UNIVERSITY OF SOUTHAMPTON

TRANSITION METAL MEDIATED SYNTHESIS OF HETEROCYCLES

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

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

DEPARTMENT OF CHEMISTRY

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UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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The work presented in this thesis illustrates the synthetic utility of transition metal chemistry through the synthesis of nitrogen and phosphorous heterocycles. A number of amino-dienes substituted with different aromatic groups were obtained from cinnamic acids and cyclised using a stoichiometric zirconium complex (Negishi's reagent) giving 3-benzyl pyrrolidines in high yield. The synthesis has also been developed on the solid-support. From Merrifield resin, the diene framework was synthesised in a combinatorial fashion, cyclised using Negishi's reagent and cleaved to give carbamate protected 3-benzyl pyrrolidines in good yield and high purity.

The synthesis of the 3-phenyl pyrrolidine pharmacophore has been developed. The optimum route to the hindered diene and enyne cyclisation precursors was *via* the radical bromination of α-methyl styrene and subsequent reaction with the appropriate amine source. Cyclisation with Negishi's reagent gave the 3-phenyl pyrrolidines in good yield and diastereoselectivity. Cyclisation of the diene using a catalytic ruthenium source (Grubbs' catalyst) gave the 3-phenyl pyrrole in moderate yield.

A novel approach to the synthesis of 6-membered phosphorous heterocycles has been explored. Insertion of lithium chloromethyltrimethylsilane into zirconacyclopentadienes followed by phosphorous metathesis yielded the air- and moisture-sensitive λ^3-phosphinines. These were subsequently protected and characterised as their Diels-Alder adducts. Insertion of lithium chloromethyltrimethylsilane into a zirconacyclopentane followed by phosphorous metathesis and hydrogen peroxide oxidation yielded a novel phosphinic acid.

ACKNOWLEDGEMENTS

Firstly, I would like to thank my supervisor Prof Richard J. Whitby for his support, faith and patience. I also thank him for giving the group the opportunity to go to Corfu for the XXth Organometallic Conference in July 2002 which was fantastic and for teaching us Black Jack as we waited for our flight home.

I thank the analytical support staff in MS (John Langley and Julie Herniman) and NMR (Joan Street and Neil Wells), both of whom, on many occasions, provided valuable data at very short notice.

I would like to thank those people both past and present who have had the pleasure and displeasure of having to share a building/floor/lab or fume cupboard with me. In particular, and in no particular order: Dr Don Macfarlane for advice and fire-extinguishing skills; Dr Steven 'Mr Garrison' Harrison for buffing your vac pump switch; Dr Gustav 'Papa G/The G-man/Gusto' Saluste for your renditions of Nessun Dorma; Dr David 'Gussett' Dossett for cleaning my teeth in Leeds and for the general sarcasm; Dr Sally 'Aunt Sally' Dixon for 70's rock; Dr David 'Norty-poohs/norty-kins/norts' Norton for your contributions to the lost art of taxidermy; Peter A. Wright for being both the Scottish Ambassador and Queen of the South; Emma Thomas, Kishore 'Ready, Steady' Reddy, David Pugh, Pam, Sofia, Thomas L, Linda Brown, Rowan Wilson, Simon C and Clare Kay for proof-reading and sharing my last days in 30:3003; Steven 'Toad' Downing and John 'Dossett mark II' Flemming for being both very different, but highly entertaining project students; Graham Burgess for the pound of mashed-up Dundee cake; The members of the Harrowven group, especially Drs Heather 'Heaatheer' Bourne and Stuart Flanagan; The members of the Richard Brown group, especially Drs John Keily, Rob Hughes, Alex Cecil, Geoff 'Psycho' Head and Steve 'Scoper' Kemp and to all the others from the 3rd floor in building 30 as you were there when it really counted...usually in the Staff Club, The Rhino, Kaos or Lennons. A special mention to Rohan, Dicko, Katie MacNamara ('s Band) and Ginger Jeff for providing the White Russians and combi-chem advice. Thank you Jamie for being Mavis, Tem for not crashing my car and Forcer for showing me the beauty of air-drums, pie sandwiches and Opa Loka IV. Thank you P.C. for the Milton March and reversing the polarity of the neutron flow and to Nathan for Van Halen at Reading and break dancing.

I thank Southampton University for a studentship and M.S.D. for financing the pyrrolidine chemistry. Thank you KH for teaching me to respect pyrophorics and AlH_3 for being key to the success of this thesis.

Thank you Paula Louise Eastman for helping me through the good times and the bad. I thank my mum, Jon, Caroline and Lucy for financial and emotional support.

Finally, I would like to dedicate this thesis to the memory of my father, Osmond William Hunter, 5th February 1938 - 19th July 1979.

Rupert Hunter
Southampton
29th March 2004

For Osmond

DESIDERATA

Go placidly amid the noise & haste, & remember what peace there may be in silence. As far as possible without surrender be on good terms with all persons. Speak your truth quietly & clearly; and listen to others, even the dull & ignorant; they too have their story.

Avoid loud & aggressive persons, they are vexations to the spirit. If you compare yourself with others, you may become vain & bitter; for always there will be greater & lesser persons than yourself. Enjoy your achievements as well as your plans.

Keep interested in your own career, however humble; it is a real possession in the changing fortunes of time. Exercise caution in your business affairs; for the world is full of trickery. But let this not blind you to what virtue there is; many persons strive for high ideals; and everywhere life is full of heroism.

Be yourself. Especially, do not feign affection. Neither be cynical about love; for in the face of all aridity & disenchantment it is perennial as the grass.

Take kindly the counsel of the years, gracefully surrendering the things of youth. Nurture strength of spirit to shield you in sudden misfortune. But do not distress yourself with imaginings. Many fears are born of fatigue & loneliness. Beyond a wholesome discipline, be gentle with yourself.

You are a child of the universe, no less than the trees & the stars; you have a right to be here. And whether or not it is clear to you, no doubt the universe is unfolding as it should.

Therefore be at peace with God, whatever you conceive Him to be, and whatever your labors & aspirations, in the noisy confusion of life keep peace with your soul.

With all its sham, drudgery & broken dreams, it is still a beautiful world. Be careful. Strive to be happy.

Max Ehrmann

ABBREVIATIONS

The following abbreviations have been used within this thesis.

ACE-Cl	α-chloroethylchloroformate
aq	aqueous
Ar	aryl
b.p.	boiling point
Bn	benzyl
BOC	*tert*-butyloxycarbonyl
Bu	butyl
^{n}BuLi	butyl lithium
^{s}BuLi	*sec*-butyl lithium
Cbz	benzyloxycarbonyl
CI	chemical ionisation mass spectrometry
conc.	concentrated
Cp	cyclopentadienyl
COSY	correlation spectroscopy
DBE	dibutylether
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEE	diethylether
DEPT	distortionless enhancement by polarisation transfer
DIBAL-H	di-*iso*-butylaluminium hydride
DIC	di-*iso*-propylcarbodiimide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMPU	dimethylpropyleneurea
EI	electron impact mass spectrometry
eq	equivalent(s)
Et	ethyl
EtOH	ethanol
GC	gas chromatography
Hex	hexyl
HOBt	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
hr	hour(s)

HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
lit.	literature
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
Me	methyl
MeCN	acetonitrile
MeOH	methanol
min	minute(s)
m.p.	melting point
MS	mass spectrometry
m/z	mass to charge ratio
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMP	*N*-Methyl pyrrolidinone
NMR	nuclear magnetic resonance
Oct	octyl
Ph	phenyl
Pr	propyl
Rf	retention factor
r.t.	room temperature
SAR	structure activity relationship
sat.	saturated
soln.	solution
temp	temperature
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMP	tetramethylpiperidine
TMS	trimethylsilyl
UV	ultraviolet

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CHAPTER 1

THE SYNTHESIS AND ELABORATION OF ZIRCONACYCLES

1. The Synthesis and Elaboration of Zirconacycles

1.1. Introduction

Traditionally, the formation of C-C bonds by organometallic species has been achieved by the reaction of electrophiles with metallic reagents such as organo-lithiums, -magnesiums and -zincs. The chemistry of organozirconium complexes is dominated by the preference of the metal to form stable 16 electron complexes, rather than the "normal" tendency of transition metals to form 18 electron complexes. This enables zirconium complexes to undergo other reaction pathways such as carbometallation and migratory insertion, giving rise to a range of useful synthetic methodologies to be available[1-3]. Indeed, since the introduction of hydrozirconation by Schwartz in 1974[2], organozirconium chemistry has played an increasing role in contemporary organic synthesis and has been the subject of several reviews[1,4-8]. From a practical perspective, a variety of zirconium sources are commercially available and their relatively low cost, toxicity and easy disposability makes their use attractive for catalytic and stoichiometric applications.

Probably the most prolific area of stoichiometric organozirconium chemistry is the synthesis of cyclic zirconium complexes or "zirconacycles". A wide range of such complexes are easily available *via* facile and well-documented protocols. Representative examples are shown in figure 1.1.

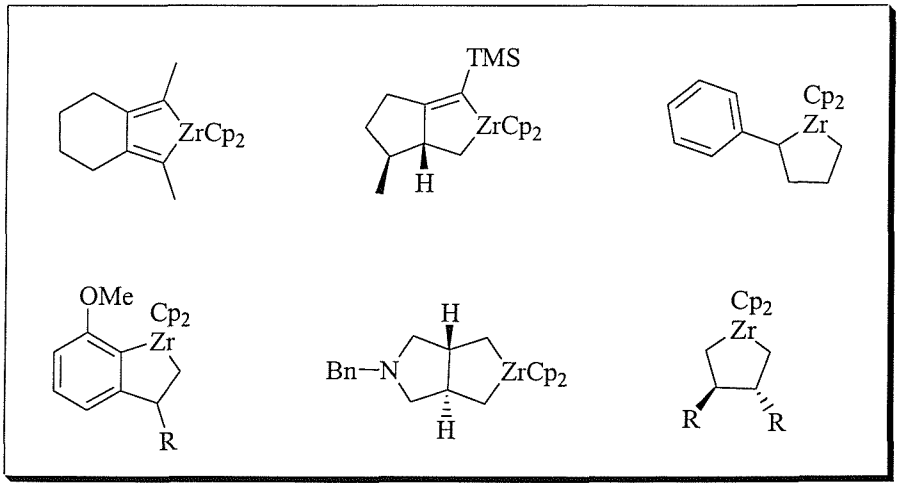


Figure 1.1 - Typical zirconacycles

The main drawback with these reagents is the low reactivity of the C-Zr bonds towards conventional electrophiles such as alkyl halides and carbonyl compounds. Further elaboration of zirconacycles is necessary if their full synthetic potential is to be realised. The aim of this project was to synthesise nitrogen and phosphorus heterocycles *via* the zirconium mediated cyclisation of alkenes and alkynes.

This chapter will briefly summarise the preparation of zirconacycles before reviewing the successful elaboration methods which have overcome the problems associated with low reactivity to electrophiles.

1.2. Zirconacycle Synthesis

Zirconacycles can be formed by the reductive coupling of unsaturated molecules by the low valent zirconocene species "Cp_2Zr^{II}". (Figure 1.2.) The majority of systems studied are derived from the co-cyclisation of alkenes and alkynes. Early examples focused on zirconacyclopentadienes[9-11] (Equation 1), but now also include *inter*[12]- and *intra*-molecular[13,14] (Equation 2 & 3) alkene cyclisation and also enyne cross-coupling[15] (Equation 4).

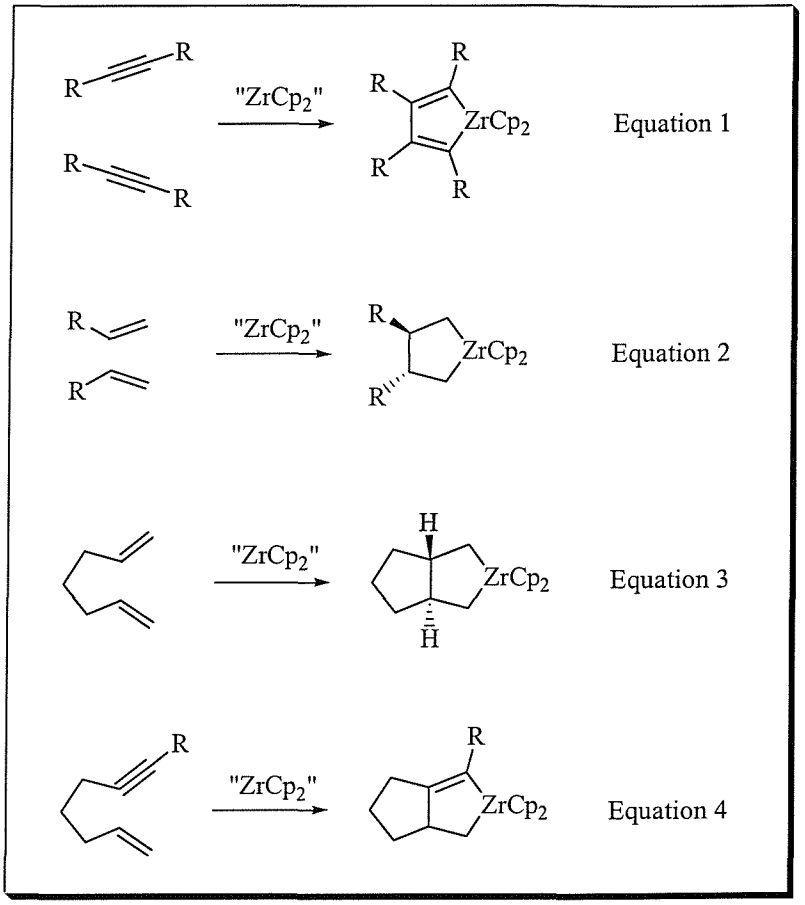


Figure 1.2 - Zirconacycle formation

Zirconocene (Cp_2Zr) is an unstable 14 electron species which can be formed by the two electron reduction of zirconocene dichloride (Cp_2ZrCl_2). A number of reduction methods have been reported including the use of alkali metals, activated magnesium powder[16], Mg/Hg amalgams and electrochemical means[17,18]. The zirconocene fragment **1** contains both a vacant, low energy orbital (σ-symmetry) and a filled non-bonding orbital (π-symmetry)[19]. This allows **1** to interact with unsaturated molecules (σ-donor and π-acceptors) such as an alkene to form the zirconacene-η^2-alkene complex **2**. The bonding in **2** can be represented as a hybrid of canonical forms **2a** (a zirconocene alkene complex) and **2b** (a zirconacyclopropane). X-ray and NMR data suggests the latter to be a more accurate representation[20-22]. Canonical form **2b** has both a vacant orbital and two strained Zr-C bonds. These allow the concerted insertion of a second unsaturated molecule such as an alkene to form zirconacycle **3**. (Figure 1.3.)

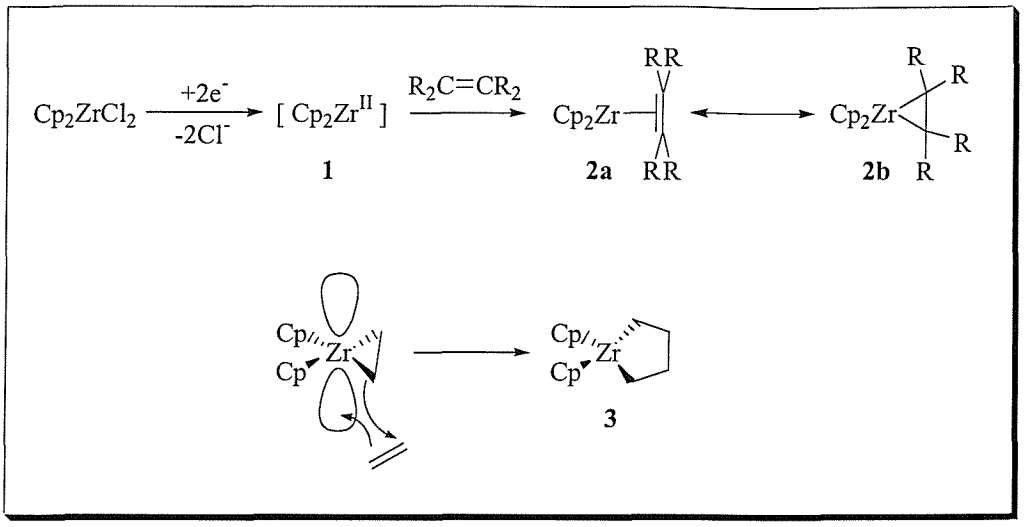


Figure 1.3 - Formation of zirconocene alkene complexes

The original methods for generating zirconocene have been surpassed in terms of convenience and reproducibility by the introduction of "Cp_2Zr" equivalents which avoid the generation of the highly reactive 14 electron species. The most widely used and easiest to form equivalent is Negishi's reagent[23] which is generated from zirconocene dichloride and two equivalents of butyl lithium. (Figure 1.4.) Initial formation of dibutyl zirconocene **4**, followed by butane elimination (*via* β-H abstraction)[24] upon warming, affords zirconocene (1-butene) **5**. The 1-butene ligand is only loosely bound to zirconium and can be readily exchanged for another π-ligand. Warming **5** to room temperature in the presence of a 1,6 diene affords the desired co-cyclisation product **6**.

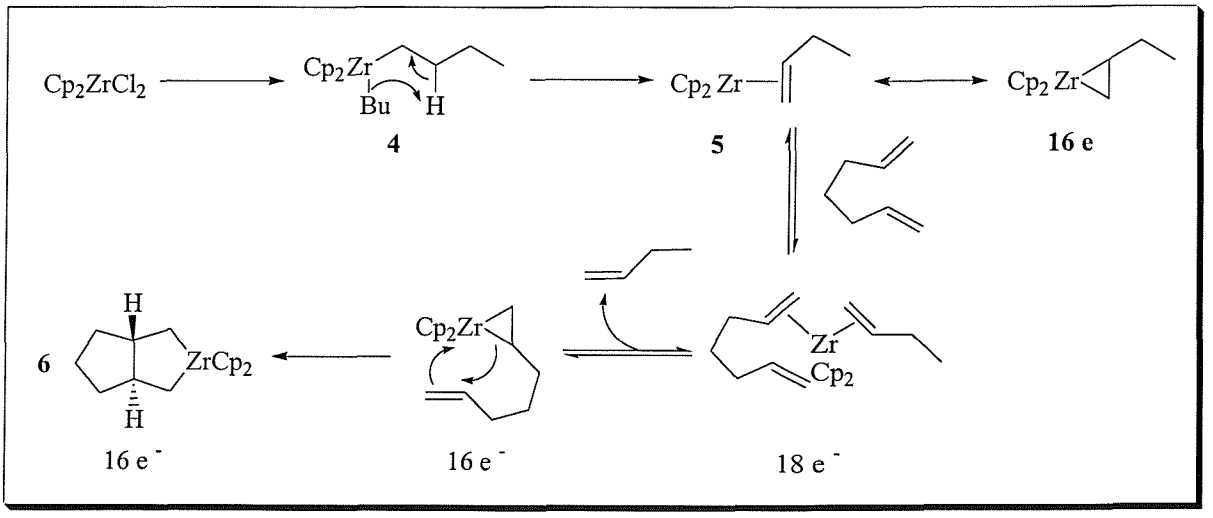


Figure 1.4 - Mechanism of cyclisation

A range of 1,n-dienes, -enynes and -diynes can be cyclised in this manner and a few representative examples are shown in figure 1.1.

1.3. Monocyclic Zirconacyclopentanoids

When Negishi's reagent is formed in the presence of 1-butene a reversible insertion reaction takes place to afford the *trans*-3,4-disubstituted monocycle **7**[12]. (Figure 1.5.) The cross-coupling of **5** with other alkenes generally leads to the formation of the statistical mixture of all the possible regioisomers because the ligand exchange process is much faster than cyclisation. The one exception being styrene insertions which are pair selective, affording the thermodynamic zirconacycle **8** as a single isomer. The aromatic substituent is believed to be regioselectively placed adjacent to zirconium due to an electronic interaction with the zirconium centre. When alkyne insertions were attempted, a different reactivity was observed whereby two equivalents of alkyne underwent homocoupling to give zirconacyclopentadiene **9**[23].

