J$  = 2.5 Hz, CH), 1.74 – 1.87 (2H, m,  $\text{CH}_2$ , Cy), 1.63 – 1.74 (2H, m,  $\text{CH}_2$ , Cy), 1.51 – 1.63 (1H, m, NH), 0.93 – 1.33 (6H, m, 3 x  $\text{CH}_2$ , Cy) ppm;  $^{13}\text{C}$  NMR (75 MHz,

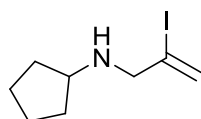
$\text{CDCl}_3$ )  $\delta$  = 82.6 (CCH), 70.9 (CH), 54.9 (CH, Cy), 35.1 ( $\text{CH}_2$ ), 33.0 (2 x  $\text{CH}_2$ , Cy), 26.1 ( $\text{CH}_2$ , Cy), 24.8 (2 x  $\text{CH}_2$ , Cy) ppm; GC-MS (EI)  $m/z$  136 [ $\text{MH}^+$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_9\text{H}_{16}\text{N}$  [ $\text{MH}^+$ ] 138.1277; found 138.1281.

### ***N*-(2-Bromoprop-2-en-1-yl)cyclopentanamine 137**



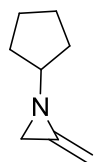
To a stirred suspension of  $\text{K}_2\text{CO}_3$  (5.89 g, 42.61 mmol) in THF (100 mL) was added cyclopentylamine (7.6 mL, 77.2 mmol) and 2,3-dibromopropene **102** (5 mL, 48.0 mmol). The reaction mixture was stirred at reflux for 16 h, allowed to cool and then partitioned between 10 % NaOH solution (200 mL) and  $\text{Et}_2\text{O}$  (200 mL). The organic phase was washed with  $\text{H}_2\text{O}$  (200 mL), brine (200 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (5 – 10 % EtOAc in petroleum ether) afforded *N*-(2-bromoprop-2-en-1-yl)cyclopentanamine **137** (6.32 g, 73 %) as an orange oil.

$\nu_{\text{max}}$  (neat) 2939, 2862, 2358, 1626, 1454, 1105, 888  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 5.75 (1H, s, =CHH), 5.51 (1H, s, =CHH), 3.42 (2H, s,  $\text{CH}_2$ ), 2.97 – 3.13 (1H, m, CH), 1.60 – 1.85 (4H, m, 2 x  $\text{CH}_2$ , Cy), 1.44 – 1.60 (3H, m, NH,  $\text{CH}_2$ , Cy), 1.24 – 1.39 (2H, m,  $\text{CH}_2$ , Cy) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 133.3 (CBr), 116.7 (=CH<sub>2</sub>), 56.8 (CH), 55.6 ( $\text{CH}_2$ ), 32.3 (2 x  $\text{CH}_2$ , Cy), 23.4 (2 x  $\text{CH}_2$ , Cy) ppm; MS ( $\text{ES}^+$ )  $m/z$  206 [ $\text{MH}^+$ ,  $^{81}\text{Br}$ ], 204 [ $\text{MH}^+$ ,  $^{79}\text{Br}$ ] HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_8\text{H}_{15}\text{BrN}$  [ $\text{MH}^+$ ,  $^{81}\text{Br}$ ]: 206.0362; found: 206.0367; calcd for  $\text{C}_8\text{H}_{15}\text{BrN}$  [ $\text{MH}^+$ ,  $^{79}\text{Br}$ ]: 204.0382; found: 204.0389.

***N*-(2-Iodoprop-2-en-1-yl)cyclopentanamine 141**

To a stirred suspension of  $\text{K}_2\text{CO}_3$  (5.8 g, 48.0 mmol) in THF (120 mL) was added cyclopentylamine (8 mL, 80.0 mmol) and 2-iodoprop-2-en-1-yl methanesulfonate **111** (10.5 g, 40.0 mmol). The reaction mixture was stirred at reflux for 18 h, allowed to cool and then partitioned between 10 % NaOH solution (200 mL) and  $\text{Et}_2\text{O}$  (200 mL). The organic phase was washed with  $\text{H}_2\text{O}$  (200 mL), brine (200 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (5 – 10 % EtOAc in petroleum ether) afforded *N*-(2-iodoprop-2-en-1-yl)cyclopentanamine **141** (6.72 g, 67 %) as an orange oil.

$\nu_{\text{max}}$  (neat) 2943, 2160, 1614, 1452, 1081, 895  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.24 (1H, s, =CHH), 5.83 (1H, s, =CHH), 3.39 (2H, s,  $\text{CH}_2$ ), 2.38 – 2.50 (1H, m, CH), 1.01 – 1.93 (9H, m, NH, 4 x  $\text{CH}_2$ , Cy) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 125.5 (=CH<sub>2</sub>), 113.1 (CI), 57.1 ( $\text{CH}_2$ ), 53.5 (CH), 32.5 (2 x  $\text{CH}_2$ , Cy), 25.4 ( $\text{CH}_2$ , Cy), 24.2 ( $\text{CH}_2$ , Cy) ppm; MS ( $\text{ES}^+$ )  $m/z$  252 [ $\text{MH}^+$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_8\text{H}_{15}\text{IN}$  [ $\text{MH}^+$ ] 252.0244; found 252.0242.

**1-Cyclopentyl-2-methyleneaziridine 142**

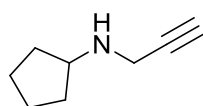
Following General Method 1, iron(III) nitrate nonahydrate, sodium (184 mg, 8 mmol) and *N*-(2-bromoprop-2-en-1-yl)cyclopentanamine **140** (1.00 g, 4.0 mmol) were reacted in ammonia (25 mL) at -33 °C for 3 h.

Following work-up 1, the product was found to be volatile and so was not fully isolated. A small portion was purified by bulb-to-bulb distillation (50 °C, 0.5

mbar) which afforded 1-cyclopentyl-2-methyleneaziridine **141** (0.1 g, 20 % as a colourless oil for characterisation.

$\nu_{\text{max}}$  (neat) 2948, 2355, 1760, 1341, 1197, 1144, 813  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 4.71 (1H, s, =CHH), 4.59 (1H, s, =CHH), 2.27 – 2.37 (1H, m, CH, Cy), 1.97 (2H, s,  $\text{CH}_2$ ), 1.64 – 1.84 (6H, m, 3 x  $\text{CH}_2$ , Cy), 1.48 – 1.59 (2H, m,  $\text{CH}_2$ , Cy) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 136.8 ( $\text{C}=\text{CH}_2$ ), 81.6 ( $=\text{CH}_2$ ), 6.80 (CH, Cy), 31.9 (2 x  $\text{CH}_2$ , Cy), 29.1 ( $\text{CH}_2$ ), 23.6 (2 x  $\text{CH}_2$ , Cy) ppm; GC–MS (EI)  $m/z$  123 [ $\text{MH}^+$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_8\text{H}_{14}\text{N}$  [ $\text{MH}^+$ ] 124.1121; found 124.1124.