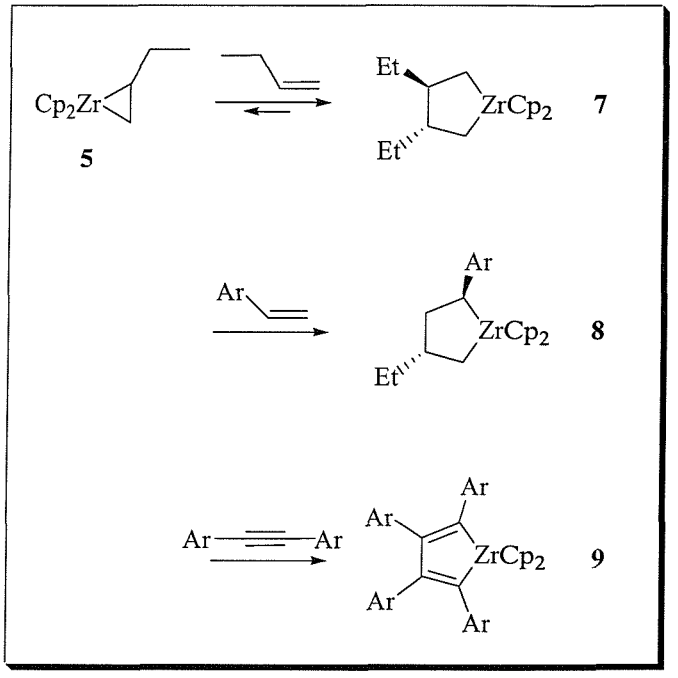


Figure 1.5 - Formation of monocycles with zirconocene (1-butene)

Takahashi extended this methodology by replacing the Cp_2Zr (1-butene) with the analogous ethylene complex **10**. (Figure 1.6.) The ethylene complex is formed by treatment of zirconocene dichloride with two equivalents of ethyl magnesium bromide in an identical manner to the formation of Negishi's reagent. This allows the formation of monosubstituted zirconacyclopentanes such as **11** to be formed[25]. When the insertion of alkynes was attempted, instead of the double insertion product **13** forming, only one equivalent of the alkyne inserted to generate the zirconacyclopentene **12**[26]. Several excess equivalents of alkyne failed to produce **13**. Takahashi has now shown that **12** can be refluxed with alkynes, nitriles, aldehydes and substituted alkenes, extruding ethane to form the pair-selective coupling complexes such as **13**[27]. The difference in reactivity between **5** and **10** has been attributed to the extra thermal stability of the ethylene complex. The ethylene ligand is much more tightly bound to the zirconium, and consequently, is much less prone to displacement by another π-ligand[27].

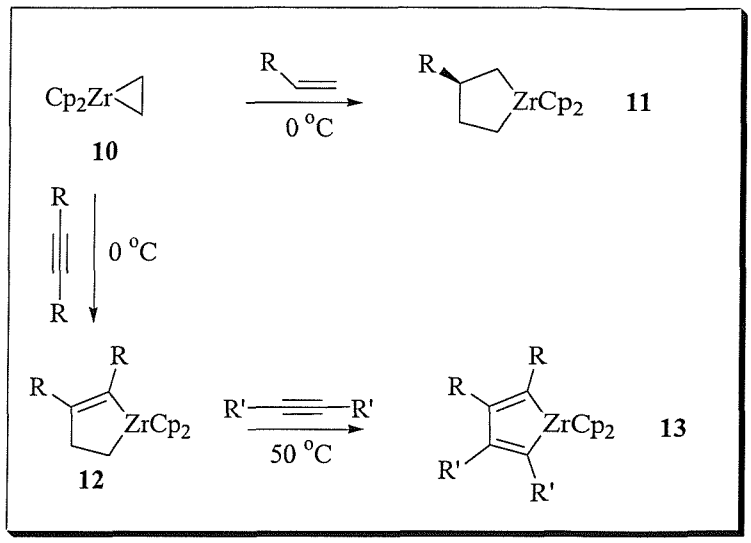


Figure 1.6 - Formation of monocycles with zirconocene ethene

1.4. Bicyclic Zirconacyclopentanoids

The analogous intramolecular couplings of non-conjugated α,ω-diynes and -enynes afford bicyclic zirconacyclopentadienes and zirconacyclopentenes respectively. (Figure 1.7.) Since early publications[23], the scope of these zirconocene (1-butene) mediated co-cyclisation reactions has been extensively investigated by Negishi and Nugent, and the results have been published in several full publications and reviews[6,8,15,16]. For this reason, only a brief summary of these reactions will be documented here. In general, the diyne cyclisation works for a variety of homologues. Terminal alkynes are not tolerated due to acidity of the alkynyl proton. The cyclisation of enynes proceeds in high yield only for 1,6- and 1,7-substrates. Again, terminal alkynes are not tolerated. The use of a removable trialkyl tin and silicon substituent has helped to overcome this limitation. A wide range of additional functionality is tolerated, including amines and silicon compounds in the ring and TBDMS protected ethers, enol ethers and exocyclic substituents.

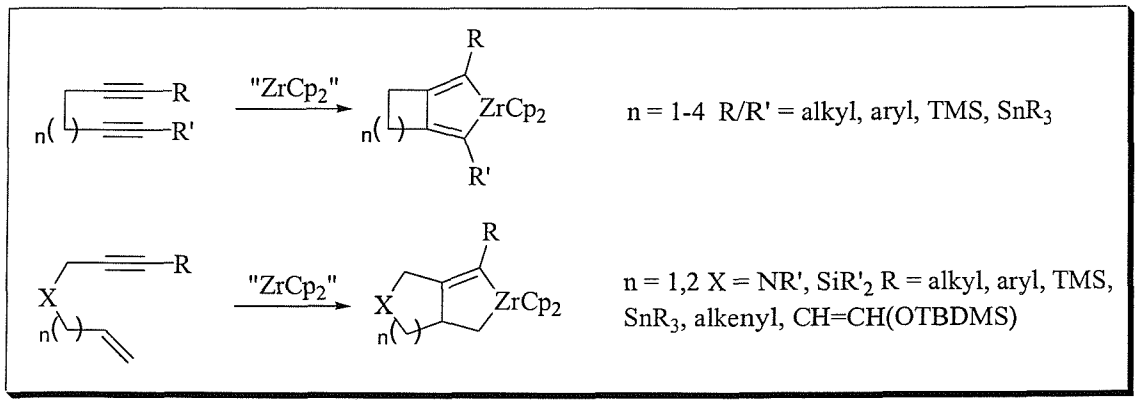


Figure 1.7 - Intramolecular formation of zirconacyclo-pentadienes and -pentenes

The first intramolecular coupling of a non-conjugated α,ω-diene was reported by Schwartz using the zirconocene *bis*-phosphine[18]. (Figure 1.8.) Cyclisation of **14** with the zirconocene *bis*-phosphine complex afforded the bicyclic zirconacyclopentane **15** as a 1:1 *cis:trans* mixture[28] (as determined by the ratio of protonation products; zirconacycle hydrolysis is discussed later in this chapter). Later work showed that the cyclisation diastereoselectivity was temperature controlled[29]. Cyclisation of **14** with Negishi's reagent for 6 hours at 30 °C afforded predominantly the *cis* zirconacycle **15a** as the kinetic product. However, heating the zirconacycle intermediate at 60 °C for 6 hours gave an 88:12 *trans:cis* mixture of diastereoisomers as the thermodynamic product.

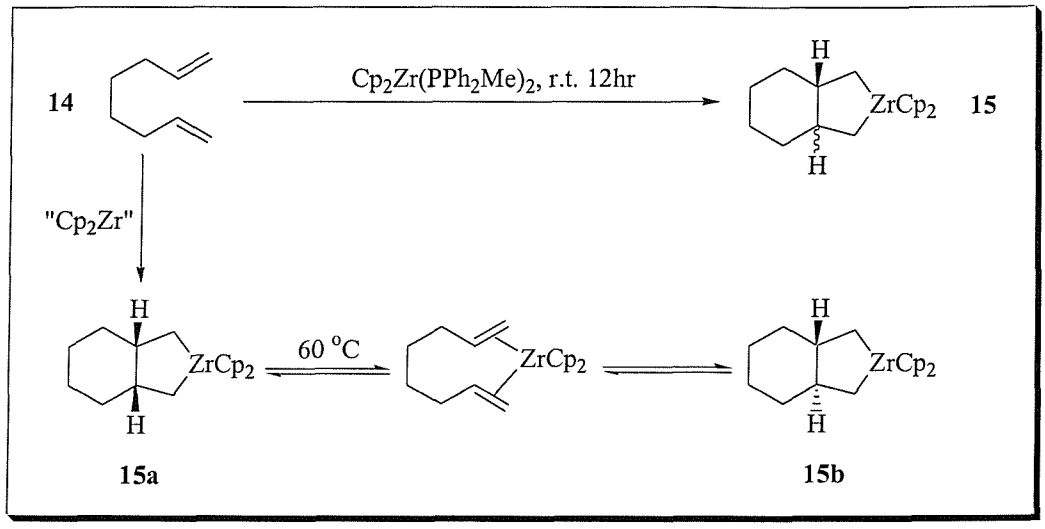


Figure 1.8 - Thermodynamic equilibria of zirconacycles

Kemp used this idea to cyclise the nitrogen containing 1,7-ocatdiene **16a** to afford zirconacycle **16b**[30]. (Figure 1.9.) The diastereoselectivity of cyclisation was determined by the ratio of the *trans* and *cis* piperidine protonation products.

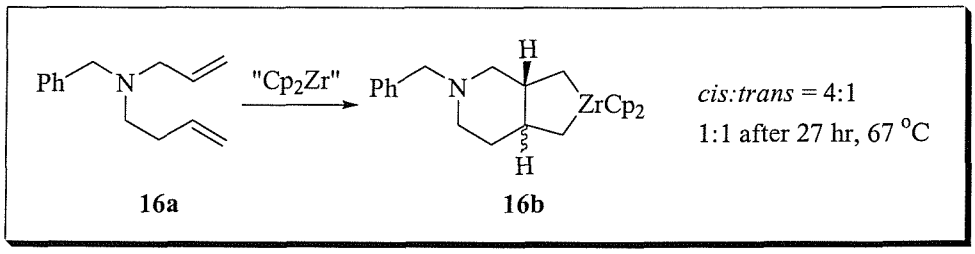


Figure 1.9 - Kemp's piperidine synthesis

The cyclisation of 1,7-octadienes containing additional unsaturation has also been reported, with the successful cyclisation of the 1,7-diene **17**[14] and 1,4,7-triene **18**[31]. (Figure 1.10.)

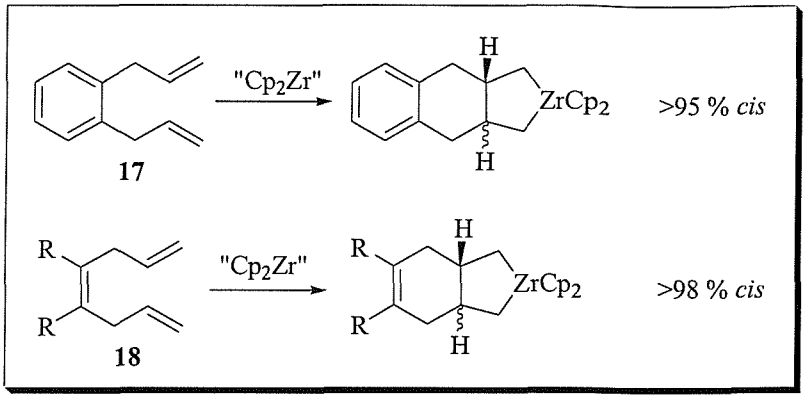


Figure 1.10 - Cyclisation of other 1,7-dienes

The cyclisation reactions of 1,6-heptadienes carried out by Negishi[14] and Nugent[13] gave a valuable insight into the scope of the zirconocene (1-butene) mediated cyclisation reactions. The cyclisation predominantly afforded the *trans* fused zirconacycles **19**, with the main exception being the cyclisation of diallylaniline which afforded predominantly the *cis* fused zirconacycle **20**. A range of heteroatoms have been shown to be compatible with the cyclisation, including X=Si and N. (Figure 1.11.)

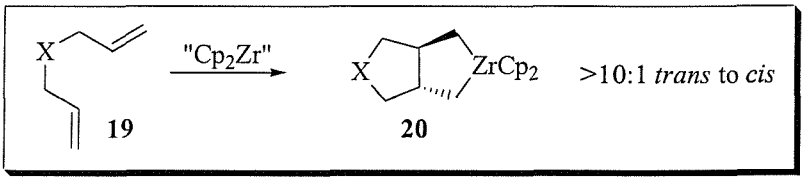


Figure 1.11 - Cyclisation of 1,6-dienes

A sub-stoichiometric version of the co-cyclisation reaction has been developed[32-35], but as the final products are not zirconium containing organometallic compounds, their syntheses and elaboration methods have not been included in this brief review.

Erker reported the synthesis of zirconaindene **22**[36,37]. Reaction of Cp_2ZrCl_2 with 2 equivalents of PhLi and subsequent thermolysis generated zirconocene benzyne **21**, which upon addition of an alkyne generated the zirconaindene **22**. (Figure 1.12.) Alkenes can also be added to generate the corresponding zirconacycloindanes.

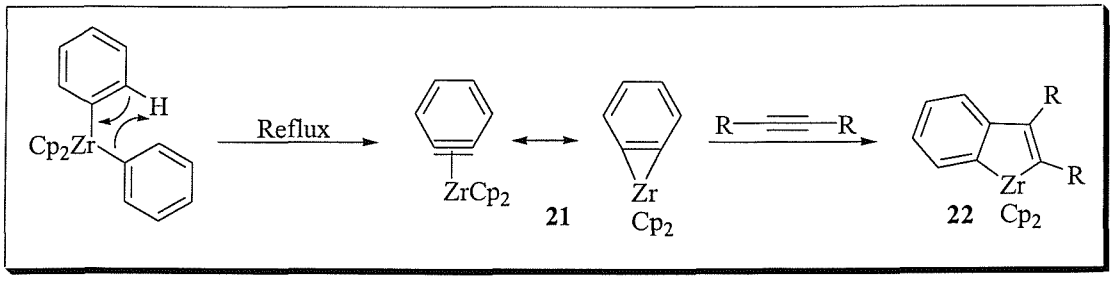


Figure 1.12 - Formation of zirconocene benzyne

Takahashi recently reported the cyclisation of the 1,3,6-heptatriene **23** to give the unsaturated zirconacycle **24**[38]. (Figure 1.13.) It was found that although the *trans* fused zirconacycle **27** was formed preferentially in an approximate ratio of 5:1 to that of the *cis* fused zirconacycle **29**, heating the zirconacycle at 50 °C for 48 hours caused isomerisation to the *cis* zirconacycle to occur *via* intermediate **28**. This ratio was determined by the relative amounts of the protonated products **25** and **26**.

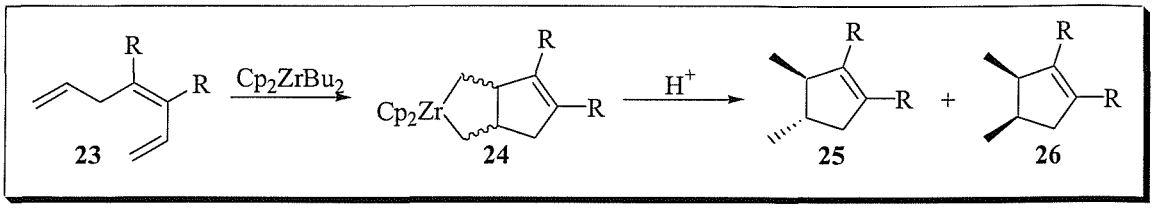


Figure 1.13 - Cyclisation of 1,3,6-heptatriene

This unusual *trans* to *cis* isomerisation is believed to occur *via* cleavage of one of the C-Zr bonds of the *cis* zirconacycle **29** because of ring strain or steric hindrance. This causes proton abstraction from a Cp ring to form the *bis* (olefin) zirconium complex **30**. (Figure 1.14.) After complex **30** has formed, it can not rearrange back to the *cis* zirconacycle **29**. This hypothesis was based on deuteration experiments which showed that after deuteration of **29** only the *mono*-deuterated product **31** was formed. Deuteration of the *trans* zirconacycle **27** gave the *bis*-deuterated product **32**.

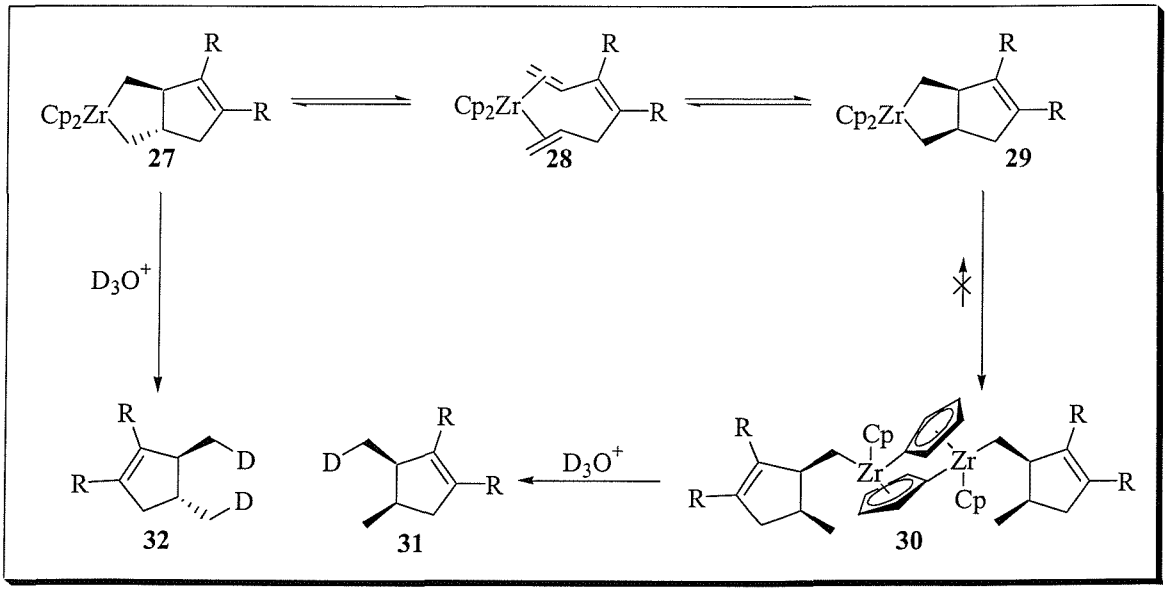


Figure 1.14 - *Trans* to *cis* isomerisation

1.5. Elaboration of Zirconacycles

The preceeding section gave an overview of the range of zirconacycles that are available to the synthetic chemist from simple organic precursors using efficient and convergent routes. One limitation of the zirconacycle is that the two C-Zr bonds are unreactive to conventional electrophiles such as carbonyl compounds and alkyl halides. The development of methods that overcome this limitation has become an active area of research and the following section gives an overview of the successful methods for zirconacycle elaboration which have established organozirconium compounds as powerful synthetic intermediates.

1.6 Protonation of Zirconacycles

Generally, zirconacycles can be protonated under acidic conditions (2M HCl) or basic conditions (aqueous $NaHCO_3$), with the choice of protonation conditions dependent upon the sensitivity of the substrate. Methanol has also found use as a protonation agent as this rapidly hydrolyses C-Zr bonds, allowing the organic product to be released. (Figure 1.15.) The stereochemistry of the zirconacycle ring fusion is retained[14] and alkenyl C-Zr bonds also retain their alkene geometry after hydrolysis[15]. Both of these facts indicate a concerted reaction mechanism *via* a four centre transition state.

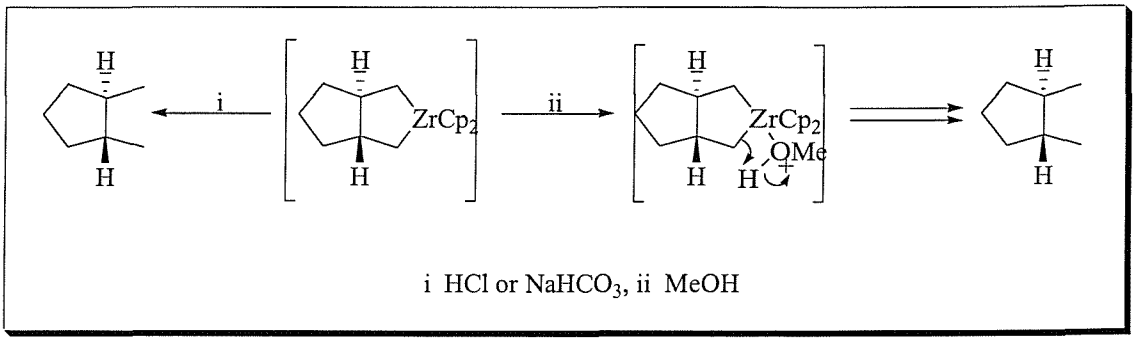


Figure 1.15 - Mechanism of protonation

1.7. Halogenation and Oxidation Of Zirconacycles

Early work by Nugent[13] and Negishi[14,15] demonstrated that zirconacyclopentane **6** could be elaborated with halogens and molecular oxygen to afford dihalides and diols respectively. (Figure 1.16.)

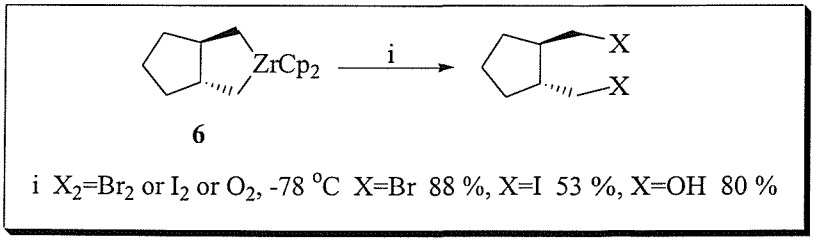


Figure 1.16 - Dihalogenation and dihydroxylation of zirconacycles

Takahashi extended this methodology to selectively monohalogenate one of the C-Zr bonds of the symmetrical zirconacycle **33**[39]. (Figure 1.17.) Takahashi found that protonation with 1 eq of methanol afforded the alkylalkoxyzirconocene **34**. The hydrolysis of the second C-Zr bond of **34** was much slower than the first, and so subsequent reaction with the halogen afforded the monohalogenated product **35**.

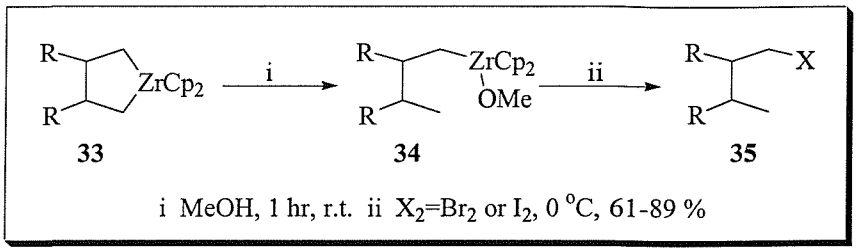


Figure 1.17 - Monohalogenation of symmetrical zirconacycles

Chemoselective monohalogenation of an unsymmetrical zirconacyclopentane is virtually impossible as both alkyl C-Zr bonds exhibit almost identical reactivity. However, zirconacyclopentenes contain two distinctively different C-Zr bonds (one alkyl and one alkenyl). With this in mind, Takahashi[40-42] demonstrated the chemoselective monohalogenation of 2,3-dialkylzirconocyclopentenes which would gain access to a large number of synthetically useful compounds such as **36**, **37** and **38** from zirconacycle **12**, in high yield. (Figure 1.18.)

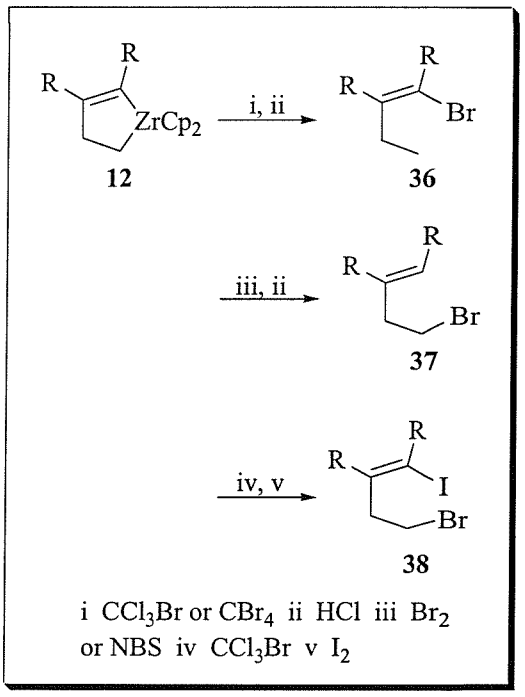


Figure 1.18 - Chemoselectivity of halogenation

1.8. Insertion of Carbenes

1.8.1. Carbon monoxide Insertion

Zirconacycle carbonylation was initially reported by Erker[43] and has been further developed by Negishi[44,45]. Both demonstrated that carbon monoxide was rapidly absorbed by a solution of zirconacycle such as **6** at 0 °C to afford after workup the carbonyl compounds **40** or **41**. (Figure 1.19.) The reaction is thought to proceed *via* donation of a lone pair of electrons from CO into the empty LUMO d-orbital of zirconium, followed by a 1,2 migration to give the acyl zirconocene **39**. Evidence for the formation of the η^2-acyl zirconium complex **39** has come from Negishi[12,14] who showed that carbon monoxide trapping can either give ketones (after oxidation with I_2) such as **41** or secondary alcohols such as **40** after protonation.

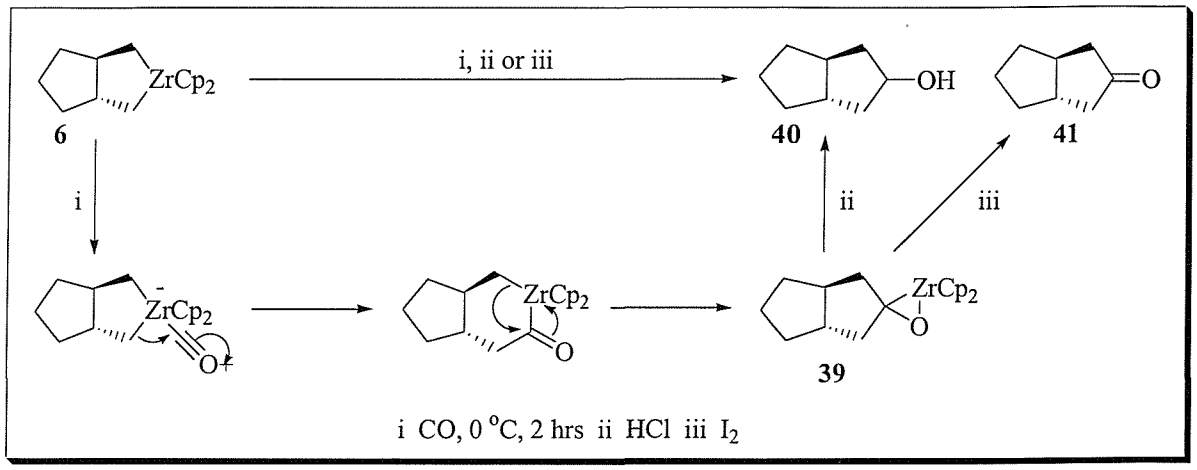


Figure 1.19 – Mechanism of zirconacycle carbonylation

More recently, Takahashi reported the insertion of CO into zirconacyclopentadienes[46]. (Figure 1.20.) The major product from the carbonylation of **42** was the cyclopentenone **43** rather than the cyclopentadienone **44** and the ratios of the two product were dependent on the reaction temperature.

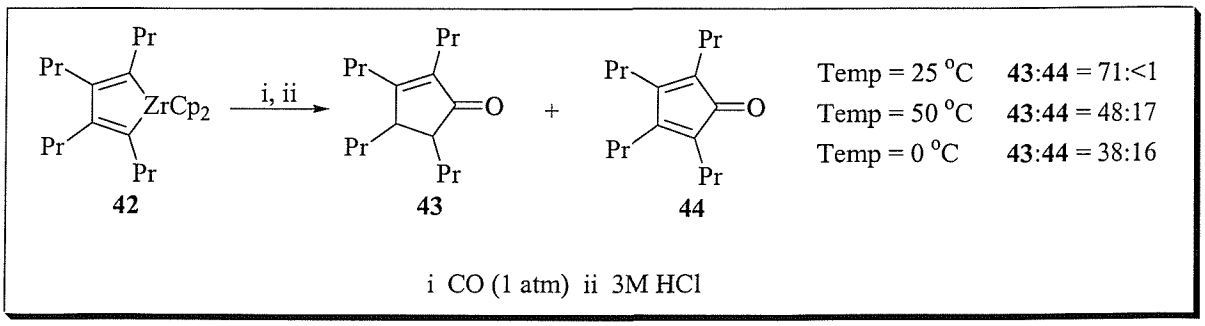


Figure 1.20 – Carbonylation of zirconacyclopentadienes

Cyclopentenone **43** is believed to form *via* rearrangement and quenching of the η^2-acyl zirconium complex **45** and subsequent tautomerism of enol **46**. (Figure 1.21.)

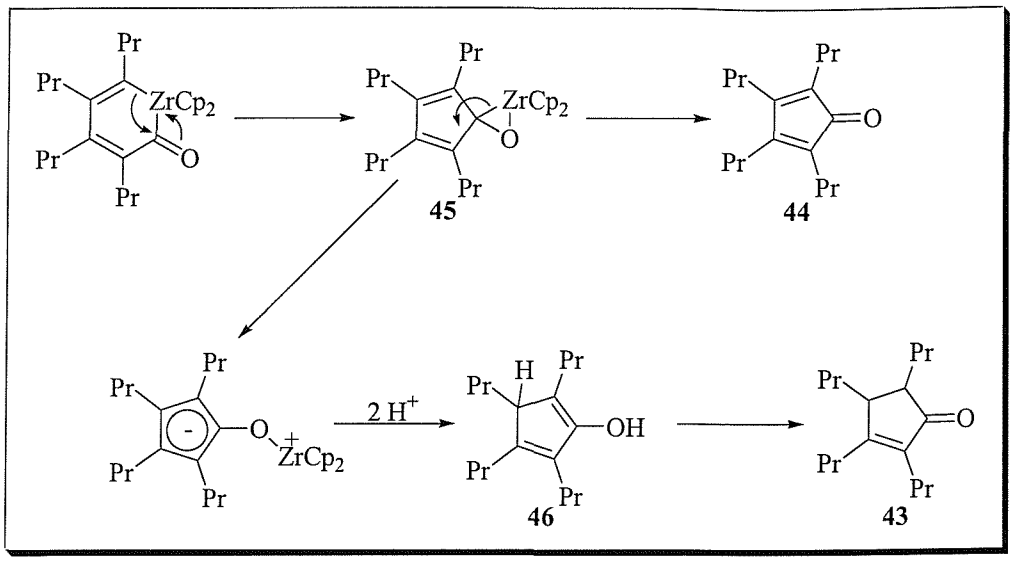


Figure 1.21 – Mechanism of formation of carbonylated products

1.8.2. Isocyanide Insertion

Isocyanides are isoelectronic with carbon monoxide, and the mechanism for their insertion is believed to be very similar. The first reported example of isocyanide insertion was by Negishi who showed that the insertion of butylisocyanide into zirconacyclopentene **47** gave aldehyde **48** after imine hydrolysis[47]. (Figure 1.22.)

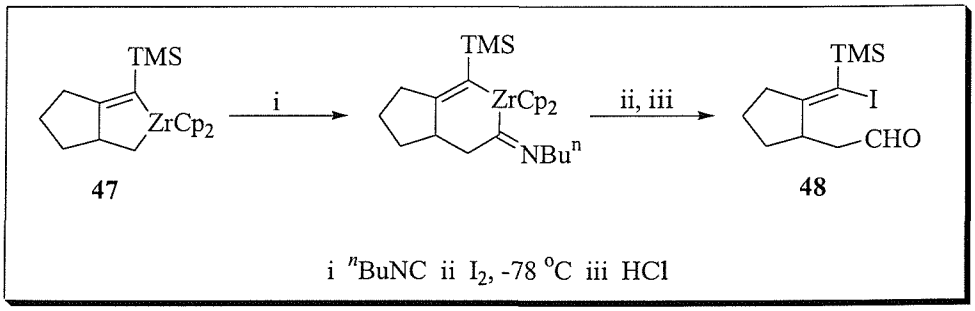


Figure 1.22 - Isocyanide insertion

Whitby[48] reported that the insertion of phenyl isocyanide into zirconacyclopentane **6** formed the iminoacyl complex **49**, which upon warming rearranged to the η^2-imine complex **50**. (Figure 1.23.) These imine complexes had been shown to be extremely potent carbometallating agents[5]. Whitby reported that **50** reacted cleanly with a variety of alkenes and alkynes to give the insertion products **51** before protonation to give **52**.

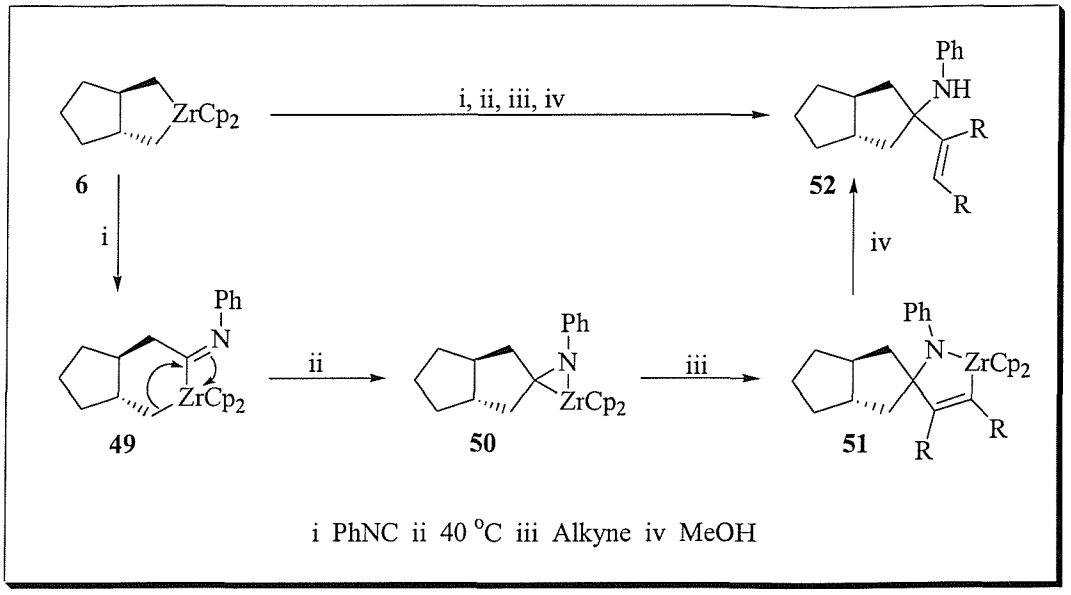


Figure 1.23 - Mechanism of isocyanide insertion

Whitby later inserted phenyl isocyanide into zirconacyclopentenes and insertion was selective into the alkyl C-Zr bond[49]. The reaction proceeds exactly as the zirconacyclopentane example until the isolation of the organic insertion product was attempted. An unusual *anti* 1,3-amine shift was observed, giving **53** in good yields. (Figure 1.24.) This rearrangement was shown to be general for a range of zirconacycles and alkyne or alkene inserted products.

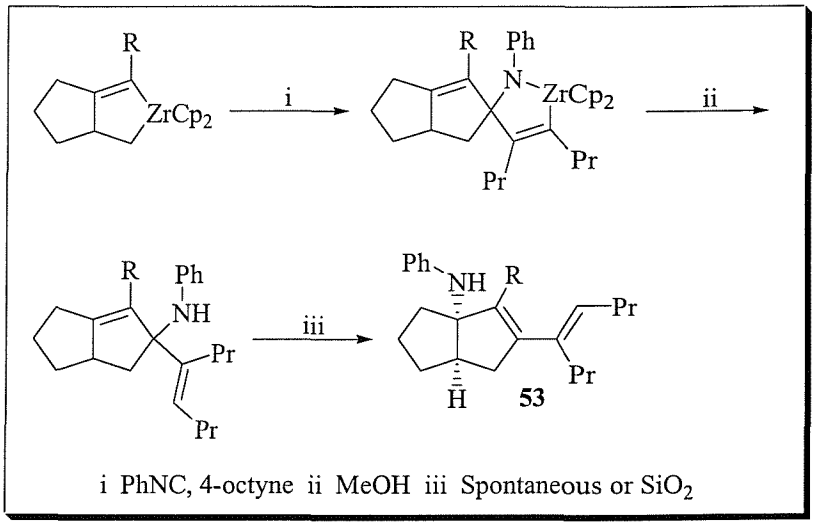


Figure 1.24 - 1,3-Amine shift

1.9. Insertion of carbenoids.

Lithio-halo-carbenoids are isoelectronic with carbenes and are used to form C-C bonds from zirconacycles. Carbenoids have electron-donating properties (which allow them to co-ordinate to a metal centre) and also have electron accepting properties (the leaving group acting as an electron sink). Initially, Negishi reported the migratory insertion of carbenoids into the acyclic zirconocene chloride **54**[50]. (Figure 1.25.) Thus, **54** reacted with a range of carbenoids to furnish the elaborated products **55**, **56** and **57** as shown.

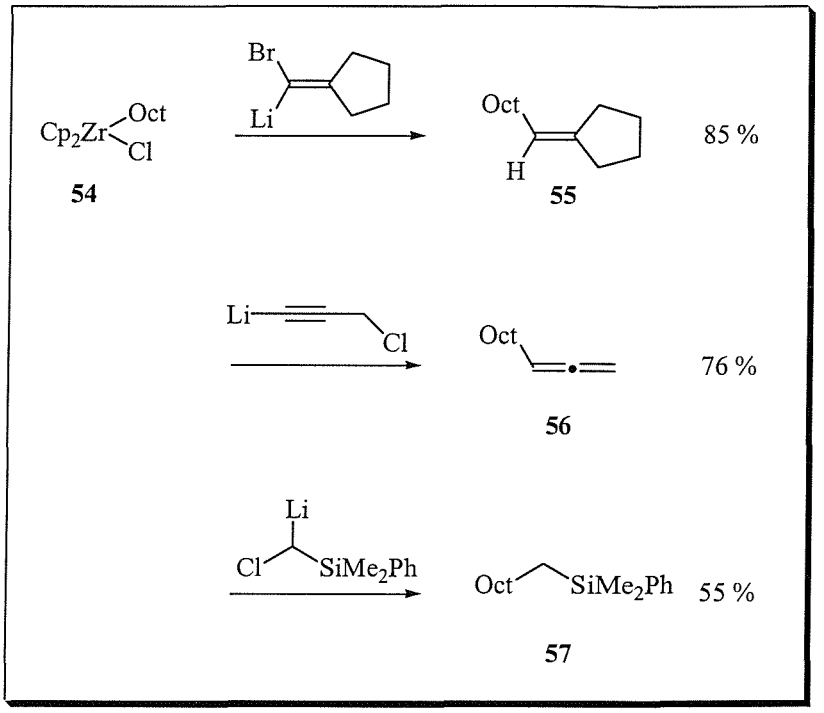


Figure 1.25 - Migratory insertion of carbenoids into acyclic zirconocene

Whitby extended this work to include cyclic zirconacycles[51-55]. (Figure 1.26.) The mechanism of carbenoid insertion proceeds *via* the 'ate' complex **58**, followed by migratory insertion to give the η^3 π-allyl zirconium complex **59**.

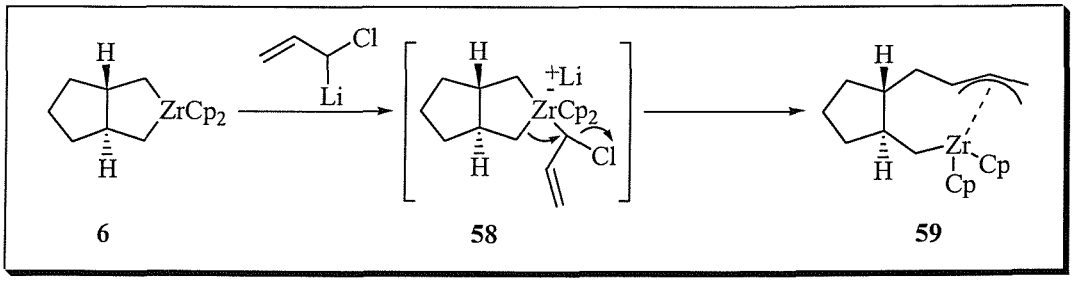


Figure 1.26 - Mechanism of allyl carbenoid insertion into zirconacycles

Unlike normal alkyl-zirconium bonds, the π-allyl zirconium complex **60** was found to react with aldehydes in the presence of Lewis acids to give products such as **61** in excellent yields and moderate 1,6 diastereocontrol. (Figure 1.27.)

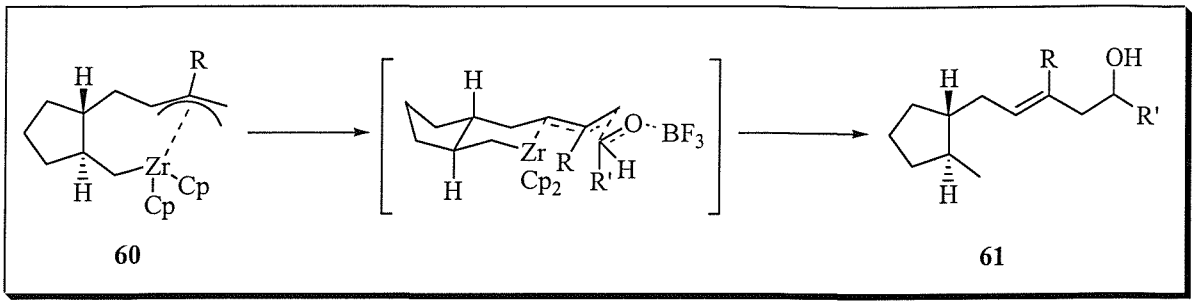


Figure 1.27 - Mechanism of Lewis acid mediated aldehyde insertion

Takahashi later showed that lithium chloromethyltrimethylsilane readily inserted into the C-Zr bond of a zirconacyclopentadiene **62** to form the zirconacyclohexadiene **63** in high yield[56]. (Figure 1.28.) Hydrolysis of **63** yielded the major product **64** and unexpected minor product **65**, *via* allylic isomerisation of the double bond.