#### ***N*-(Prop-2-yn-1-yl)cyclopentanamine **144****

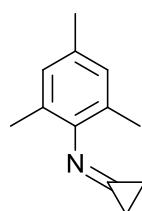


To a stirred suspension of  $\text{K}_2\text{CO}_3$  (1.8 g, 14.7 mmol) in THF (25 mL) was added cyclopentylamine (2.6 mL, 26.8 mmol) and propargyl bromide **143** (80 % sol. 2 g, 13.4 mmol). The reaction mixture was stirred at reflux for 20 h, allowed to cool and then partitioned between 10 % NaOH solution (50 mL) and  $\text{Et}_2\text{O}$  (50 mL). The organic phase was washed with  $\text{H}_2\text{O}$  (50 mL), brine (50 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (5 – 10 % EtOAc in petroleum ether) *N*-(prop-2-yn-1-yl)cyclopentanamine **144** (515 mg, 31 %) as a pale, yellow oil.

$\nu_{\text{max}}$  (neat) 2956, 2861, 2155, 1452, 1330, 1114, 907  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.38 (2H, d,  $J$  = 2.5 Hz,  $\text{CH}_2$ ), 3.20 – 3.31 (1H, m, CH), 2.16 (1H, t  $J$  = 2.5 Hz, CH), 1.72 – 1.85 (2H, m,  $\text{CH}_2$ , Cy), 1.58 – 1.72 (2H, m,  $\text{CH}_2$ , Cy), 1.41 – 1.58 (3H, m, NH,  $\text{CH}_2$ , Cy), 1.23 – 1.36 (2H, m,  $\text{CH}_2$ , Cy), ppm;  $^{13}\text{C}$  NMR (75

MHz, CDCl<sub>3</sub>)  $\delta$  = 82.0 (CCH), 70.3 (CH, Cy), 57.5 (CH<sub>2</sub>, Cy), 36.2 (CH<sub>2</sub>), 32.2 (2 x CH<sub>2</sub>, Cy), 23.4 (2 x CH<sub>2</sub>, Cy) ppm; GC-MS (EI)  $m/z$  123 [MH<sup>+</sup>]; HRMS (ES<sup>+</sup>) calcd for C<sub>8</sub>H<sub>14</sub>N [MH<sup>+</sup>] 124.1121; found 124.1122.

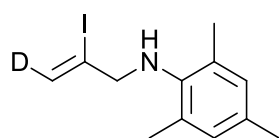
### ***N*-Cyclopropylidene-2,4,6-trimethylaniline 145**



2-Methylidene-1-(2,4,6-trimethylphenyl)aziridine **114** (100 mg, 0.58 mmol) was heated to reflux in toluene for 30 mins. The reaction was cooled to room temperature and the solvent removed *in vacuo* to give *N*-cyclopropylidene-2,4,6-trimethylaniline **145** as a dark brown oil. The product was not isolated.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.86 (2H, s, CH, Ph), 2.27 (3H, s, CH<sub>3</sub>), 2.03 (6H, s, 2 x CH<sub>3</sub>), 1.72 – 1.65 (2H, m, CH<sub>2</sub>), 1.33 – 1.24 (2H, m, CH<sub>2</sub>) ppm; MS (ES<sup>+</sup>)  $m/z$  174 [MH<sup>+</sup>].

### **Deuterated *N*-(2-iodoprop-2-en-1-yl)-2,4,6-trimethylaniline 155**



To a stirred solution of propargyl alcohol **109** (3.0 mL, 51.5 mmol) and imidazole (4.6 g, 67.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at 0 °C was added TMSCl (8.5 mL, 67.0 mmol). The reaction was warmed to room temperature whereupon it was quenched with H<sub>2</sub>O (30 mL). The phases were separated and the aqueous phase extracted with pentane (30 mL). The combined organic fractions were washed with brine, dried over MgSO<sub>4</sub>, filtered and the solvent removed by distillation (40 °C). The crude product was isolated by vacuum distillation to give trimethyl-prop-2-ynyloxy-silane **157** (1.7 g, 26%) as a colourless oil.

To a solution of sodium iodide (2.5 g, 16.7 mmol) and TMSCl (2.0 mL, 15.7 mmol) in MeCN (25 mL) at 0 °C was added trimethyl-prop-2-ynyloxy-silane **157** (1.76 mL, 13.75 mmol) and D<sub>2</sub>O (0.15 mL). The reaction mixture was then stirred for 4 h at room temperature before being quenched with sat. NaHCO<sub>3</sub> (30 mL). The aqueous phase was extracted Et<sub>2</sub>O (2 x 30 mL). The combined organic fractions were washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (30 mL), dried over MgSO<sub>4</sub> and the solvent was removed *in vacuo* giving deuterated 2-iodoprop-2-en-1-ol **158** as a dark orange oil. The product was used directly in the following step without purification.

To a stirred solution of deuterated 2-iodoprop-2-en-1-ol (1.0 g, 5.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added MsCl (0.5 mL, 6.4 mmol). The mixture was cooled to 0 °C, Et<sub>3</sub>N (0.9 mL, 6.4 mmol) was added. After 2 h the solvent was removed *in vacuo* and the resulting crude product was diluted with Et<sub>2</sub>O (20 mL) and washed with H<sub>2</sub>O (40 mL), sat. NH<sub>4</sub>Cl (40 mL) and brine (40 mL). The organic phase was dried over MgSO<sub>4</sub>, filtered and the solvent removed under vacuum to afford deuterated 2-iodoprop-2-en-1-yl methanesulfonate **159** (1.2 g) as a brown oil which was used directly without purification.

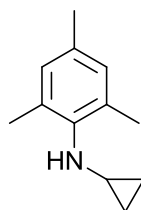
To a stirred suspension of K<sub>2</sub>CO<sub>3</sub> (0.7 g, 5.06 mmol) in THF (10 mL) was added 2,4,6-trimethylaniline (1.2 mL, 8.56 mmol) and deuterated 2-iodoprop-2-en-1-yl methanesulfonate (1.2 g, 4.58 mmol). The reaction mixture was stirred at reflux for 18 h and then partitioned between 10 % NaOH solution (20 mL) and Et<sub>2</sub>O (20 mL). The organic phase was washed with H<sub>2</sub>O (20 mL), brine (20 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (0 – 20 % CH<sub>2</sub>Cl<sub>2</sub> in petroleum ether) afforded



deuterated *N*-(2-iodoprop-2-en-1-yl)-2,4,6-trimethylaniline **155** (1.3 g, 4.32 mmol, 72 %) as a dark, orange oil.

$\nu_{\text{max}}$  (neat) 2912, 1617, 1483, 1221, 900, 852  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.82 (2H, s, 2 x CH, Ph), 6.35 – 6.31 (0.63H, m, =CHH), 5.86 – 5.81 (0.86H, m, =CHH), 3.76 – 3.71 (1.65H, m,  $\text{CH}_2$ ), 3.29 (1H, br s, NH), 2.28 (6H, s, 2 x  $\text{CH}_3$ ), 2.22 (3H, s,  $\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR (175 MHz,  $\text{CDCl}_3$ )  $\delta$  = 141.8 (C, Ph), 131.7 (MeC, Ph), 129.7 (2 x MeC, Ph), 129.6 (2 x CH, Ph), 126.2 (=CH<sub>2</sub>), 126.1 (t, =CHD), 109.6 (CI), 60.3 ( $\text{CH}_2$ ), 60.0 (t, CHD), 20.5 (2 x  $\text{CH}_3$ ), 18.5 ( $\text{CH}_3$ ) ppm; MS ( $\text{ES}^+$ )  $m/z$  302 [ $\text{MH}^+$ ], 303 [ $\text{MDH}^+$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{12}\text{H}_{17}\text{IN}$  [ $\text{MH}^+$ ] 302.0400; found 302.0399 (29 %),. calcd for  $\text{C}_{12}\text{H}_{16}\text{DIN}$  [ $\text{MH}^+$ ] 303.0463; found 303.0471 (71 %).

#### *N*-Cyclopropyl-2,4,6-trimethylaniline **160**

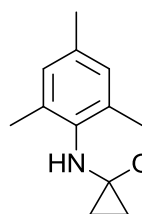


A solution of 2-methylidene-1-(2,4,6-trimethylphenyl)aziridine **114** (100 mg, 0.57 mmol) in THF (5 mL) was heated to reflux for 5 h.

The mixture was then cooled to 0 °C before  $\text{LiAlH}_4$  (2 M in THF, 140  $\mu\text{L}$ , 0.285 mmol) was carefully added and the mixture stirred for a further 40 min while slowly warming to room temperature. The reaction was carefully quenched with  $\text{H}_2\text{O}$ , until  $\text{H}_2$  evolution ceased.  $\text{Et}_2\text{O}$  (20 mL) was then added followed by  $\text{MgSO}_4$  and the whole mixture was filtered through celite<sup>®</sup> which was washed through with  $\text{Et}_2\text{O}$ . The solvent was removed *in vacuo* and the crude product was purified by column chromatography (0 – 20 %  $\text{CH}_2\text{Cl}_2$  in petroleum ether) to give *N*-cyclopropyl-2,4,6-trimethylaniline **160** (30 mg, 45 %) as a brown oil.

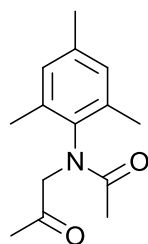
$\nu_{\max}$  (neat) 2918, 1485, 1255, 1014, 852, 610  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.81 (2H, s, 2 x CH, Ph), 3.32 (1H, br s, NH), 2.52 – 2.62 (1H, m, CH), 2.26 (6H, s, 2 x  $\text{CH}_3$ ), 2.23 (3H, s,  $\text{CH}_3$ ), 0.59 – 0.67 (2H, m,  $\text{CH}_2$ ), 0.44 – 0.53 (2H, m,  $\text{CH}_2$ ) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 143 (C, Ph), 130.3 ( $\text{CH}_3\text{C}$ , Ph), 129.4 (2 x  $\text{CH}_3\text{C}$ , Ph), 128.2 (2 x CH, Ph), 30.2 (CH), 20.5 ( $\text{CH}_3$ ), 19.21 (2 x  $\text{CH}_3$ ), 8.84 (2 x  $\text{CH}_2$ ), ppm; MS ( $\text{ES}^+$ )  $m/z$  176 [ $\text{MH}^+$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{12}\text{H}_{18}\text{N}$  [ $\text{MH}^+$ ] 176.1443; found 176.1434.

### ***N*-(1-Ethoxycyclopropyl)-2,4,6-trimethylaniline 161**



A solution of 2-methylenecyclopropylamine derivative **114** (100 mg, 0.58 mmol) in EtOH (5 mL) was heated to reflux for 5 h. The solution was cooled to room temperature, concentrated *in vacuo* and the crude product purified by column chromatography (0 – 100 % EtOAc in petroleum ether) to afford *N*-(1-ethoxycyclopropyl)-2,4,6-trimethylaniline **161** (76 mg, 60 %) as a brown oil.

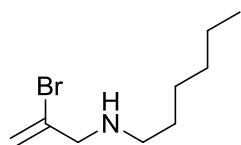
$\nu_{\max}$  (neat) 2919, 1484, 1308, 1222, 1063, 852  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.78 (2H, s, 2 x CH, Ph), 4.11 (1H, br s, NH), 3.67 (2H, q,  $J$  = 7.2 Hz,  $\text{CH}_2\text{CH}_3$ ), 2.26 (6H, s, 2 x  $\text{CH}_3$ ), 2.21 (3H, s,  $\text{CH}_3$ ), 1.16 (3H, t,  $J$  = 7.2 Hz,  $\text{CH}_2\text{CH}_3$ ), 1.06 – 1.01 (2H, m,  $\text{CH}_2$ ), 0.77 – 0.72 (2H, m,  $\text{CH}_2$ ) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 139.3 (NC, Ph), 129.6 ( $\text{CH}_3\text{C}$ , Ph), 128.9 (2 x CH, Ph), 127.6 (2 x  $\text{CH}_3\text{C}$ , Ph), 71.2 (NCO), 60.4 ( $\text{OCH}_2$ ), 19.8 ( $\text{CCH}_3$ ), 18.8 (2 x  $\text{CCH}_3$ ), 15.7 (2 x  $\text{CH}_2$ ), 14.8 ( $\text{CH}_2\text{CH}_3$ ) ppm; MS ( $\text{ES}^+$ )  $m/z$  220 [ $\text{MH}^+$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{14}\text{H}_{22}\text{NO}$  [ $\text{MH}^+$ ] 220.1696; found 220.1695.

***N*-(2-Oxopropyl)-*N*-(2,4,6-trimethylphenyl)acetamide **164****

To a mixture of  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (25.9 mg, 0.025 mmol), triphenylphosphine (13.9 mg, 0.05 mmol) and 2-methyldiene-1-(2,4,6-trimethylphenyl)aziridine **114** (129 mg, 0.75 mmol) in THF (1 mL) in a sealed tube was added acetic acid (28  $\mu\text{L}$ , 0.5 mmol).

The tube was sealed and heated at 100 °C for 16 h before cooling to room temperature. The reaction mixture was diluted with EtOAc and filtered through celite before being concentrated under vacuum. The crude product was purified by column chromatography (10 – 100 % EtOAc in PE) to give *N*-(2-oxopropyl)-*N*-(2,4,6-trimethylphenyl)acetamide **164** (52 mg, 30 %) as a dark orange oil.