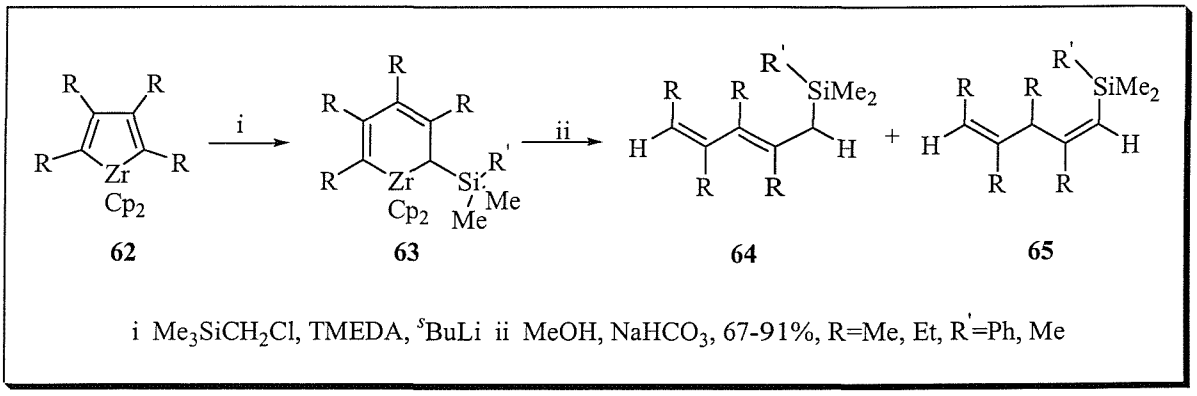


Figure 1.28 - Migratory insertion of lithium chloromethyltrimethylsilane

More recently, Whitby reported the insertion of a wide range of electron-rich and electron-poor carbenoids into zirconacyclo-pentanes and -pentenes[57]. (Figure 1.29.) Insertion of methylene carbenoid into zirconacycle **66** was achieved by reaction of ICH_2Cl with BuLi at -100 °C. This generated zirconacycle **67** which subsequently gave a 5:2 ratio of the homologated methylethylcyclopentane **68** and the dimethylcyclopentane **69** derived from the starting zirconacycle **66**. Increasing the equivalents of carbenoid increased the conversion of **66** to **67** but also generated *bis*-inserted products that could not be separated.

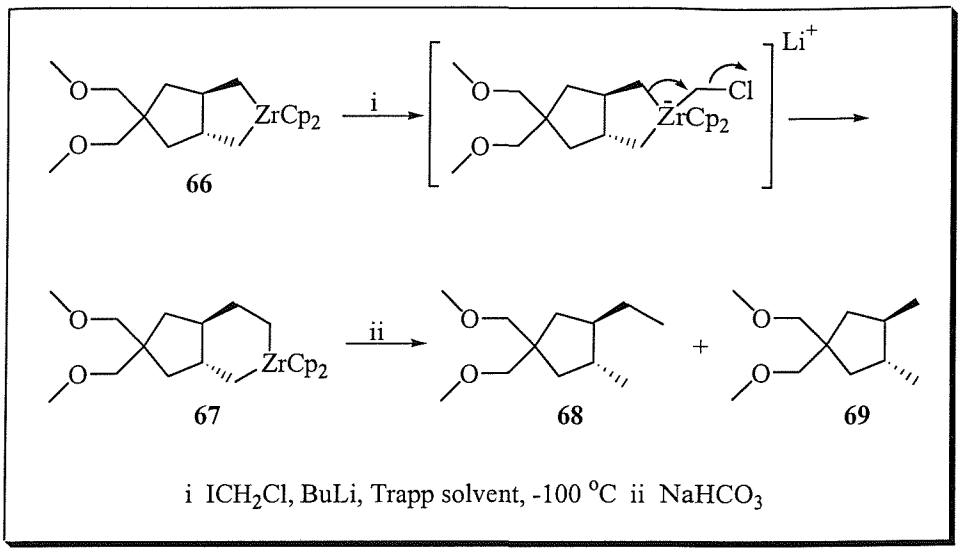


Figure 1.29 - Migratory insertion of methylene carbenoid

The insertion of α-stannyl carbenoid was investigated and shown to insert into **66**. (Figure 1.30.) Although **70** was isolated in a low 11 % yield, this is still a useful result as introducing a 'handle" such as a stannyl group may allow further functionalisation at a later stage.

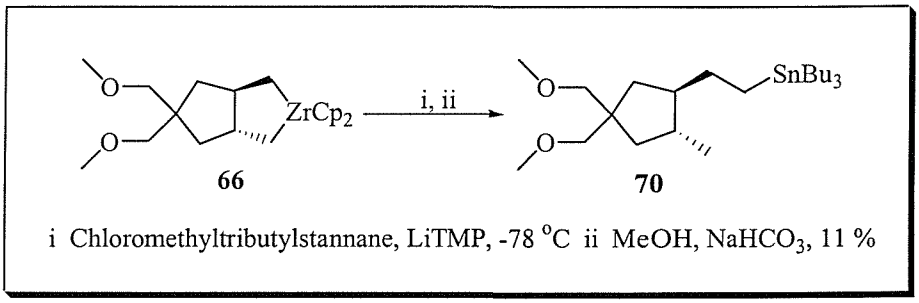


Figure 1.30 - Migratory insertion of methyltributylstannane carbenoid

The insertion of ether- and thioether-substituted carbenoids were explored. Insertion of lithium chloromethylethyl ether at -78 °C into **71** gave the desired ether-substituted product **72** in a modest 45 % yield. (Figure 1.31.)

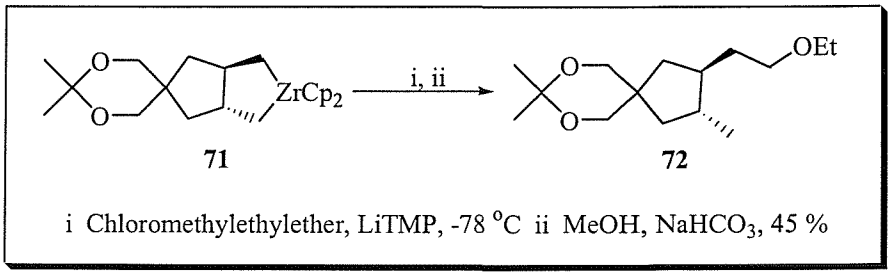


Figure 1.31 - Migratory insertion of ether-substituted carbenoid

Similarly, insertion of lithium chloromethylphenyl sulphide was achieved under identical conditions to give the thioether-substituted product **73** in 77 %. (Figure 1.32.) Interesting, no *bis*-insertion was observed, even after addition of 10 equivalents of carbenoid.

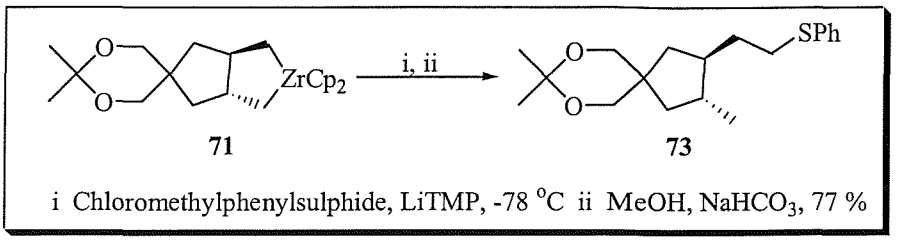


Figure 1.32 - Migratory insertion of thioether-substituted carbenoid

The insertion of lithium diethyl chloromethylphosphonate into both zirconacyclopent-anes and -enes was fast and clean and even using a large excess of the carbenoid generated no *bis*-insertion products. (Figure 1.33.)

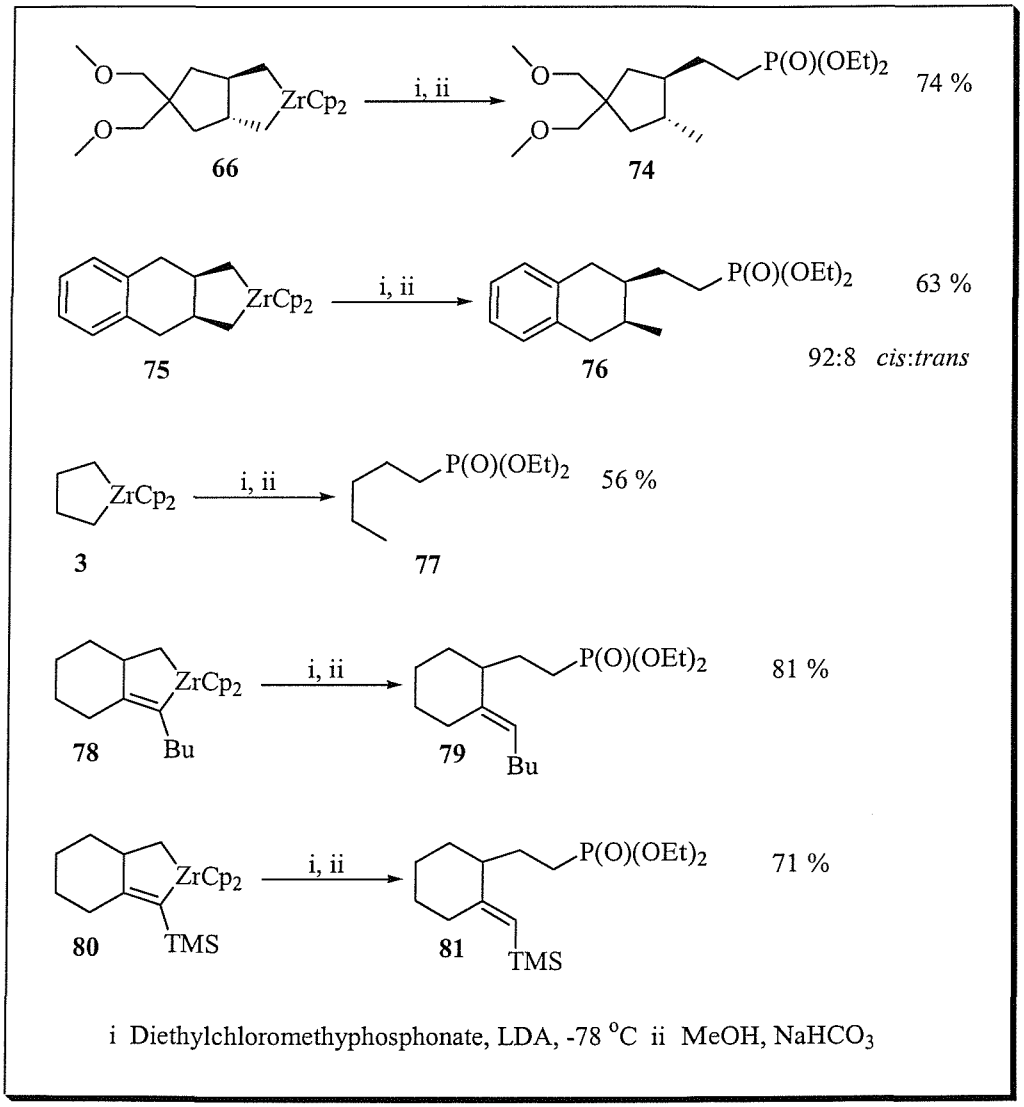


Figure 1.33 - Migratory insertion of phosphonate-substituted carbenoid

Insertion of lithium chloromethylphenylsulphone into **66** and **83** were clean and high yielding to give **82** and **84** respectively. (Figure 1.34.) The zirconacycles were thermally stable at room temperature and no *bis*-insertion was observed during the reaction.

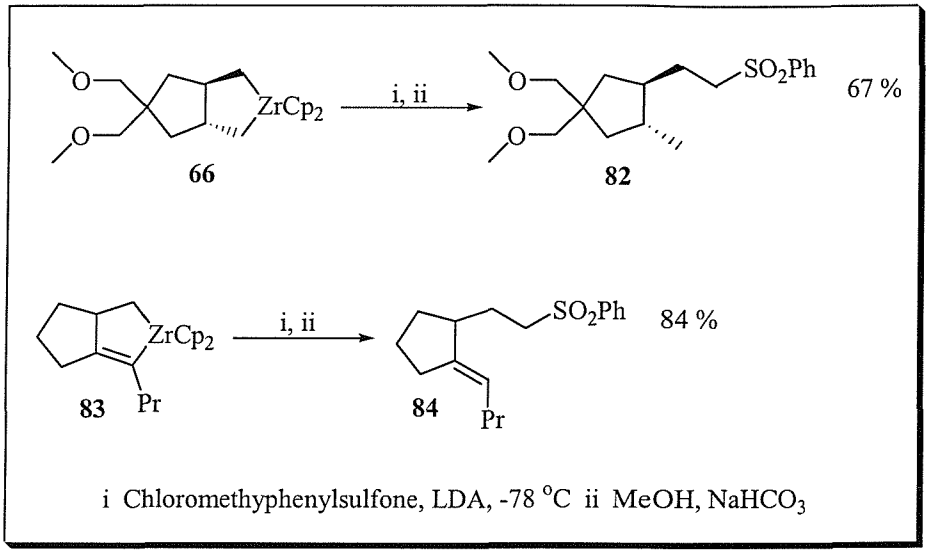


Figure 1.34 - Migratory insertion of sulphone-substituted carbenoid

However, in the case of zirconacycle **85**, a different reactivity was observed when the insertion of the lithium chloromethylphenylsulphone was attempted. Zirconacycle **85** was thermally unstable and the reaction needed to be quenched below -40 °C to get a good yield of the expected product. If zirconacycle **85** was allowed to warm to room temperature before quenching, the diene **89** was the major product. (Figure 1.35.) This was believed to occur *via* a β-hydride elimination/re-addition process. Thus, transfer of a β-hydride in **85** to the zirconium gives the zirconium hydride **86**, which can re-add to the alkene to afford the zirconacyclopentene **87**. Irreversible elimination of the phenylsulphinate to afford **88** followed by protonolysis gives diene **89**. The additional conformational constraints provided by the fused 5-member rings in **66** and **83** probably prevents the orbital alignment needed for the β-hydride transfer.

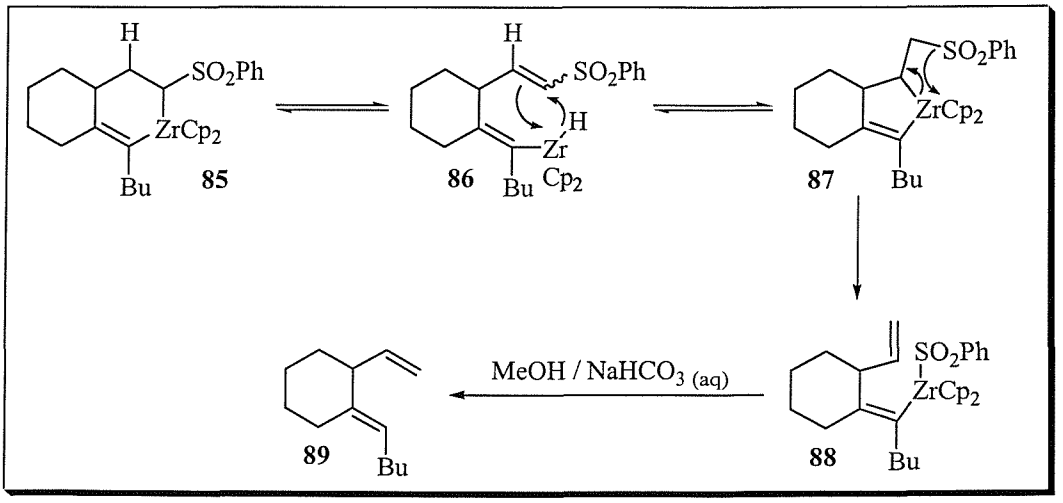


Figure 1.35 - Mechanism of β-hydride transfer

Insertion of lithium chloroacetonitrile (1.3 eq) into **66** gave the expected insertion product **90** in a low 24 % yield. (Figure 1.36.) The major compound isolated was **91** (45 %) due to *bis*-insertion of the carbenoid. Reducing the amount of carbenoid to 1 equivalent improved the ratio of **90/91** to 2:1, but did not improve the yield of **90**. Increasing to 2 equivalents of carbenoid gave a 57 % isolated yield of the *bis*-insertion product **91**. Similarly, reaction of 2 equivalents of carbenoid with zirconacyclopentane **15** gave the *bis*-inserted product **92** as an 88:12 *trans*:*cis* mixture in a 58 % yield.

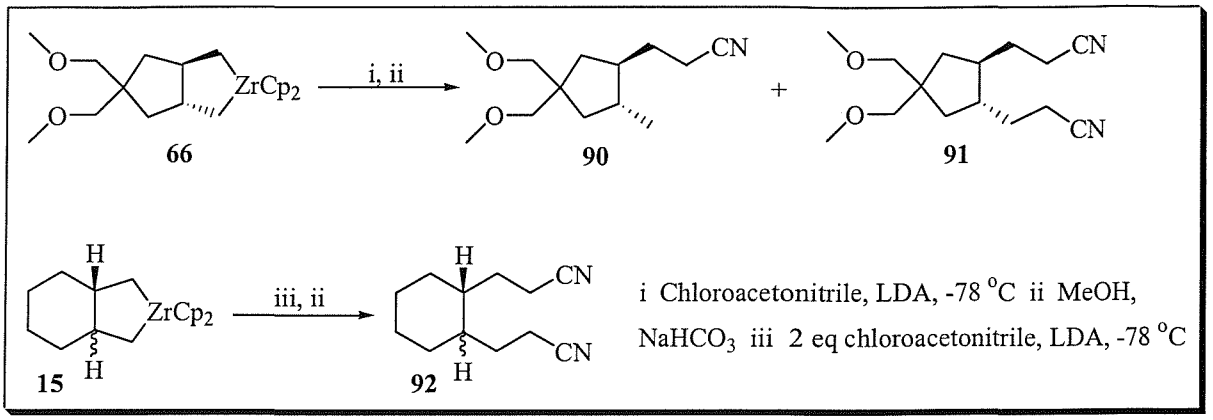


Figure 1.36 - Insertion of lithium chloroacetonitrile into zirconacyclopentanes

Insertion of 1.3 equivalents of carbenoid into zirconacyclopentenes **83** and **80** gave clean conversion to the *mono*-inserted products **93** and **94**. (Figure 1.37.) To force *bis*-insertion, **83** was treated with 5 equivalents of carbenoid and gave **95** in a low 16 % yield. The second insertion occurs into the same side as the first because insertion into the alkenyl C-Zr bond is unfavourable.

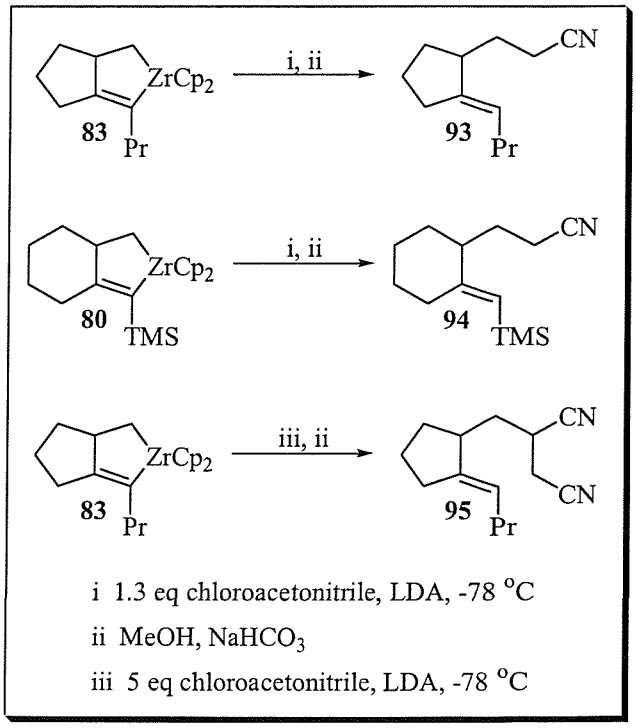


Figure 1.37 - Insertion of lithium chloroacetonitrile into zirconacyclopentenes

Addition of LiTMP to a mixture of zirconacyclopentane **71** and 1-chloro-2-methylprop-1-ene gave 30 % conversion to the zirconacyclohexane **96**. (Figure 1.38.) Addition of 5 equivalents of carbenoid gave a 20:1 ratio of **96** to **71**, but also gave unidentified side-products and consequently **97** was only isolated in 33 % yield.

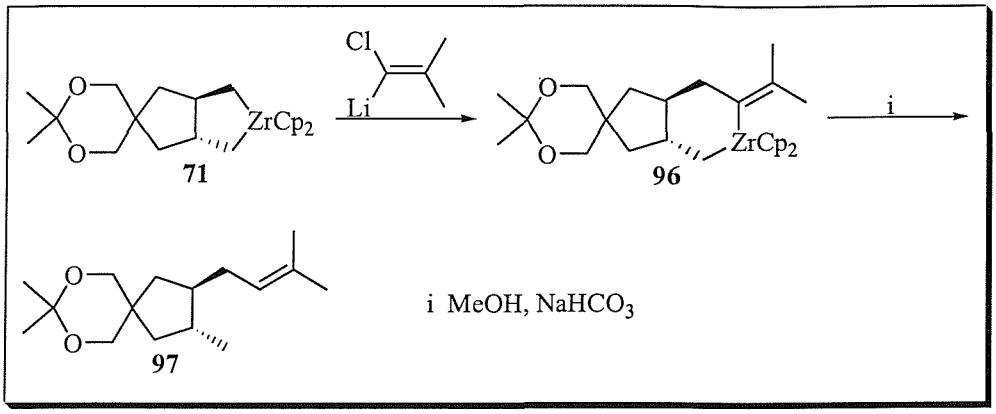


Figure 1.38 - Insertion of 1-lithio-1-chloroalkenes into zirconacyclopentenes

The insertion of lithiated β-bromostyrene **98** into zirconacycle **66** gave a very surprising result in that the expected insertion product **99** was also accompanied by a substantial amount of the *bis*-insertion product **100**, where the second insertion had taken place into the more hindered side of the zirconacyclohexane. (Figure 1.39.) Increasing the amount of carbenoid to 2 equivalents gave **100** in 64 % yield. Interestingly, insertion of the carbenoid into zirconacyclopentene **101** only gave the *mono*-insertion product **102**, even when 5 equivalents of carbenoid were added.

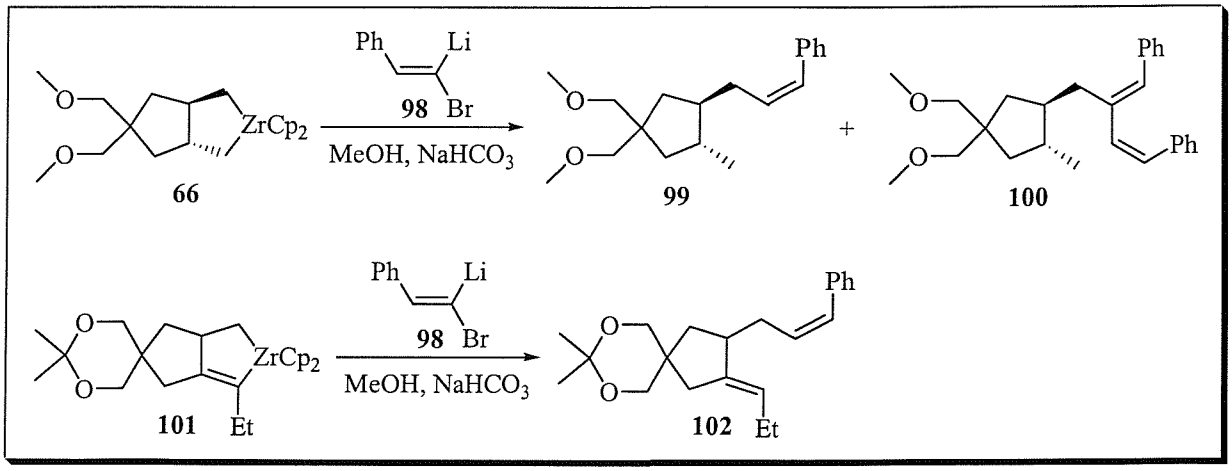


Figure 1.39 - Insertion of lithium β-bromostyrene into zirconacyclo-pentanes and -pentenes

1.10. Metathesis With Main-Group Elements

1.10.1. Reaction with Main-Group Halides

Zirconacyclopent-anes[13,58],-enes[59,60] and -adienes[60,61] have been shown to undergo metathesis with elements from group III (B, Ga, In), group IV (Si, Ge, Sn), group V (P, As, Sb, Bi) and group VI (S, Se) of the periodic table. The traditional zirconium-based route to main group heterocycles, by treatment with the metal di-,tri- or tetra-halide under mild conditions, is in general, easier than the traditional route of preparing the dilithium reagent. This metathesis allows the preparation of rare heterocycles such as arsoles, stilboles and bismoles, some of which are known to have unusual solid state properties. Representative examples are shown below in figure 1.40.

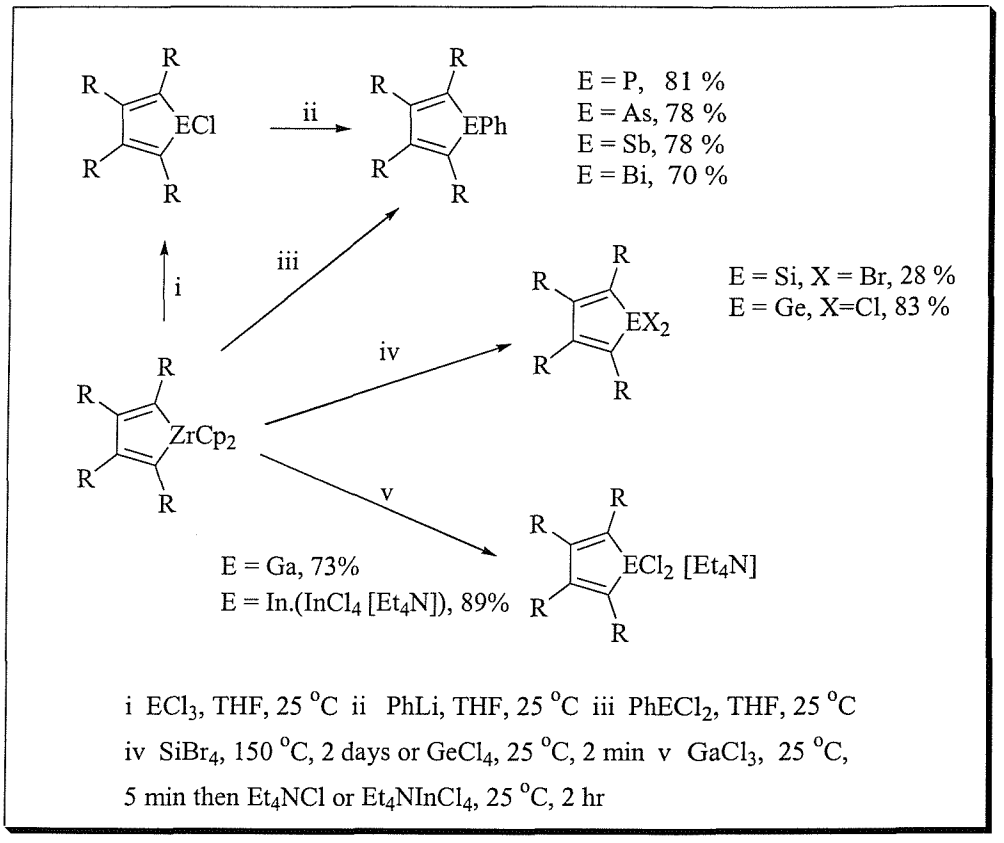


Figure 1.40 - Metathesis with main-group halides

The azazirconacyclopentadiene can react with S_2Cl_2 to give the isothiazole in 65 % yield[53]. (Figure 1.41.) Similarly, zirconacyclopentenes can react with S, Sn and Se chlorides to give the desired heterocyclic compounds.

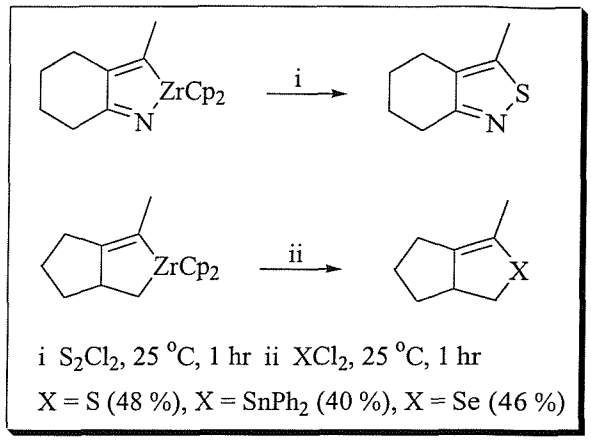


Figure 1.41 - Metathesis with S, Sn and Se chlorides

Unfortunately, despite the incorporation of group V elements into zirconacyclopentadienes, RNHCl and $RNCl_2$ do not undergo this metathesis reaction[62].

1.10.2. Reaction with Main-Group Oxides

Tilley generated thiophene-1-oxides by reaction of zirconacyclopentadienes with SO_2[63,64]. (Figure 1.42.) This resulted in the elimination of Cp_2ZrO and the generation of the sulphoxide products in high yield.

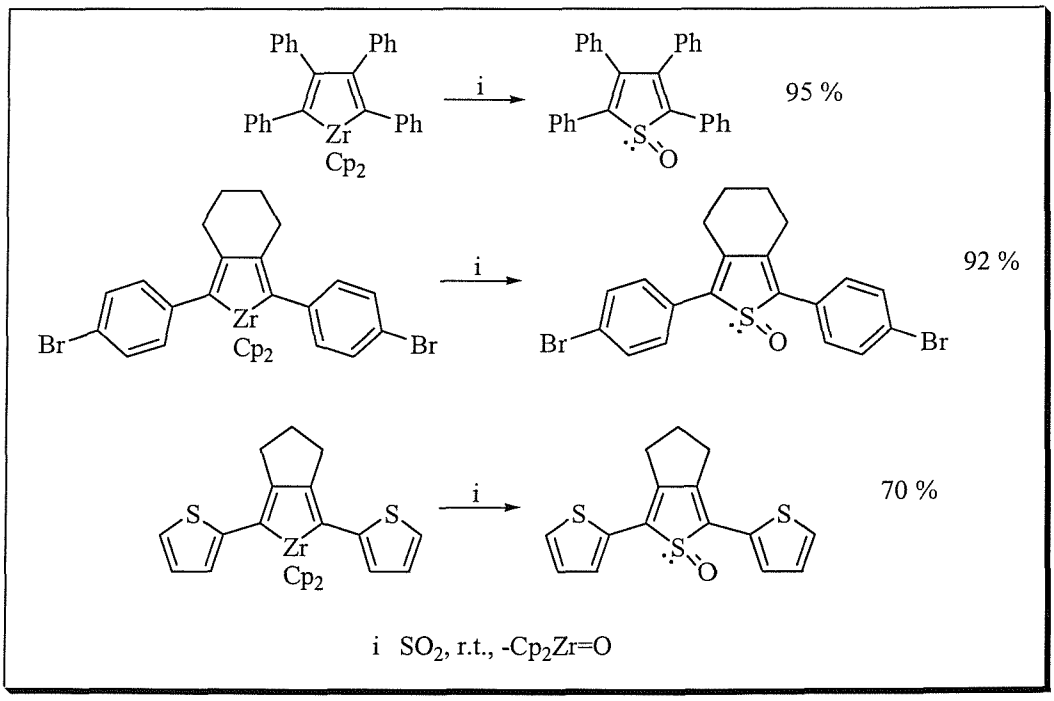


Figure 1.42 - Metathesis with SO_2

A similar idea was used by Xi who showed that it was possible for zirconacyclopentadiene **13** to undergo metathesis with C in the presence of $AlCl_3$ to form cyclopentadiene **103**[65]. (Figure 1.43.)

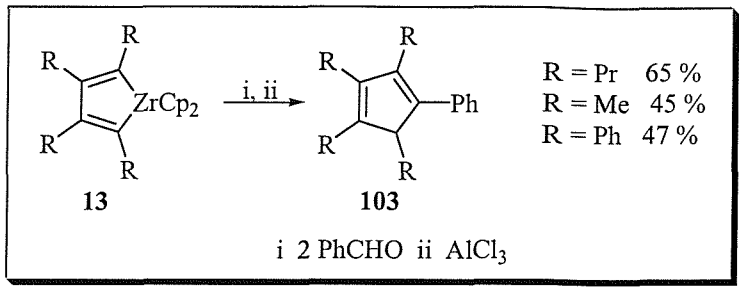


Figure 1.43 - Formation of cyclopentadienes

The mechanism is believed to involve initial co-ordination of the aldehyde to $AlCl_3$. (Figure 1.44.) The resulting adduct is able to insert into the C-Zr of the zirconacyclopentadiene **13** to form the aluminacyclopentadiene **104**. The activated carbonyl group inserts into an Al-C bond of **104** to afford the oxaaluminacycle **105**. It is proposed that the driving force of the reaction to **103** is the formation of the cyclopentadienyl ring and the strong Al=O double bond of the oxo aluminium species by-product.

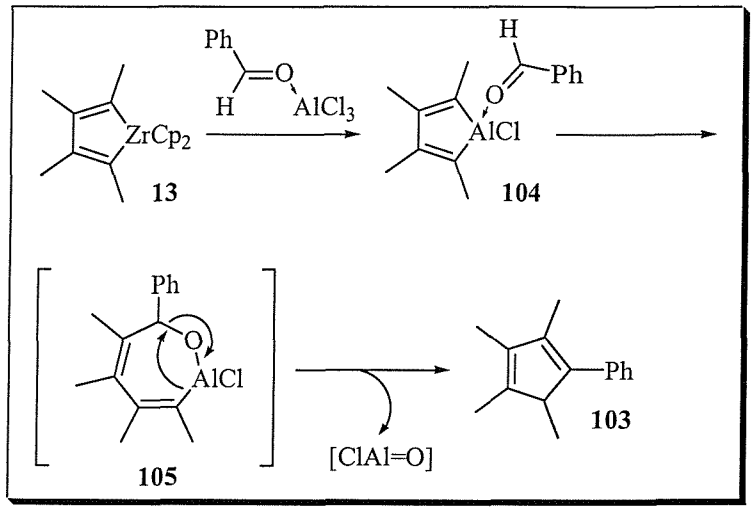


Figure 1.44 - Mechanism of cyclopentadiene formation

Tilley reported that nitrosobenzene was able to insert into the C-Zr bond of zirconacyclopentadiene **106** to give the *N*-phenyl pyrrole **108** in high yield[66]. (Figure 1.45.) The air-stable, 7-membered zirconacycle intermediate **107** was characterised by X-Ray structure analysis.

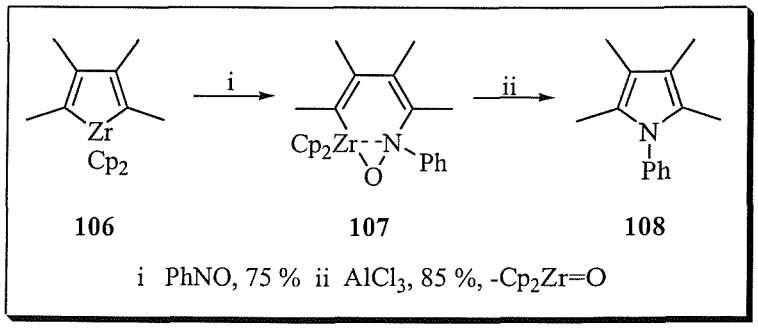


Figure 1.45 - Tilley's pyrrole synthesis

1.11. Transmetallation Reactions

The reactivity of organometallic species can be modified by transmetallation to alternative metals. Several research groups have found that transmetallation of zirconacycles often increase the nucleophilicity of the new carbon-metal bonds.

1.11.1. Transmetallation to Magnesium

One of the first examples of the successful transmetallation of the C-Zr bond was reported by Negishi[25]. The reaction of zirconacycle **109** with ethyl magnesium bromide resulted in a regioselective transmetallation of the more hindered C-Zr bond to Mg to form **110**. (Figure 1.46.) This high regioselectivity was documented as being largely steric in origin, the more hindered C-Zr bond being more labile and hence reactive. Grignard **110** could be further elaborated with alkyl halides, a reaction not possible for the parent zirconacycle **109**.

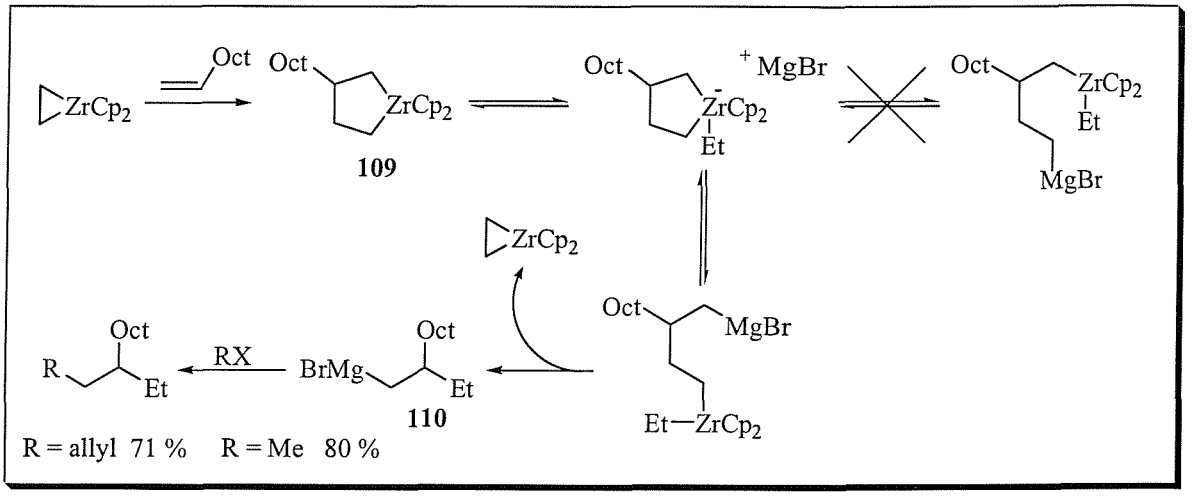


Figure 1.46 - Stoichiometric transmetallation from zirconium to magnesium

Negishi noticed that as zirconocene ethylene was also produced in the reaction, the overall transformation should be sub-stoichiometric in zirconium. (Figure 1.47.) Indeed, treatment of 1-decene with EtMgBr (2 eq) and Cp_2ZrCl_2 (10 mol%) at 0 °C for 24 hr afforded Grignard **110** in 80 % yield.

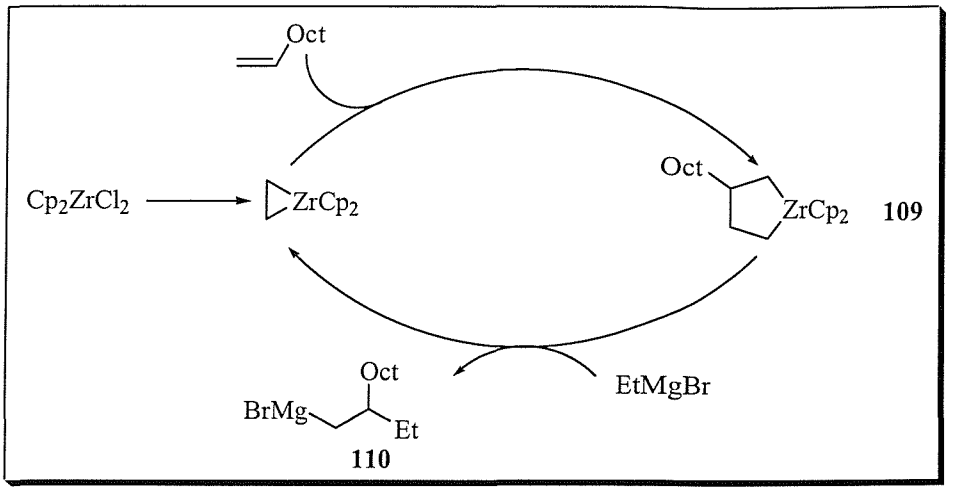


Figure 1.47 - Transmetallation from zirconium to magnesium

1.11.2. Transmetallation to Tin

As mentioned earlier, metathesis reactions of zirconacycles with group IV (Si, Ge, Sn) dihalides are well known. Takahashi extended this idea to transmetallate a single C-Zr bond chemoselectively by reaction with a group IV monohalide[67]. (Figure 1.48.) Reaction of **12** with trimethyltin chloride was both high yielding and chemoselective, to afford the alkyl stannane **111** exclusively. Reactions with various Ge and Si monohalides were unsuccessful.

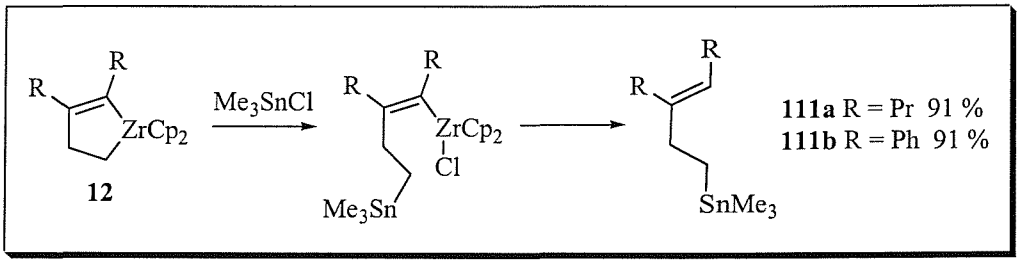


Figure 1.48 - Transmetallation from zirconium to tin

1.11.3. Transmetallation to Copper

Transmetallation of a zirconacycle C-Zr bond to copper was first demonstrated in 1994[68]. Takahashi found that zirconacyclopentadienes such as **112** and **116** could be allylated *via* transmetallation to copper and further reaction with allyl chloride affording **113** and **117**. (Figure 1.49.) Takahashi showed that the diallylated compounds **113** and **117** could be cyclised to zirconacycles **114** and **118** and carbonylated to give the novel tricyclic ring systems **115** and **119** in high yield.