$\nu_{\text{max}}$  (neat) 3310, 2924, 1736, 1638, 1377, 1172, 731  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.25 (2H, s, 2 x CH, Ph), 4.48 (2H, s,  $\text{CH}_2$ ), 2.61 (3H, s,  $\text{CCH}_3$ ), 2.61 (3H, s,  $\text{CCH}_3$ ), 2.54 (3H, s,  $\text{NC(O)CH}_3$ ), 2.12 (2H, s,  $\text{C(O)CH}_3$ ) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 200.8 (NCO), 171.0 (CO), 138.1 (NC, Ph), 137.6 ( $\text{CH}_3\text{C}$ , Ph), 135.3 (2 x  $\text{CH}_3\text{C}$ , Ph), 129.2 (2 x CH, Ph), 58.0 ( $\text{CH}_2$ ), 27.8 ( $\text{C(O)CH}_3$ ), 20.2 ( $\text{NC(O)CH}_3$  and  $\text{CCH}_3$ ), 17.5 (2 x  $\text{CCH}_3$ ) ppm; MS ( $\text{ES}^+$ )  $m/z$  234 [ $\text{MH}^+$ ]; HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{14}\text{H}_{19}\text{NO}_2\text{Na}$  [ $\text{MNa}^+$ ] 256.1308; found 256.1310.

***N*-(2-Bromoprop-2-en-1-yl)hexan-1-amine **170****

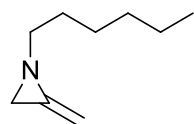
To a stirred suspension of  $\text{K}_2\text{CO}_3$  (6.3 g, 45.6 mmol) in THF (80 mL) was added hexylamine (5.4 mL, 38.0 mmol) and 2,3-dibromopropene **102** (7.4 mL, 76.0 mmol). The reaction

mixture was stirred at reflux for 16 h, allowed to cool and then partitioned

between 10 % NaOH solution (160 mL) and Et<sub>2</sub>O (160 mL). The organic phase was washed with H<sub>2</sub>O (160 mL), brine (160 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (1 % Et<sub>3</sub>N and 10 % EtOAc in petroleum ether) afforded *N*-(2-bromoprop-2-en-1-yl)hexan-1-amine **170** (8.0 g, 95 %) as a yellow oil.

$\nu_{\text{max}}$  (neat) 2925, 2855, 1626, 1458, 889 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 5.78 (1H, s, =CHH), 5.55 (1H, s, =CHH), 3.46 (2H, s, BrCCH<sub>2</sub>), 2.54 (2H, t, *J* = 7.17 Hz, NHCH<sub>2</sub>), 1.85 (1H, br s, NH), 1.55 – 1.44 (2H, m, CH<sub>2</sub>), 1.38 – 1.23 (6H, m, 3 x CH<sub>2</sub>), 0.89 (3H, t, *J* = 6.87 Hz, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 133.5 (CBr), 117.6 (=CH<sub>2</sub>), 57.4 (BrCCH<sub>2</sub>), 47.8 (NHCH<sub>2</sub>), 31.7 (CH<sub>2</sub>), 29.8 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>), 14.1 (CH<sub>3</sub>) ppm; MS (ES<sup>+</sup>) *m/z* 222 [MH<sup>+</sup>, <sup>81</sup>Br], 220 [MH<sup>+</sup>, <sup>79</sup>Br]; HRMS (ES<sup>+</sup>) calcd for C<sub>9</sub>H<sub>19</sub>BrN [MH<sup>+</sup>, <sup>81</sup>Br]: 222.0675; found: 222.0680; calcd for C<sub>9</sub>H<sub>19</sub>BrN [MH<sup>+</sup>, <sup>79</sup>Br]: 220.0695; found: 220.0700.

### 1-Hexyl-2-methylideneaziridine **171**

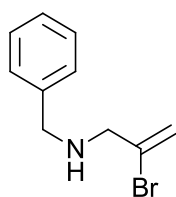


Following General Method 1, iron(III) nitrate nonahydrate, sodium (517 mg, 18.0 mmol) and *N*-(2-bromoprop-2-en-1-yl)hexan-1-amine **170** (2.0 g, 9.0 mmol) were reacted in ammonia (35 mL) at -33 °C for 3 h. Following work-up 1, purification by bulb-to-bulb distillation (90 °C, 0.5 mbar) afforded 1-hexyl-2-methylideneaziridine **171** (660 mg, 52 %) as a colourless oil.

$\nu_{\text{max}}$  (neat) 2928, 2857, 1764, 1458, 1181, 923, 815 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.72 (1H, s, =CHH), 4.66 (1H, s, =CHH), 2.48 (2H, t, *J* = 7.17 Hz,

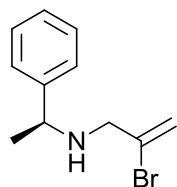
NCH<sub>2</sub>CH<sub>2</sub>), 2.03 (2H, s, CH<sub>2</sub>C), 1.61 (2H, m, CH<sub>2</sub>), 1.43-1.27 (m, 6H, 3 x CH<sub>2</sub>), 0.89 (3H, t, *J* = 6.87 Hz, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 137.5 (C=CH<sub>2</sub>), 82.5 (=CH<sub>2</sub>), 59.7 (CH<sub>2</sub>), 31.7 (CH<sub>2</sub>), 30.6 (=CCH<sub>2</sub>), 29.8 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>), 14.0 (CH<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* 140 [MH<sup>+</sup>]; HRMS (ES<sup>+</sup>) calcd for C<sub>9</sub>H<sub>18</sub>N [MH<sup>+</sup>] 140.1434; found 140.1440.

### ***N*-Benzyl-2-bromoprop-2-en-1-amine **174****<sup>145</sup>



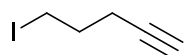
To a stirred suspension of K<sub>2</sub>CO<sub>3</sub> (7.1 g, 51.1 mmol) in THF (125 mL) was added benzylamine (10.2 mL, 92.54 mmol) and 2,3-dibromopropene **102** (6 mL, 46.45 mmol). The reaction mixture was stirred at room temperature for 18 h and then partitioned between 10 % NaOH solution (200 mL) and Et<sub>2</sub>O (200 mL). The organic phase was washed with H<sub>2</sub>O (200 mL), brine (200 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (1 % Et<sub>3</sub>N and 10 % EtOAc in petroleum ether) afforded *N*-benzyl-2-bromoprop-2-en-1-amine **174** (10.50 g, 100 %) as a pale, yellow oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.29 - 7.13 (5H, m, 5 x CH, Ph), 5.71 (1H, d, *J* = 1.7 Hz, =CHH), 5.52 (1H, d, *J* = 1.7 Hz, =CHH), 3.65 (2H, s, PhCH<sub>2</sub>), 3.38 (2H, s, NHCH<sub>2</sub>), 1.73 (1H, br s, NH) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 139.7 (C, Ph), 133.5 (CBr), 128.5 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.2 (CH, Ph), 118.0 (=CH<sub>2</sub>), 56.6 (NHCH<sub>2</sub>), 51.5 (PhCH<sub>2</sub>) ppm; MS (ES<sup>+</sup>) *m/z* 228 [MH<sup>+</sup>, <sup>81</sup>Br], 226 [MH<sup>+</sup>, <sup>79</sup>Br]. Data is in accordance with literature values.<sup>145</sup>

**2-Bromo-*N*-[(1*S*)-1-phenylethyl]prop-2-en-1-amine **183**<sup>44</sup>**

To a stirred suspension of  $K_2CO_3$  (5.89 g, 42.61 mmol) in THF (100 mL) was added (*S*)-(-)-1-phenylamine **182** (10 mL, 77.20 mmol) and 2,3-dibromopropene (5 mL, 38.71 mmol). The reaction mixture was stirred at room temperature for 18 h and then partitioned between 10 % NaOH solution (200 mL) and  $Et_2O$  (200 mL). The organic phase was washed with  $H_2O$  (200 mL), brine (200 mL), dried over  $MgSO_4$ , filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (1 %  $Et_3N$  and 5 - 10 % EtOAc in petroleum ether) afforded 2-bromo-*N*-[(*S*)-1-phenylethyl]prop-2-en-1-amine **183** (7.86 g, 84 %) as a pale, yellow oil.

$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  = 7.13-7.31 (5H, m, 5 x CH, Ph), 5.60 (1H, d,  $J$  = 1.5 Hz, =CHH), 5.48 (1H, d,  $J$  = 1.5 Hz, =CHH), 3.73 (1H, q,  $J$  = 6.7 Hz, CH), 3.29 (1H, d,  $J$  = 15.4 Hz, CHH), 3.17 (1H, d,  $J$  = 15.4 Hz, CHH), 1.72 (1H, br s, NH), 1.29 (3H, d,  $J$  = 6.7 Hz,  $CH_3$ ) ppm;  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  = 144.2 (C, Ph), 133.2 (CBr), 127.9 (2 x CH, Ph), 126.5 (2 x CH, Ph), 126.2 (CH, Ph), 117.2 (=CH<sub>2</sub>), 55.0 (CH), 54.5 (CH<sub>2</sub>), 23.7 (CH<sub>3</sub>) ppm; MS ( $ES^+$ )  $m/z$  242 [ $MH^+$ ,  $^{81}Br$ ], 240 [ $MH^+$ ,  $^{79}Br$ ]. Data is in accordance with literature values.<sup>44</sup>

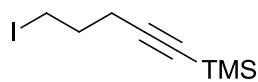
**5-iodopent-1-yne **210**<sup>139</sup>**

To a solution of NaI (12.4 g, 82.88 mmol) in butanone (60 mL) was added 5-chloropent-1-yne **209** (1.77 mL, 16.58 mmol) whereupon the mixture was heated to reflux for 18 h. After cooling, the mixture was filtered; the filtrate was diluted with  $H_2O$  (60 mL) and extracted with  $Et_2O$  (2 x 60 mL). The combined organic extracts were washed with  $H_2O$  (60 mL), brine (60 mL), dried

over  $\text{MgSO}_4$ , filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (100 % *iso*-hexane) to give 5-iodopent-1-yne **210** (1.46 g, 45 %) as a pale yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.31 (2H, t,  $J$  = 6.83 Hz,  $\text{CH}_2$ ), 2.33 (2H, dt,  $J$  = 2.69 Hz,  $J$  = 6.83 Hz,  $\text{CH}_2$ ), 2.04 – 1.96 (3H, m, CH,  $\text{CH}_2$ ) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 82.3 (C), 69.4 (CH), 31.9 ( $\text{CH}_2$ ), 19.5 ( $\text{CH}_2$ ), 4.8 ( $\text{CH}_2$ ) ppm. Data is in accordance with literature values.<sup>139</sup>

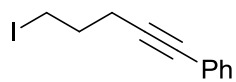
#### 5-Iodo-1-trimethylsilylpent-1-yne **212**<sup>140</sup>



To a solution of 5-chloropent-1-yne **211** (1.77 mL, 16.6 mmol) in THF (20 mL) at  $-78\text{ }^\circ\text{C}$  was added *n*-butyllithium (1.6 M in hexanes, 12.5 mL, 22.2 mmol) dropwise. After 10 min TMS-Cl (3.25 mL, 25.6 mmol) was added dropwise whereupon the mixture was allowed to slowly warm to room temperature. The mixture was stirred for 16 h before being poured into water (15 mL). The layers were separated and the aqueous phase extracted with EtOAc (20 mL) and the combined organic phases were washed with brine (40 mL), dried over  $\text{MgSO}_4$ , filtered and the solvent removed *in vacuo*. A solution of NaI (6.4 g, 42.6 mL) in acetone (35 mL) was added to the crude mixture which was heated to reflux for 24 h. After cooling, the reaction mixture was diluted with petroleum ether (30 mL), washed with  $\text{H}_2\text{O}$  (60 mL), dried over  $\text{MgSO}_4$ , filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (100 % *iso*-hexane) to give 5-iodo-1-trimethylsilylpent-1-yne **212** (2.90 g, 65 %) as a colourless oil.

$\nu_{\max}$  (neat) 2957, 2175, 1425, 1248, 1167, 1020, 836  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.28 (2H, t,  $J$  = 7.16 Hz,  $\text{CH}_2$ ), 2.35 (2H, t,  $J$  = 7.16 Hz,  $\text{CH}_2$ ), 2.04 – 1.94 (2H, m,  $\text{CH}_2$ ), 0.14 (9H, s, 3 x  $\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 104.7 (TMS-C), 85.8 (C- $\text{CH}_2$ ), 32.0 ( $\text{CH}_2$ ), 20.8 ( $\text{CH}_2$ ), 5.0 ( $\text{CH}_2$ ), 0.01 (3 x  $\text{CH}_3$ ) ppm. Data is in accordance with literature values.<sup>140</sup>

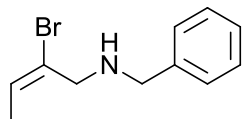
#### (5-iodopent-1-yn-1-yl)benzene **214**<sup>141</sup>



To a solution of phenylacetylene (3.6 mL, 32.8 mmol) in THF (35 mL) at  $-78^\circ\text{C}$  was added dropwise *n*-BuLi (1.6 M in hexanes, 20.0 mL, 32.0 mmol). The mixture was stirred at  $-78^\circ\text{C}$  for 1 h whereupon the mixture was added *via* canula to a stirred solution of 1,3-diiodopropane **213** (2.75 mL, 24.8 mmol) in THF (4 mL) at  $0^\circ\text{C}$ . The resulting mixture was heated at reflux for 3h, cooled and carefully hydrolysed with  $\text{H}_2\text{O}$  (20 mL). The mixture was extracted with  $\text{Et}_2\text{O}$  (3 x 100 mL) and the combined organic fractions washed with brine (200 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (100% *iso*-hexane) to afford (5-iodopent-1-yn-1-yl)benzene **214** (3.01 g, 45 %) as a pale, yellow oil.