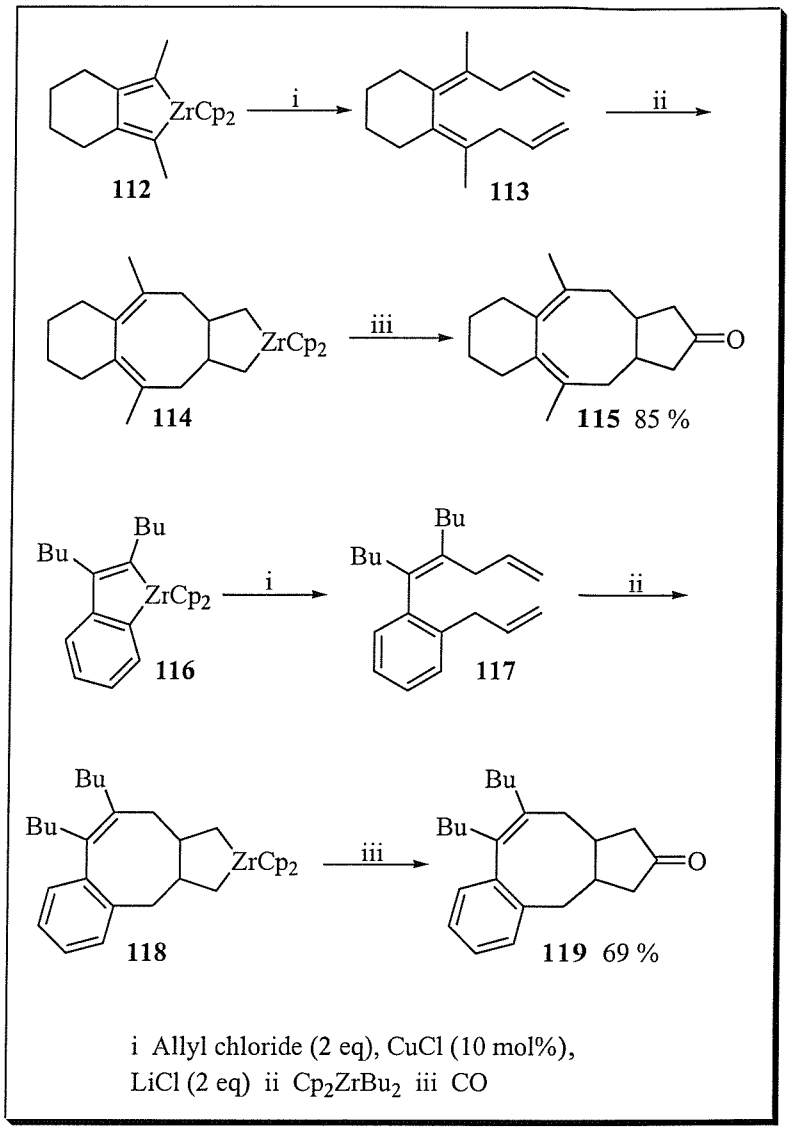


Figure 1.49 - Diallylation of zirconacyclopentadienes

Takahashi later published the alkylation of zirconacyclopentadienes using benzyl bromides and catalytic CuCl to form acyclic dienes as well as 8- and 9-membered ring systems[69]. (Figure 1.50.) The formation of the 8- and 9-membered rings is attributed to the structural rigidity of the bromides used.

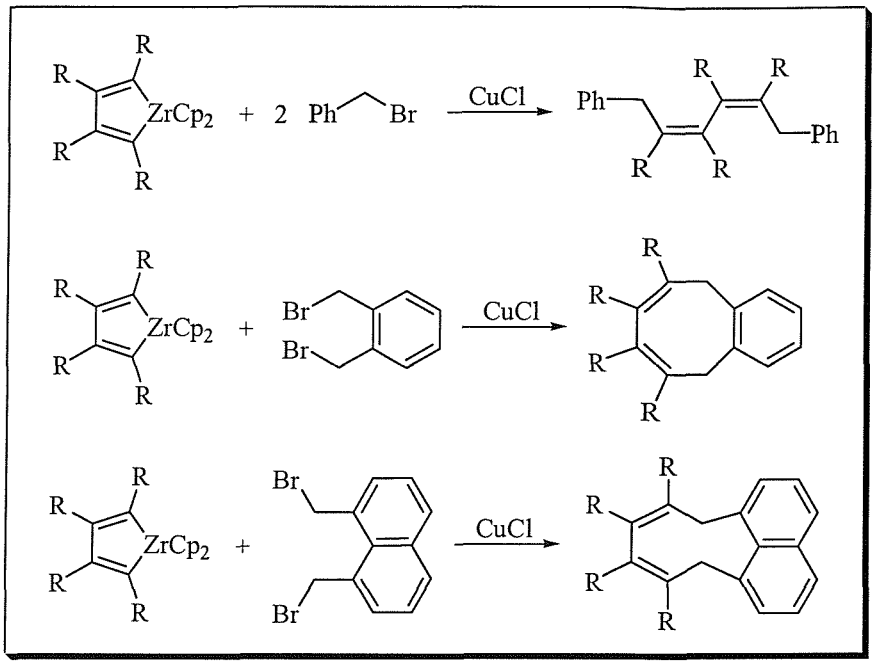


Figure 1.50 - Copper mediated addition to benzyl bromides

A similar coupling of zirconacyclopentadienes with alkynes *via* copper transmetallation was reported by Takahashi[70]. Zirconacycle **120** was reacted in the presence of stoichiometric CuCl/LiCl with activated alkynes to afford highly substituted benzene derivatives **121** in excellent yields (80-90 %). (Figure 1.51.) The yields obtained were severely reduced when less electrophilic alkynes were used. Reaction of **120** with (*E*)- or (*Z*)-diethyl fumarate both gave the same product **123** indicating a stepwise mechanism. Although the mechanism was not fully elucidated, the authors suggest **122** as the intermediate, as two equivalents of copper were required, and precipitation of metallic copper was observed in all reactions.

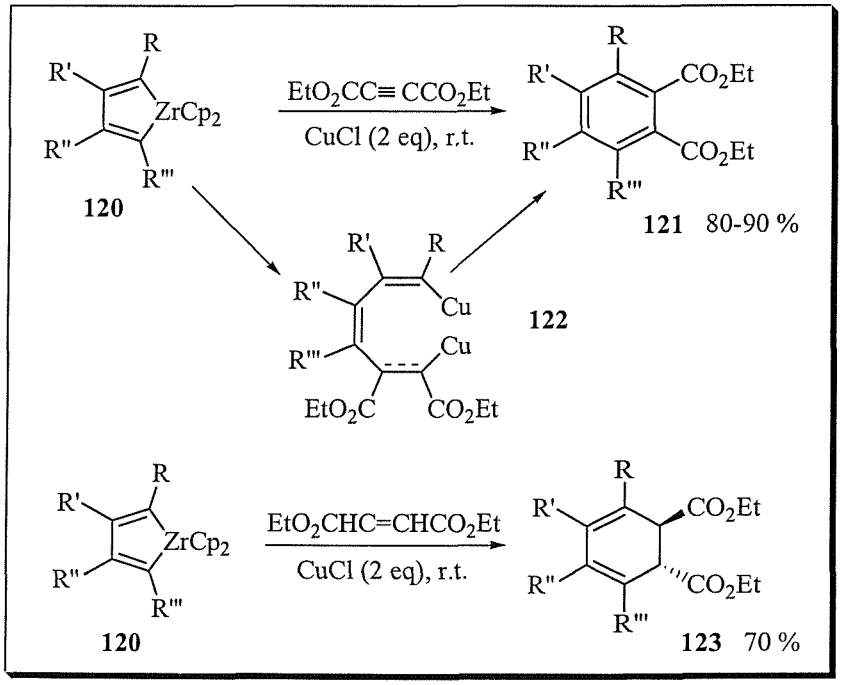


Figure 1.51 - Copper mediated formation of benzene derivatives

In 1998, Takahashi reported a similar reaction whereby zirconacyclopentadienes reacted with 3-iodopropenoates in a cross coupling-conjugate addition reaction to give cyclopentadienes[71]. (Figure 1.52.) Two equivalents of CuCl were used to give excellent yields for a number of substituted zirconacyclopentadienes.

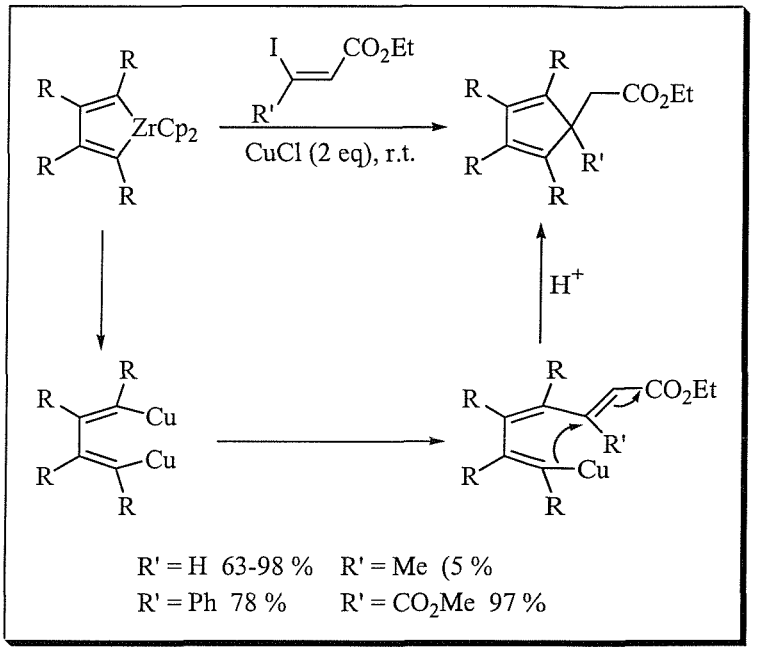


Figure 1.52 - Copper mediated formation of cyclopentadienes

The copper mediated allylation reaction (figure 1.49) was applied to zirconacyclopentenes with the hope of functionalising one of the two C-Zr bonds chemoselectively[72]. Allylation of zirconacyclopentenes **124** in the presence of CuCl (0.1-1 eq) occurred exclusively at the alkenyl C-Zr bond with retention of alkene stereochemistry, affording **126** (81-95 %). (Figure 1.53.) Although allylation of the alkyl C-Zr bond in **125** was kinetically slow, diallylated products **127** could be obtained under more forcing conditions.

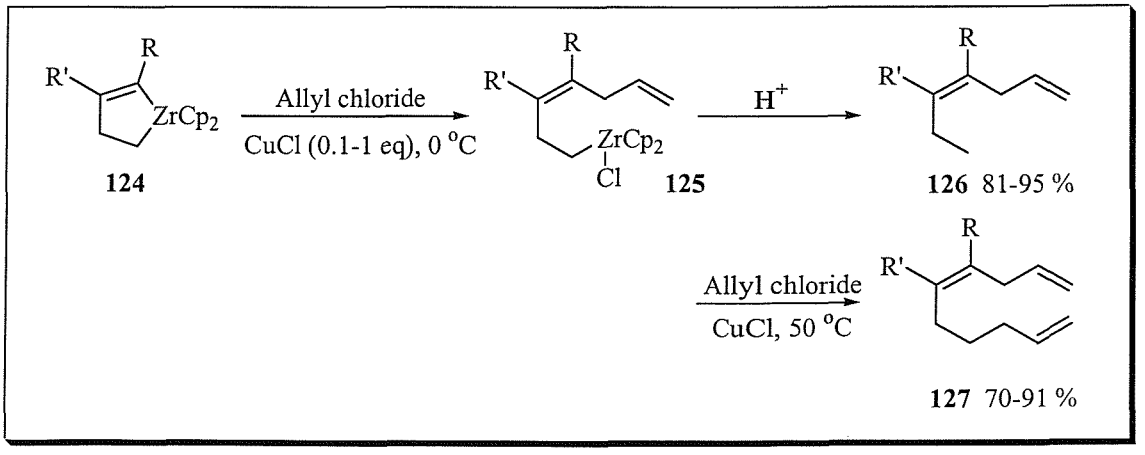


Figure 1.53 - Copper mediated allylation

The intermediate alkyl zirconocene chloride **125** was characterised by NMR and in a separate reaction was treated with MeLi to generate the novel zirconacycle **128** after β-H abstraction and *in situ* co-cyclisation. (Figure 1.54.)

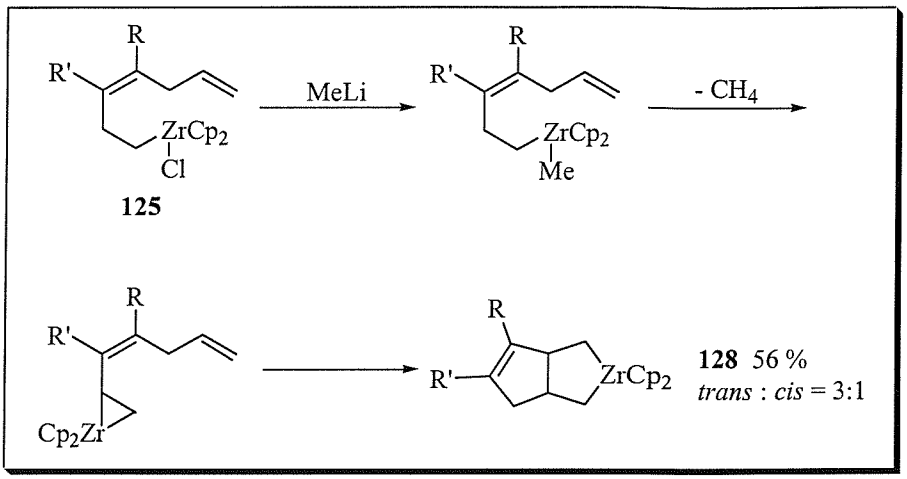


Figure 1.54 - Formation of novel zirconacycles

It was also possible to reverse the chemoselectivity of the mono-allylation reaction to specifically functionalise the other alkyl C-Zr bond of **124**. The first step was the transmetallation of the alkenyl carbon in **124** from Zr to Cu, giving **129**. (Figure 1.55.) After treatment of **124** with stoichiometric CuCl, a single equivalent of MeOH was added. Subsequent allylation gave the alkyl allylated products **130** in good yields. The use of MeOD gave 94 % deuterium incorporation at the alkenyl carbon, indicating that chemoselective hydrolysis had occurred in the presence of the Zr-C bond. The ability to reverse the chemoselectivity of the zirconacyclopentene allylation to afford either **126** or **130** makes this an extremely useful elaboration method.

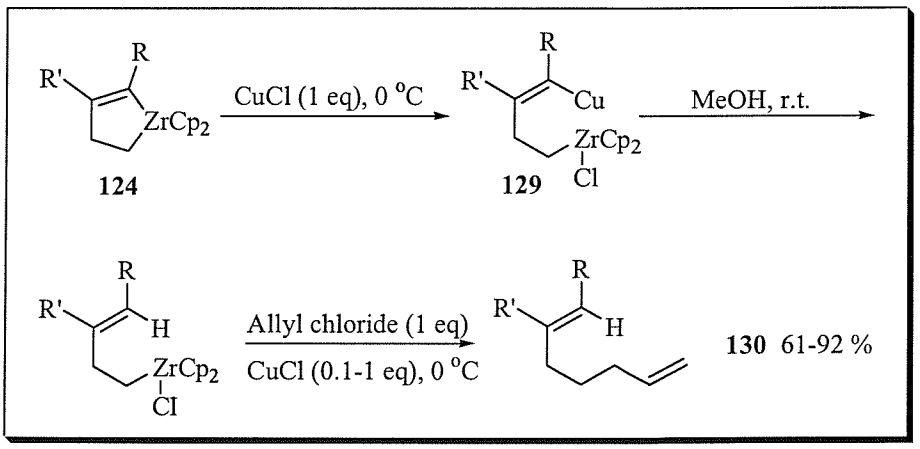


Figure 1.55 - Chemoselective alkyl allylation

Lipshutz[73] reported a similar chemoselective transmetallation to copper of the alkenyl C-Zr bond in a variety of zirconacyclopentenes. Initial studies showed that the transmetallation of the alkenyl C-Zr bond in **131** with CuCl allowed high yielding conjugate addition to enones, such as cyclohexenone, to give **133** after hydrolysis.

(Figure 1.56.) The zirconium enolate **132** was also quenched with NBS and NIS to afford dihalides **134.** Enolate **132** was also reacted with benzaldehyde in the hope of effecting an aldol coupling. Initially the reaction was slow, but it was found that by adding TBAF (forming enolate **135**) resulted in a dramatic rate enhancement giving **136** after hydrolysis in 78 % yield. The alkyl C-Zr bond remaining in **135** was expected to be preserved after the subsequent aldol reaction, potentially allowing further functionalisation.

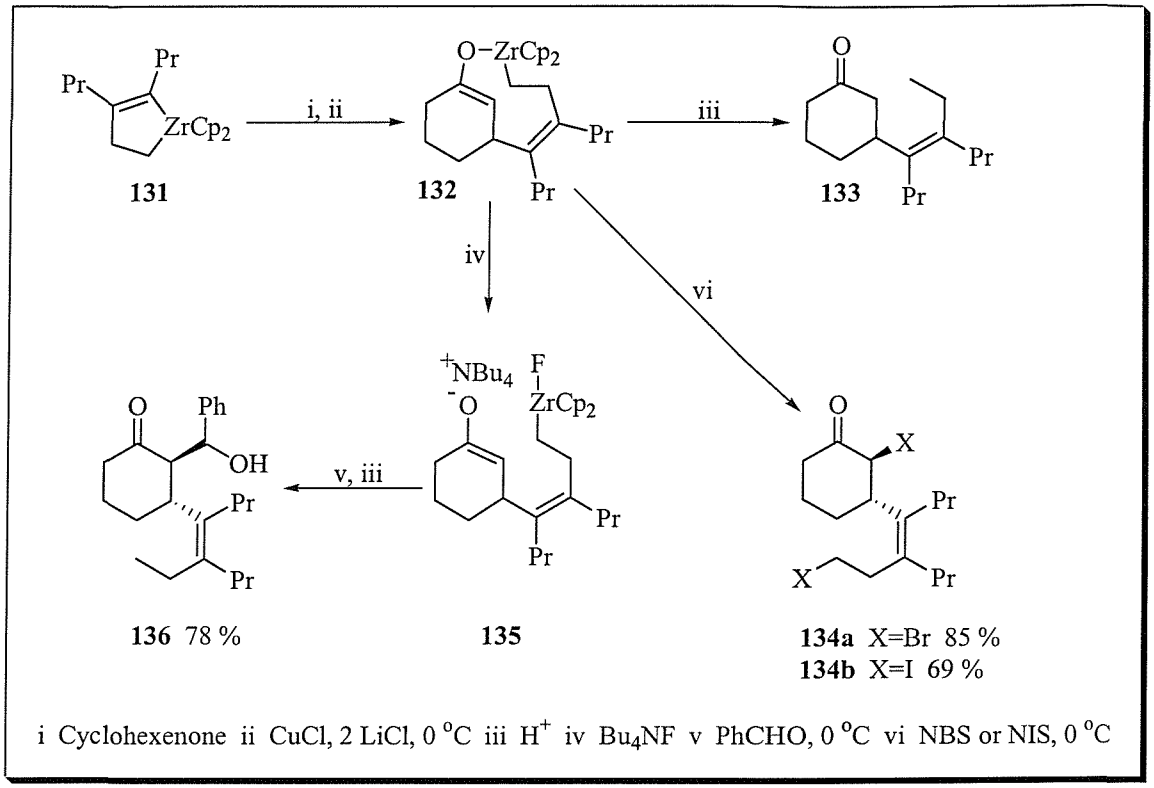


Figure 1.56 - Copper mediated addition to enones and further elaboration

Thus, the reaction of **131** with CuCl, cyclopentenone, TBAF and benzaldehyde, followed by an NBS quench yielded **137** in 60 % yield. (Figure 1.57.) This reaction represented the culmination of a one-pot, seven step sequence (from Cp_2ZrCl_2) in which one C-X and three C-C bonds were created by organozirconium and copper chemistry working in tandem.

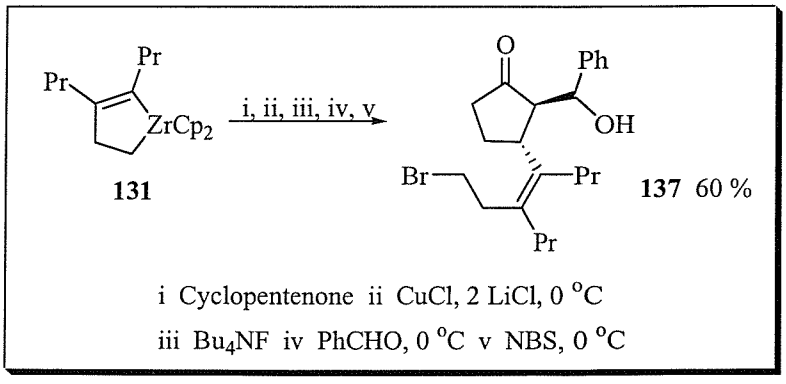


Figure 1.57 - Five-step elaboration of a zirconacyclopentene

Takahashi extended the scope of zirconium to copper transmetallations[74] and showed that zirconacyclopentadienes reacted with benzal halides in the presence of 2 equivalents of CuCl and DMPU to give pentasubstituted cyclopentadienes in moderate to good yields. (Figure 1.58.) It was also found that reaction of zirconacyclopentadienes with 1,1-dibromo-1-alken-3-yne and 1,1-dibromo-1,3-alkadiene afforded fulvene derivatives in good yields.