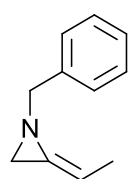
$\nu_{\max}$  (neat) 3052, 2901, 1597, 1489, 1425, 1219, 1167, 913  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.41 – 7.36 (2H, m, 2 x CH, Ph), 7.30 – 7.25 (3H, m, 3 x CH, Ph), 3.35 (2H, t,  $J$  = 6.72 Hz,  $\text{CH}_2$ ), 2.55 (2H, t,  $J$  = 6.72 Hz,  $\text{CH}_2$ ), 2.08 (2H, tt,  $J$  = 6.72 Hz,  $J$  = 6.72 Hz,  $\text{CH}_2$ ) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 131.6 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.9 (CH, Ph), 123.7 (C), 88.1 (C), 81.7 (C), 32.3 ( $\text{CH}_2$ ), 20.6 ( $\text{CH}_2$ ), 5.5 ( $\text{CH}_2$ ) ppm. Data is in accordance with literature values.<sup>141</sup>



**(2E)-N-Benzyl-2-bromobut-2-en-1-amine 215**<sup>39</sup>

To a stirred solution of (*E*)-2-bromobut-2-en-1-ol **129** (8.3 g, 55.0 mmol) in THF (120 mL) at  $-30\text{ }^{\circ}\text{C}$  was added triethylamine (19 mL, 131.6 mmol). Methanesulfonyl chloride (4.5 mL, 58.9 mmol) was added to the mixture followed by benzylamine (12.2 mL, 111.7 mmol). The mixture was heated to reflux for 18 h and then cooled to room temperature. The mixture was partitioned between Et<sub>2</sub>O (200 mL) and 10 % NaOH solution (200 mL). The organic phase was washed with 10 % NaOH solution (200 mL), brine (200 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give the crude product. Purification by column chromatography (10 % EtOAc in petroleum ether) afforded (*E*)-*N*-benzyl-2-bromobut-2-en-1-amine **215** (9.24 g, 70 %) as an orange oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.41 – 7.20 (5H, m, 5 x CH, Ph), 6.13 (1H, q, *J* = 7.5 Hz, =CH), 3.72 (2H, s, CH<sub>2</sub>Ph), 3.51 (2H, s, CH<sub>2</sub>), 2.16 (1H, br s, NH), 1.60 (3H, d, *J* = 7.5 Hz, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  138.8 (C, Ph), 129.2 (=CH), 128.2 (2 x CH, Ph), 127.8 (2 x CH, Ph), 126.5 (CH, Ph), 124.4 (CBr), 50.6 (CH<sub>2</sub>CBr), 49.4 (PhCH<sub>2</sub>), 14.5 (CH<sub>3</sub>) ppm; MS (ES<sup>+</sup>) *m/z* 242 [MH<sup>+</sup>, <sup>81</sup>Br], 240 [MH<sup>+</sup>, <sup>79</sup>Br]. Data is in accordance with literature values.<sup>39</sup>

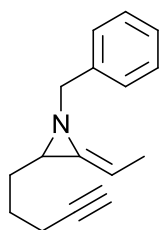
**(2Z)-1-Benzyl-2-ethylideneaziridine 216**<sup>39</sup>

Following General Method 1, iron(III) nitrate nonahydrate, sodium (960 mg, 41.7 mmol) and (*E*)-*N*-benzyl-2-bromobut-2-en-1-amine **215** (4.0 g, 16.6 mmol) were reacted in ammonia (80 mL) at  $-78\text{ }^{\circ}\text{C}$

for 1 h. Following work-up 1, purification by bulb-to-bulb distillation afforded (2Z)-1-benzyl-2-ethylideneaziridine **216** (1.6 g, 61 %) as a colourless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.38 – 7.22 (5H, m, 5 x CH, Ph), 5.09 (1H, q,  $J$  = 6.63 Hz, CH), 3.70 (2H, br s,  $\text{PhCH}_2$ ), 2.08 (2H, br s,  $\text{CH}_2$ ), 1.68 (3H, d,  $J$  = 6.63 Hz,  $\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 138.5 (C, Ph), 129.9 (C=CH), 128.4 (2 x CH, Ph), 128.2 (2 x CH, Ph), 127.3 (CH, Ph), 95.2 (CH), 62.1 ( $\text{CH}_2$ ), 31.3 ( $\text{CH}_2$ ), 13.4 ( $\text{CH}_3$ ) ppm; MS ( $\text{ES}^+$ )  $m/z$  160 [ $\text{MH}^+$ ]. Data is in accordance with literature values.<sup>39</sup>

#### (2Z)-1-benzyl-2-ethylidene-3-(pent-4-yn-1-yl)aziridine **218**



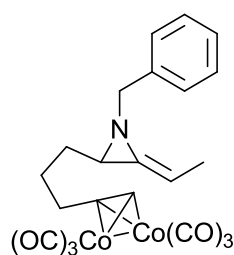
To a solution of (2Z)-1-benzyl-2-ethylideneaziridine **216** (1.0 g, 6.3 mmol) in THF (50 mL) at  $-78^\circ\text{C}$  was added TMEDA (1.1 mL, 7.3 mmol) followed by *sec*-BuLi (1.4 M solution in cyclohexane, 9.4 mL, 7.5 mmol). The mixture was stirred at  $-78^\circ\text{C}$  for 6 h whereupon the reaction was quenched with 5-iodo-1-trimethylsilylpent-1-yne **212** (2.0 g, 7.5 mmol) in THF (2 mL). The reaction was allowed to warm up to room temperature and then stirred for 16 h. Water (30 mL) was carefully added and the mixture stirred for 2 min before the layers were separated. The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3 x 30 mL), and the combined organic phases were washed with brine (30 mL) and concentrated *in vacuo* to afford (Z)-1-benzyl-2-ethylidene-3-(5-(trimethylsilyl)pent-4-ynyl)aziridine **217**.

To a solution of (Z)-1-benzyl-2-ethylidene-3-(5-(trimethylsilyl)pent-4-ynyl)aziridine **217** (2.06 g, 6.9 mmol) in THF (60 mL) at  $0^\circ\text{C}$  was added TBAF (1 M in THF, 8.6 mL, 8.6 mmol). The mixture was stirred at  $0^\circ\text{C}$  for 2 h, whereupon it

was quenched with sat.  $\text{NH}_4\text{Cl}$  solution (30 mL). The aqueous phase was extracted twice with  $\text{Et}_2\text{O}$  (30 mL) and the combined organic phases were washed with brine (60 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (10 % EtOAc in petroleum ether) to afford (2Z)-1-benzyl-2-ethylidene-3-(pent-4-yn-1-yl)aziridine **218** (1.46 g, 96 %) as a pale, yellow oil.

$\nu_{\text{max}}$  (neat) 3297, 2929, 1779, 1725, 1453, 1127, 736  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.37 – 7.26 (5H, m, 5 x CH, Ph), 5.11 (1H, q,  $J$  = 6.74 Hz, =CH), 4.19 (1H, d,  $J$  = 13.25 Hz, NCHH), 3.27 (1H, d,  $J$  = 13.25 Hz, NCHH), 2.09 (2H, td,  $J$  = 7.09 Hz,  $J$  = 2.77 Hz,  $\text{CH}_2\text{C}$ ), 1.99 (1H, br t,  $J$  = 5.85 Hz,  $\text{CH}_2\text{CHN}$ ), 1.91 (1H, t,  $J$  = 2.77 Hz, CCH), 1.71 (3H, d,  $J$  = 6.74 Hz,  $\text{CH}_3$ ), 1.61 – 1.54 (2H, m,  $\text{CH}_2$ ), 1.51 – 1.42 (2H, m,  $\text{CH}_2$ ) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 138.6 (C, Ph), 135.2 (C=CH), 128.5 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.3 (CH, Ph), 94.9 (C=CH), 84.2 ( $\text{CH}_2\text{C}$ ), 68.4 (CCH), 61.7 ( $\text{NCH}_2$ ), 42.5 (NCH), 31.1 ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ), 18.1 ( $\text{CH}_2\text{C}$ ), 13.3 ( $\text{CH}_3$ ) ppm; MS ( $\text{ES}^+$ )  $m/z$  226 [ $\text{MH}^+$ ], HRMS ( $\text{ES}^+$ ) calcd for  $\text{C}_{16}\text{H}_{20}\text{N}$  [ $\text{MH}^+$ ] 226.1590; found 226.1593.

#### (2Z)-1-Benzyl-2-ethylidene-3-(pent-4-yn-1-yl)aziridine/cobalt complex **220**



To a solution of (2Z)-1-benzyl-2-ethylidene-3-(pent-4-yn-1-yl)aziridine **218** (65 mg, 0.28 mmol) in toluene (1 mL) was added dicobalt hexacarbonyl (99 mg, 0.29 mmol). The mixture was stirred at room temperature for 16 h whereupon it is filtered through celite<sup>®</sup> and washed through with EtOAc. The solvent was removed *in vacuo* to give the crude product. Purification by column

chromatography (0-10 % EtOAc in petroleum ether) and then filtration through florisil<sup>®</sup> afforded (2Z)-1-benzyl-2-ethylidene-3-(pent-4-yn-1-yl)aziridine/cobalt complex **220** (57 mg, 40 %) as a red oil.

$\nu_{\text{max}}$  (neat) 2921, 2090, 1993, 1443, 1128, 737  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.37 – 7.27 (5H, m, 5 x CH, Ph), 5.93 (1H, s, CCH), 5.10 (2H, q,  $J$  = 6.8 Hz, C=CH), 4.16 (1H, d,  $J$  = 13.3 Hz, CHH), 3.32 (1H, d,  $J$  = 13.3 Hz, CHH), 2.78 (2H, br t,  $\text{CH}_2\text{C}$ ), 2.01 (1H, br t,  $\text{CH}_2\text{CH}$ ), 1.70 (3H, d,  $J$  = 6.8 Hz,  $\text{CH}_3$ ), 1.68 – 1.63 (2H, m,  $\text{CH}_2$ ), 1.62 – 1.55 (2H, m,  $\text{CH}_2$ ) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 138.5 (C, Ph), 135.1 (C=CH), 128.5 (2 x CH, Ph), 128.4 (2 x CH, Ph), 127.3 (CH, Ph), 95.0 (C=CH), 73.3 (CCH), 61.7 ( $\text{NCH}_2$ ), 42.8 ( $\text{CH}_2\text{CH}$ ), 33.8 ( $\text{CCH}_2$ ), 31.7 ( $\text{CH}_2$ ), 29.48 ( $\text{CH}_2$ ), 13.2 ( $\text{CH}_3$ ) ppm. 6 x CO not visible. Due to stability in solution Mass spectrometry was not possible.

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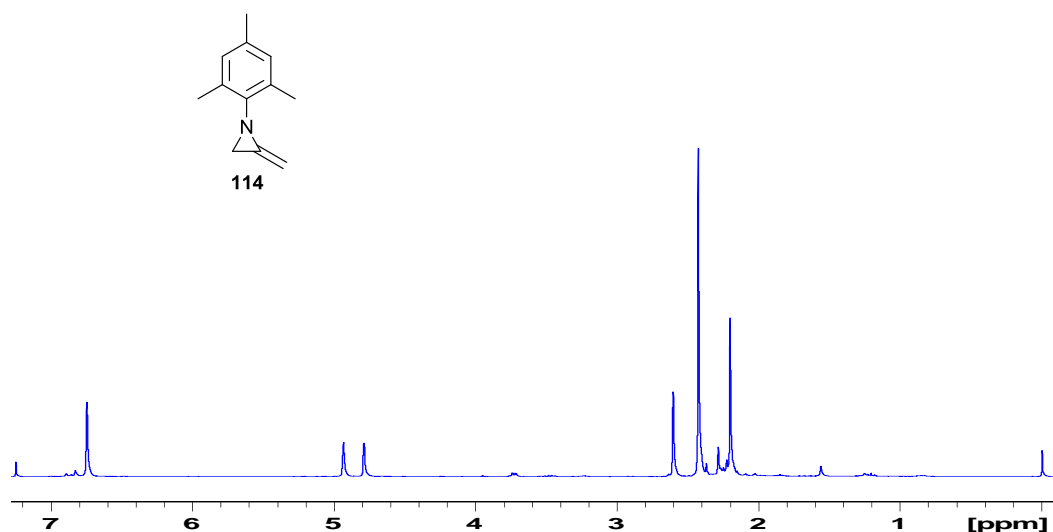
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# **Appendix**



1.  $^1\text{H}$  NMR Spectra of 114

## 2. Direct Competition Experiments – Full Data

Entry	X	Time (min)	Flask (mL)	Catalyst (mg)	Reaction 1	Reaction 2
					137/138 : 48 : 139 (%)	137/138 : 48 : 139 (%)
1	Br	30	—	—	0 : 92 : 8	17 : 56 : 27
2	Br	10	—	—	77 : tr : 22	9 : 54 : 37
3	I	10	—	—	0 : 96 : 4	24 : 20 : 56
4	I	10	100	—	tr : 70 : 30	12 : 47 : 41
5	I	10	50	—	0 : 94 : 6	6 : 55 : 39
6	I	10	50	2	24 : 38 : 38	13 : 49 : 38
7	I	10	50	10	7 : 73 : 20	13 : 66 : 21
8	I	10	50	15	tr : 90 : 10	8 : 70 : 22
9	I	20	50	10	tr : 59 : 41	0 : 100 : tr
10	Br	10	50	10	0 : 89 : 11	3 : 70 : 27

Table 1.7. Full data. tr = peak visible but too small to integrate.

Entry	Equiv. NaNH <sub>2</sub>	t (min)	T (°C)	138 : 48 : 139	
				140 : 142 : 144	
				Run 1	Run 2
1	2	10	−33	2 : 80 : 18	0 : 95 : 5
				38 : 12 : 50	0 : 86 : 14
2	1	10	−33	41 : 29 : 3	36 : 34 : 30
				1 : tr : tr	1 : tr : tr
3	2	5	−33	tr : 97 : 3	tr : 98 : 2
				tr : 87 : 13	tr : 93 : 7
4	2	10	−78	14 : 86 : tr	13 : 87 : tr
				55 : 45 : tr	53 : 47 : tr
5	2	30	−78	7 : 91 : 2	42 : 58 : tr
				57 : 43 : tr	100 : tr : 0
6	2	10	−78	10 : 86 : 4	35 : 65 : tr
				3 : 94 : 4	38 : 62 : tr

Table 1.9. Full data. tr = peak visible but too small to integrate.