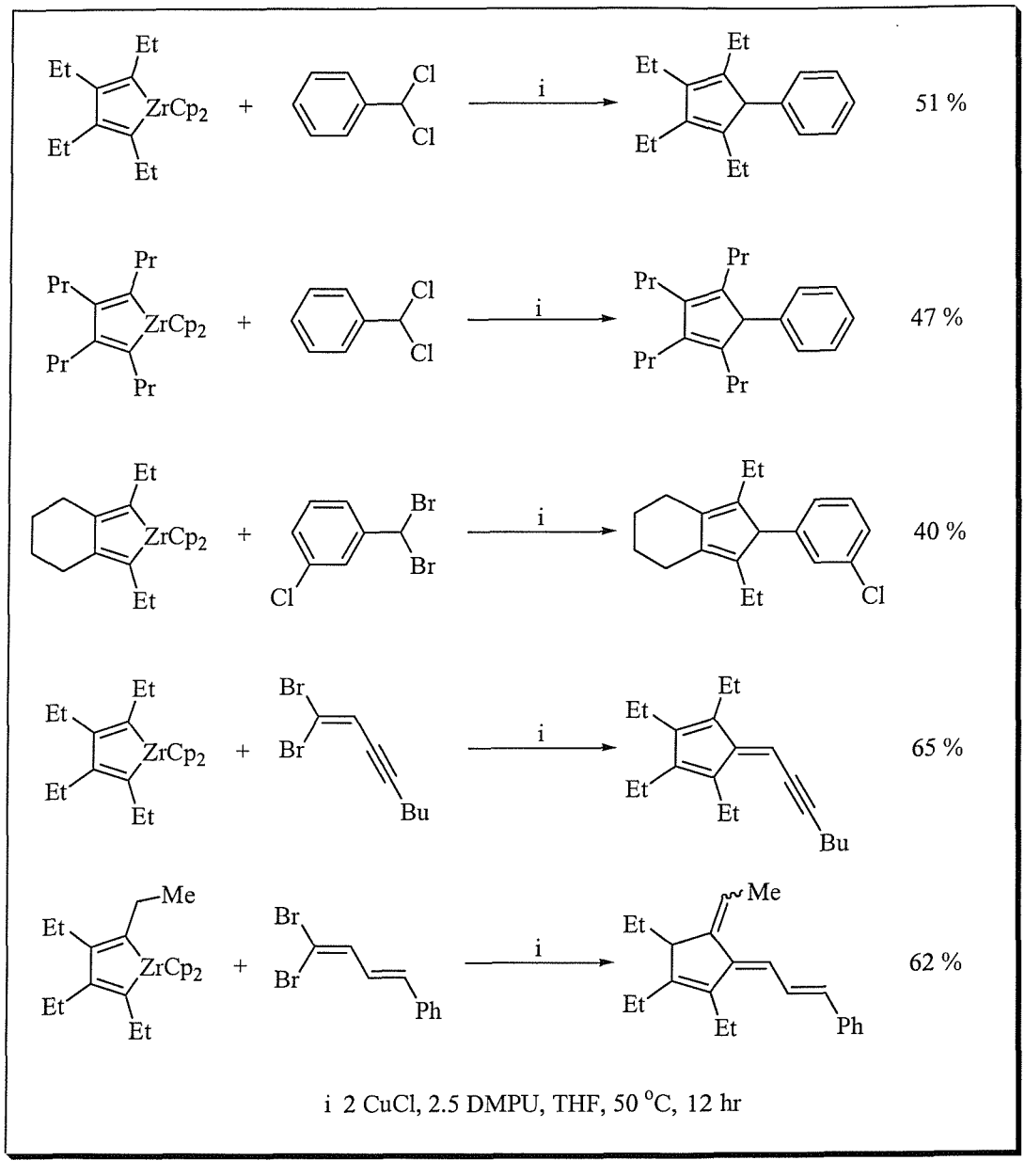


Figure 1.58 - Copper mediated cyclopentadienyl and fulvene formation

Takahashi also showed that zirconacyclopentadienes could undergo reaction with propargyl or allyl halides to afford a variety of vinylated cyclic compounds such as highly substituted styrenes, methylenecycloheptadienes and vinylcyclohexadienes in good yield[75]. (Figure 1.59.)

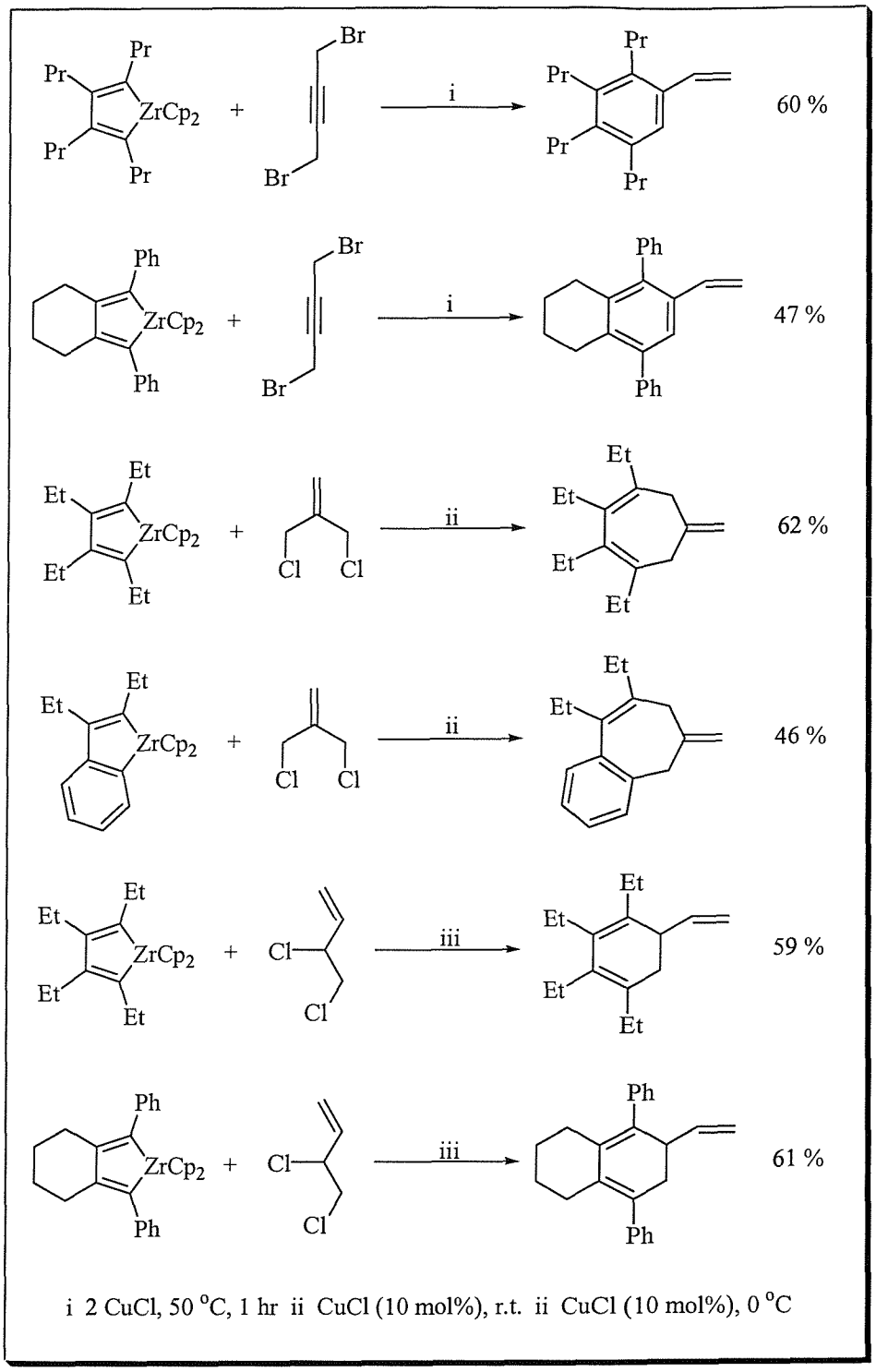


Figure 1.59 - Copper mediated synthesis of vinylated compounds

1.11.4. Transmetallation to Nickel

At present, there has been relatively little research published regarding the transmetallation of the C-Zr bond to C-Ni.

Takahashi initially reported that zirconacyclopentadienes could be reacted with an alkyne in the presence of a stoichiometric amount of $NiCl_2(PPh_3)_2$ to give benzene derivatives in good yields[76]. Representative examples are shown below in figure 1.60.

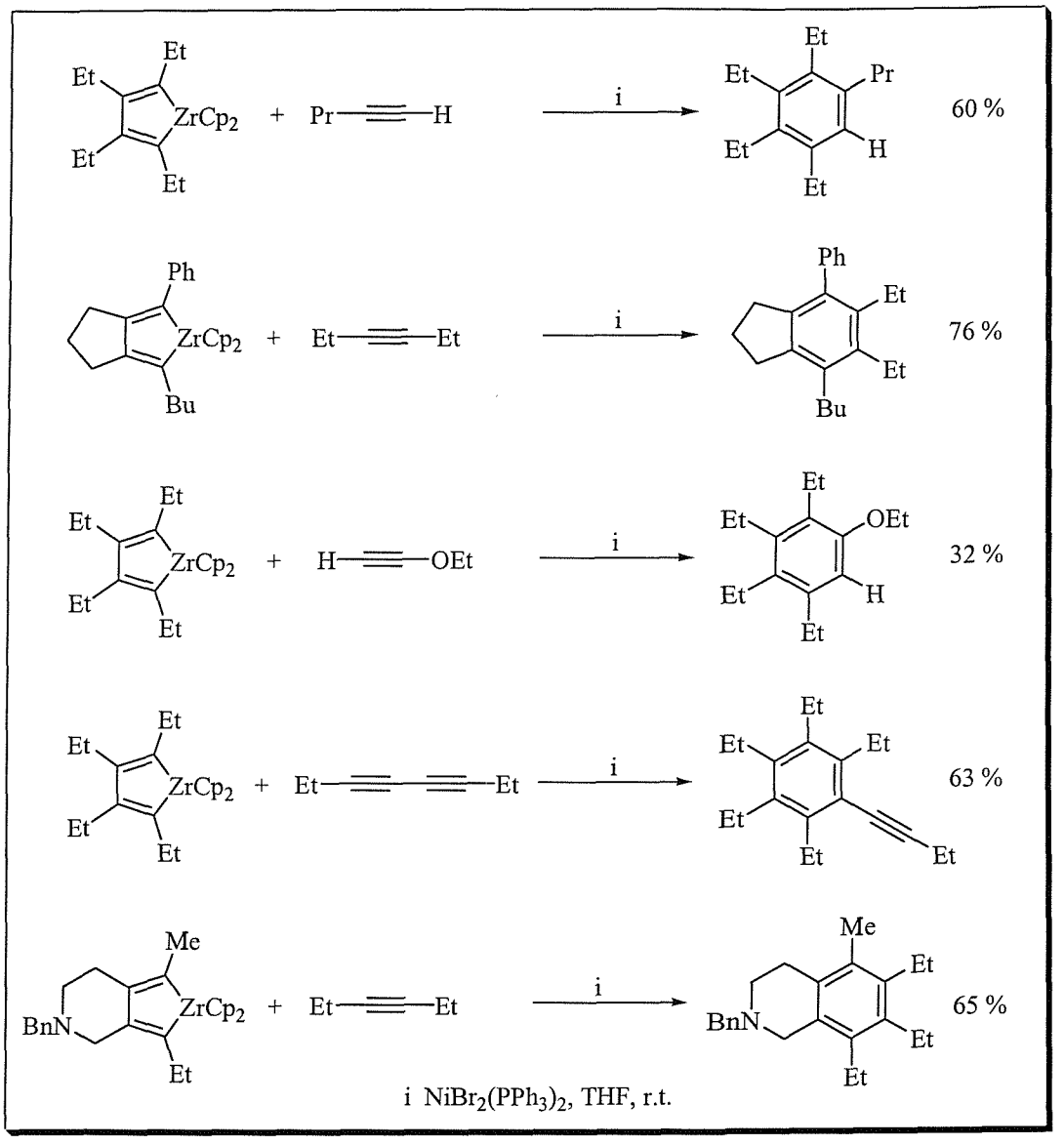


Figure 1.60 - Nickel mediated arene synthesis

This mechanism of this coupling is believed to occur by transmetallation of both Zr-C bonds of **13** simultaneously to give the nickelacyclopentadiene **138** with elimination of zirconocene dibromide. (Figure 1.61.) The insertion of the alkyne component into one of the C-Ni bonds affords the nickelacycloheptatriene **139**. Compound **139** undergoes reductive elimination to give the benzene derivative **140** and a Ni^0-complex that decomposes to metallic nickel and free ligands.

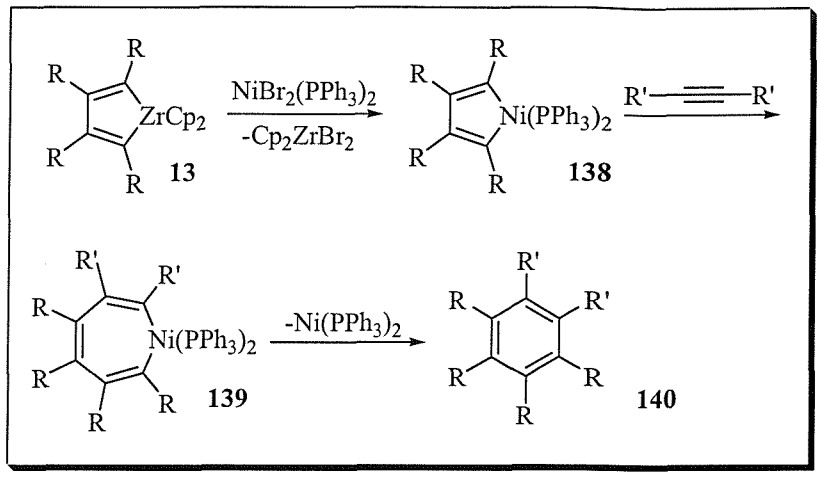


Figure 1.61 - Nickel mediated arene formation

Takahashi later reported that zirconacyclopentadienes reacted with two equivalents of alkynyl halides in the presence of a catalytic amount of $NiCl_2(PPh_3)_2$ to afford multi-substituted arylalkynes[77]. (Figure 1.62.)

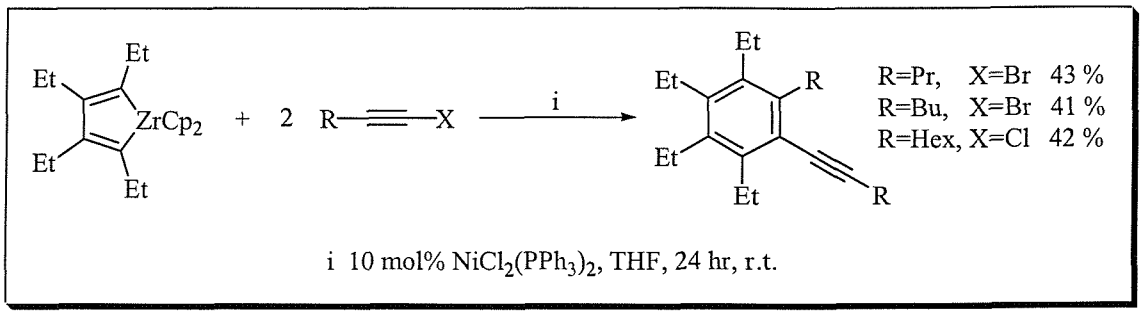


Figure 1.62 - Nickel-catalysed arylalkyne formation

The precise mechanism for this transformation has not been fully established. However, it is thought to proceed either *via* path A or B. (Figure 1.63.) In path A, it is suggested that the alkyne inserts into the C-Ni bond of the nickelacyclopentadiene **138** to afford the nickelacycloheptatriene **141**. Compound **141** undergoes reductive elimination to give the benzene derivative **142**. The Ni^0 species is able to insert into the Ni-X bond to give **143** and facilitate a further alkyne coupling to give the final arylalkyne **144**. Alternatively, path B implies that nickelacycloheptatriene **141** can rearrange directly to **143** before undergoing direct alkyne coupling to the arylalkyne **144**.

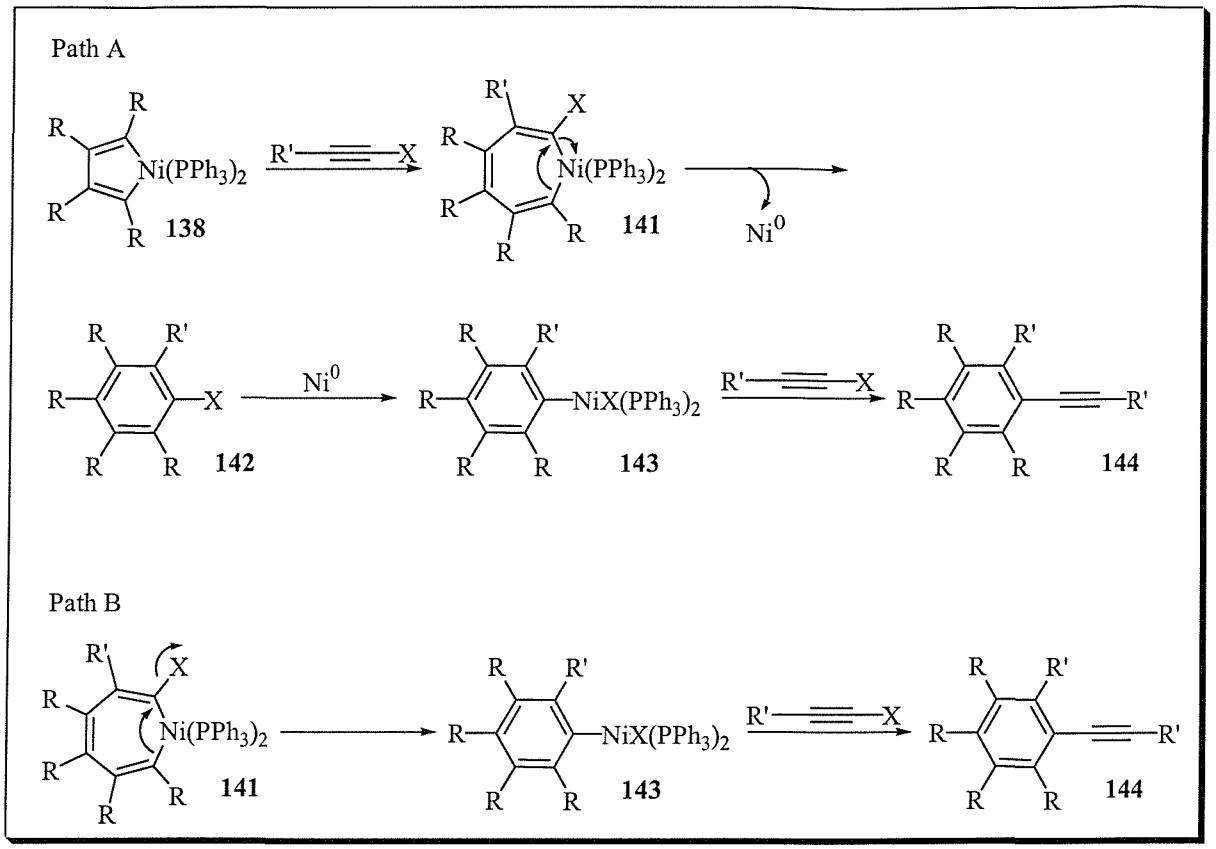


Figure 1.63 - Mechanism of nickel-catalysed arylalkyne formation

1.12. Conclusions

Over the last twenty years, efficient synthetic methods have been developed for a vast array of different zirconacycles. Facile procedures have allowed *inter*- and *intra*-molecular homo- and cross-coupling of alkenes and alkynes using organozirconium to be developed. The resulting zirconacycles can be elaborated using a wide range of well-documented protocols including protonation, halogenation, carbene/carbenoid insertion, metathesis and transmetallation. Consequently, zirconium complexes have become a valuable precursor to many synthetically useful compounds.

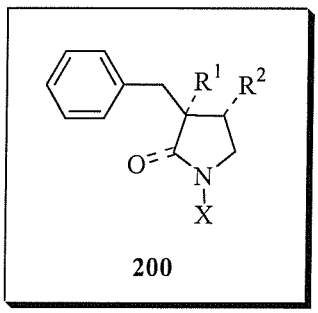
CHAPTER 2

THE SYNTHESIS OF 3-BENZYL PYRROLIDINES

2. The Synthesis of 3-Benzyl Pyrrolidines

2.1. Introduction to 3-Benzyl Nitrogen Heterocycles

There has been significant research into the synthesis of substituted 5-membered nitrogen heterocycles as they have shown potent biological activity. Compounds such as **200** possessing a benzyl group at C_3 are of synthetic importance as these compounds exhibit a wide range of biological activities. (Figure 2.1.)