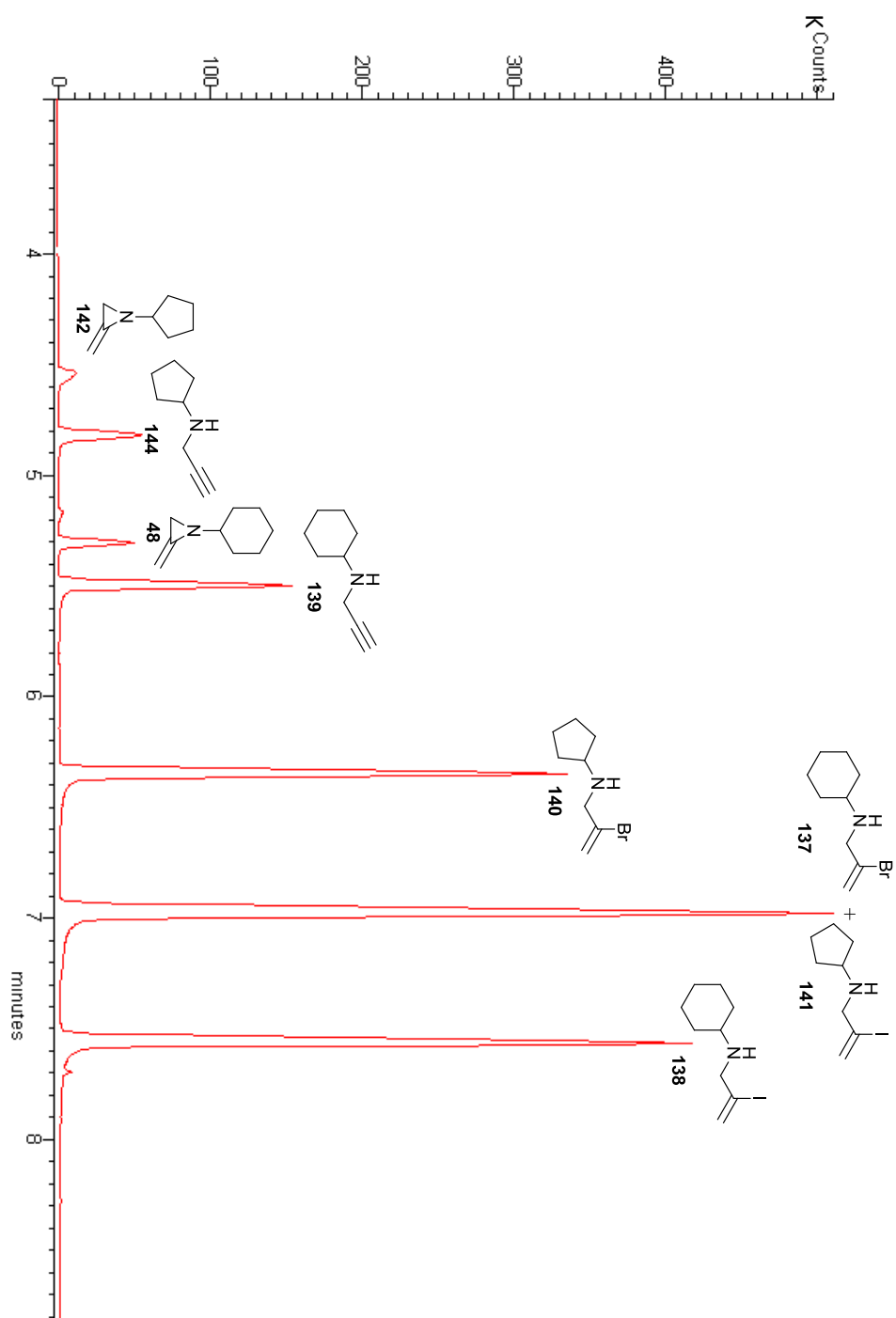
Run	138 (%)	48 (%)	139 (%)	141 (%)	142 (%)	144 (%)
1a	80	2	0	8	12	0
1b	26	74	tr	3	69	0
2a	88	10	2	95	5	tr
2b	87	10	3	93	5	2

Table 1.10. Full data. tr = peak visible but too small to integrate.

Run	137 (%)	48 (%)	139 (%)	140 (%)	142 (%)	144 (%)
1a	20	77	3	20	72	8
1b	40	55	5	50	45	5

Table 1.11. Full data

## 2. GC-MS Trace



### 3. Kinetic Study – Full Data

Full data from Graph 2.1

<b>t (s)</b>	<b>[114]</b>	<b>ln(1/[114])</b>
0	1	0
1800	0.8	0.223144
3600	0.6	0.510826
5400	0.5	0.693147
7200	0.35	1.049822
9000	0.3	1.203973
10800	0.2	1.609438
12600	0.15	1.89712
14400	0.1	2.302585
16200	0.05	2.995732

Full data from Graph 2.3.

<b>t (s)</b>	<b>336 K</b>	
	<b>[114]</b>	<b>ln(1/[114])</b>
0	1	0
1800	0.8	0.223144
3600	0.66	0.415515
5400	0.5	0.693147
7200	0.46	0.776529
9000	0.35	1.049822
10800	0.3	1.203973
12600	0.25	1.386294
14400	0.16	1.832581
16200	0.13	2.040221

18000	0.1	2.302585
19800	0.09	2.407946

t (s)	330	
	[114]	ln(1/[114])
0	1	0
1800	0.85	0.162519
3600	0.74	0.301105
5400	0.62	0.478036
7200	0.55	0.597837
9000	0.48	0.733969
10800	0.43	0.84397
12600	0.38	0.967584
14400	0.33	1.108663
16200	0.29	1.237874
18000	0.25	1.386294
19800	0.23	1.469676
21600	0.2	1.609438
23400	0.18	1.714798
25200	0.15	1.89712
27000	0.13	2.040221

t (s)	361 K	
	[114]	ln(1/[114])
0	1	0
900	0.37	0.994252
1800	0.08	2.525729
2700	0.02	3.912023
3600	0.01	4.60517

<b>t (s)</b>	<b>346 K</b>	
	<b>[114]</b>	<b>ln(1/[114])</b>
0	1	0
600	0.77	0.261365
1200	0.58	0.544727
1800	0.4	0.916291
2400	0.3	1.203973
3000	0.2	1.609438
3600	0.18	1.714798
4200	0.13	2.040221
4800	0.09	2.407946
5400	0.07	2.65926
6000	0.05	2.995732

<b>t (s)</b>	<b>342 K</b>	
	<b>[114]</b>	<b>ln(1/[114])</b>
0	1	0
1800	0.7	0.356675
3600	0.44	0.820981
5400	0.28	1.272966
7200	0.18	1.714798
9000	0.11	2.207275
10800	0.07	2.65926
12600	0.04	3.218876
14400	0.02	3.912023