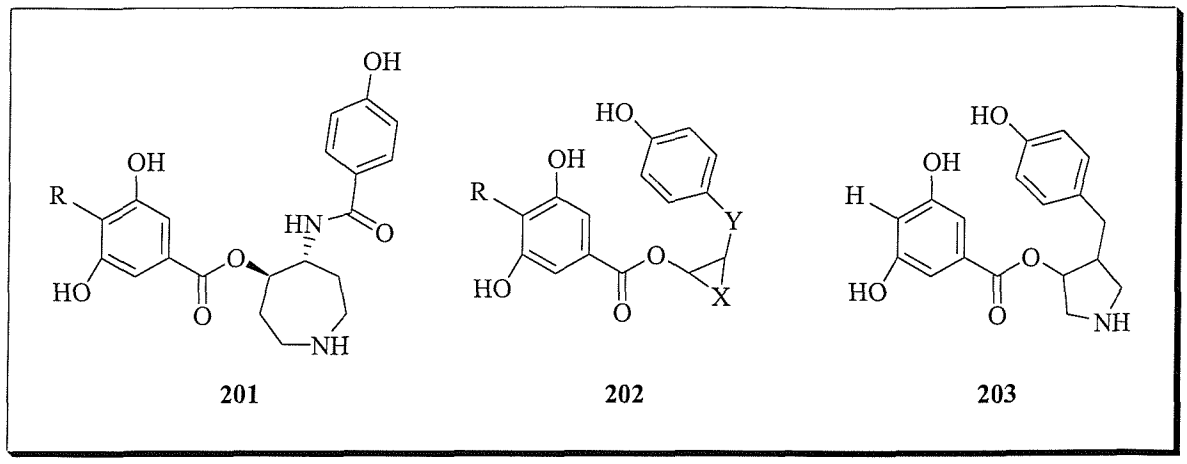
200

Figure 2.1 - 3-Benzyl pyrrolidine target

2.1.1. Activity of 3-Benzyl Pyrrolidines

The pharmacological effects of 3-benzyl pyrrolidines have not been extensively explored in the literature. However, in the last 10 years, an increasing number of 3-benzyl pyrrolidine compounds have been synthesised and screened for biological activity.

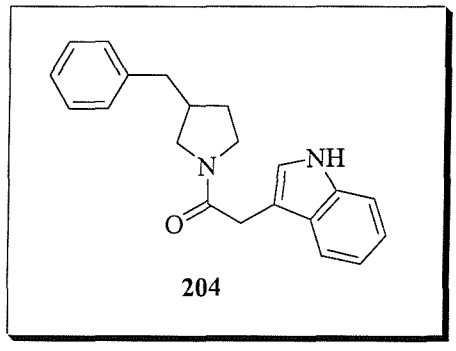
Protein kinase C (PKC) is a family of serine/threonine specific kinases. Activated PKC phosphorylates numerous proteins which are involved in many biological systems[78-80]. Enhanced activation of PKC had been implicated as a major factor in the formation of many diseases such as cancer, asthma, rheumatoid arthritis, diabetic complications, psoriasis and central nervous system disorders. As a consequence, inhibitors of PKC may be useful in the therapeutic treatment of such diseases[81]. Eli Lilly reported that balanol **201** was a potent PKC inhibitor. (Figure 2.2.) Initially isolated from a metabolite of the fungus *Verticillium balanoides*[82], and later from a species of *Fusarium* at Nippon Roche[83], structure-activity relationship (SAR) studies were undertaken based on **202**[84], with variation of R, X and Y. Interestingly, with R=H, the replacement of carboxamide moiety with a methylene group ($Y=CH_2$) and the 7-membered azepine core with a pyrrolidine ring ($X=CH_2NHCH_2$) led to the vastly more potent PKC inhibitor **203**[84,85].



201 **202** **203**

Figure 2.2 - PKC Inhibitors

There is evidence that cyclic somatostatin and neurokinin A analogues bind to their receptors in a β-turn conformation[86,87]. Willems reported the synthesis of 1-acyl-3-benzyl pyrrolidine **204** as a conformationally strained, non-peptide β-turn mimetic which had a high affinity for the NK-3 receptor[88]. (Figure 2.3.)



204

Figure 2.3 - NK-3 receptor antagonist

The endogenous brain peptide L-prolyl-L-leucyl-glycinamide **205** (PLG) has been demonstrated to exhibit a variety of biological activities[89,90]. (Figure 2.4.) PLG is proposed to exert these effects through the modulation of dopaminergic receptors in the central nervous system[91]. Thus, PLG induces an increase in the affinity of dopamine receptor agonists and enhances the number of high-affinity dopamine D_2 binding sites[92]. The β-analogue **206** of PLG was synthesised and significant enhancement of the binding of the dopamine receptor agonist [^{3}H]pramipexole to dopamine D_2 receptors was observed[93].

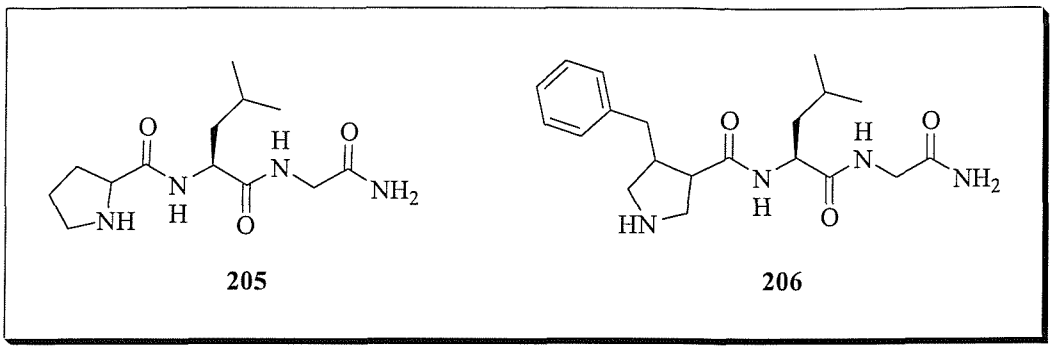


Figure 2.4 - Dopamine receptor antagonists

Growth hormone (GH), which is secreted by the pituitary gland, has important functions in the enhancement of anabolic processes[94]. The discovery of a group of small oligopeptides[95] which when administered, promote the pituitary to release GH, led to intense efforts to identify other small molecule mimetic Growth Hormone Secretagogues (GHS)[96]. Yang reported the synthesis of a series of 3-benzyl pyrrolidine and piperidines based on **207**[97]. (Figure 2.5.) Variation of R, Y, X and n led to potent GHS, although it was found that the piperidines had much higher *in vitro* potency that the pyrrolidines.

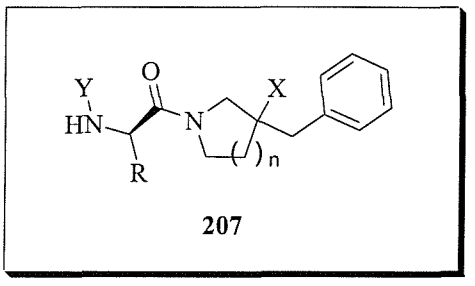


Figure 2.5 - Growth hormone secretagog

2.1.2. Activity of 3-Benzyl Lactams

The 3-benzyl lactams have been shown to exhibit a wide range of biological activities and are therefore potential drug candidates for the treatment of many diseases. A series of 3-alkyl, 3-benzyl-substituted 2-pyrrolidinones were prepared and evaluated for their anticonvulsant activities[98]. (Figure 2.6.) Lactam **208** was shown to be an effective anticonvulsant and compared favourably in activity to current antieplileptic drugs such as ethosuximide, phenobarbital and valporic acid. However, lactams **209** and **210** are also very effective anticonvulsants against seizures induced by maximal electroshock. Hence, 3,3-disubstituted 2-pyrrolidinones have a broad spectrum of action and may be useful for the treatment of human epilepsy.

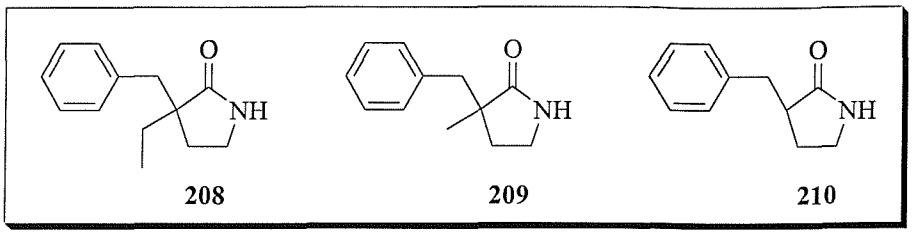


Figure 2.6 - Anticonvulsant compounds

The inhibition of cysteine proteases is being studied as a strategy to combat parasitic diseases such as Chagas' disease, leishmaniasis and malaria. Scheidt reported that the conformationally constrained inhibitors **211**, **212** and **213** were very effective inhibitors of the *Leishmania major* cathepsin B-like cysteine protease[99]. (Figure 2.7.)

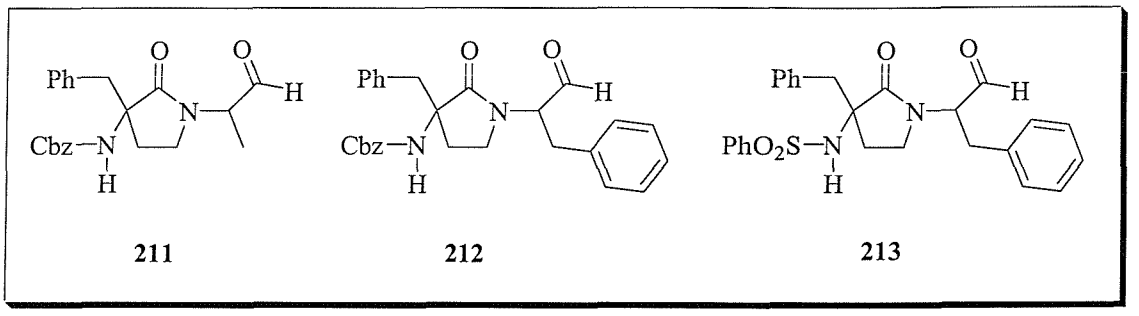


Figure 2.7 - Cysteine protease inhibitors

Dolbeare synthesised a series of PLG peptidomimetic lactams **214** to test the hypothesis that attaching a hydrophobic moiety to the lactam ring would mimic the isobutyl side chain of the leucyl residue of PLG[100]. (Figure 2.8.) It was hoped that this would increase the dopamine receptor modulating activity. By substituting the ring with a benzyl group at the 3-position (R=benzyl), **215** gave the greatest enhancement in binding of [^{3}H]-*N*-propylnorapomorphine to dopamine receptors isolated from bovine striatal membranes.

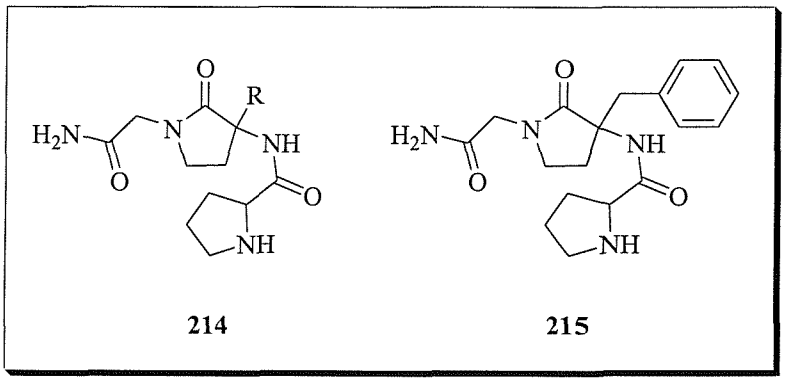


Figure 2.8 - PLG peptidomimetic lactams

An important use of 3-benzyl lactams has been in the fight against HIV and AIDS. The importance of HIV protease inhibitors in the treatment of AIDS is now well established[101,102]. Salituro synthesised a set of HIV protease inhibitors based on **216**, with variation of X and R[103]. (Figure 2.9.) In particular, **217** displayed excellent potent inhibitory activity.

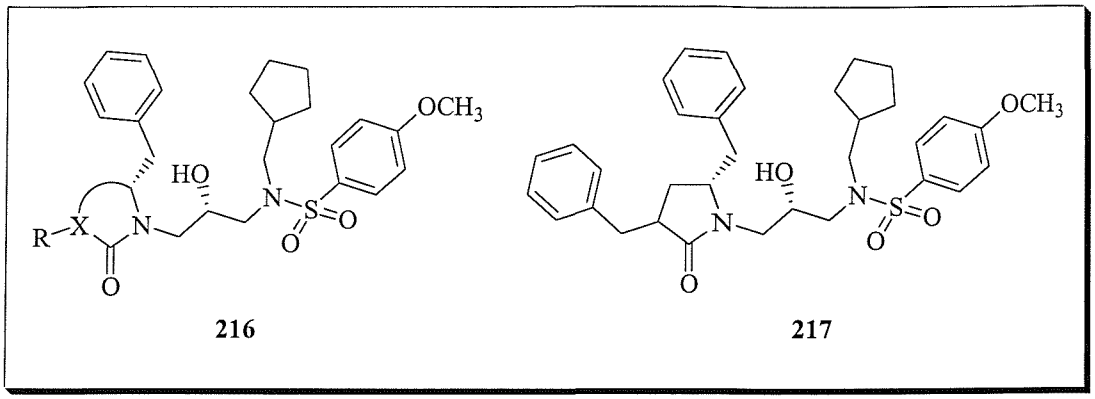


Figure 2.9 - HIV protease inhibitors

The HIV protease inhibitor **217** was further modified and a series of potential inhibitors based on **218** were synthesised[104], with variation at X and Y. (Figure 2.10.) This generated compound **219** which had a similar potency to currently marketed HIV protease inhibitors.

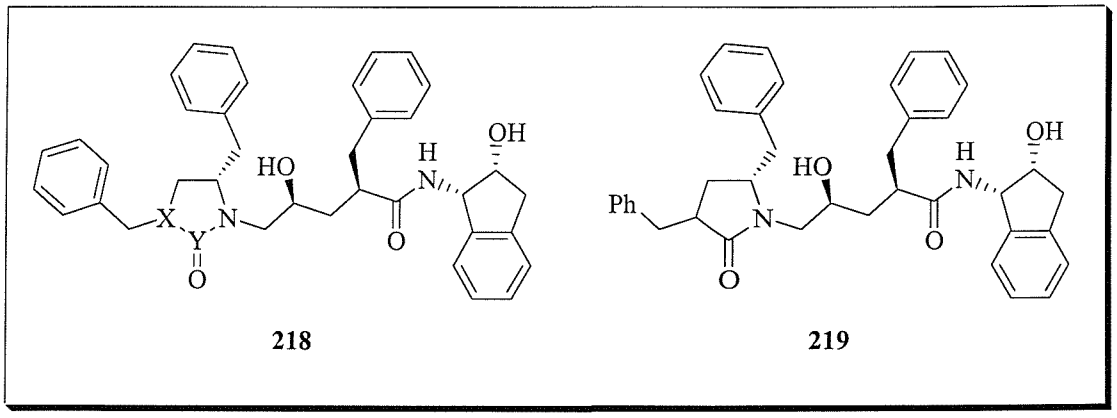


Figure 2.10 - High potency HIV protease inhibitors

Due to these and other pharmacological reports of the 3-benzyl pyrrolidine pharmacophores [105,106], we felt that these compounds would make biologically active targets for synthesis *via* transition metal mediated diene cyclisation.

2.1.3. Diene Cyclisation to Nitrogen Heterocycles

We initially wanted to focus on the formation of the pyrrolidine ring skeleton using the cyclisation of dienes as there are fewer methods for cyclising dienes in the literature, in comparison to enyne and diyne cyclisations.

Macfarlane had shown that it was possible to cyclise **220a** using Negishi's reagent to form the 3-benzyl pyrrolidine **221a** in high yield and as a 5:1 *trans* to *cis* mixture of diastereoisomers[107]. (Figure 2.11.)

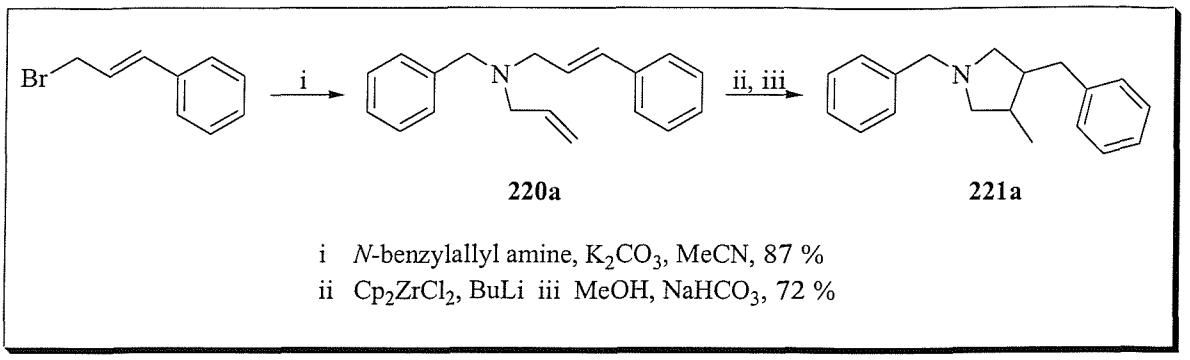


Figure 2.11 - Zirconium mediated synthesis of 3-benzyl pyrrolidines

2.2. Results and Discussion

2.2.1. Synthetic Approach to 3-Benzyl Pyrrolidines

To investigate the potential pharmaceutical activity of the benzyl pyrrolidines, it was necessary to develop a route to the cyclisation precursor which would allow easy variation of the aromatic group. Disconnection of pyrrolidine **221** gave diene **220**. (Figure 2.12.) It was felt that diene **220** could be realised *via* carbonyl reduction of **222**, which in turn could be synthesised *via* a Heck coupling of PhI with **223**. Alternatively, **222** could be synthesised *via* amide coupling of commercially available cinnamic acid **225** with amine **224**. However, we were keen to use **222** as an intermediate in our synthesis as amides containing the cinnamyl motif have been shown to exhibit anticonvulsant activity[108].

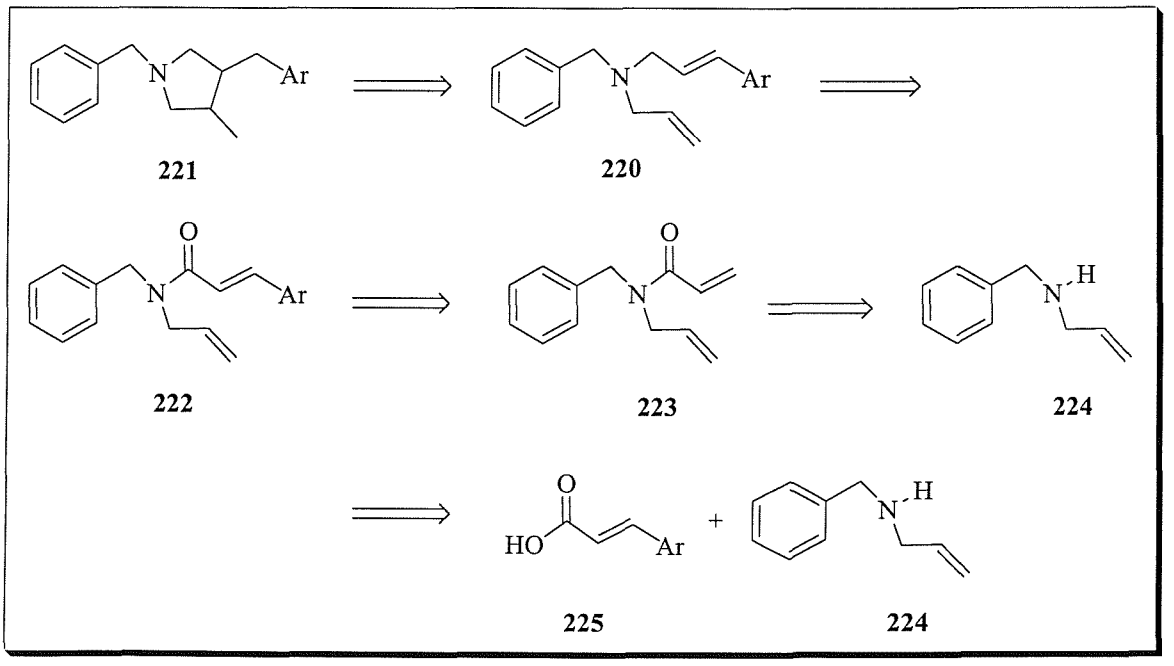


Figure 2.12 - Retrosynthetic analysis of 3-benzyl pyrrolidines

2.2.2. Diene Synthesis: Method 1 Using Heck conditions

Dienyl amide **223** was readily synthesised from **224** with acryloyl chloride in aqueous base in a moderate 51 % yield. Amide **223** was treated with a 2-fold excess of iodobenzene under Heck conditions. Initial oxidative addition of Pd into the carbon-iodine bond, followed by addition to the more electron poor double bond generated **226**. (Figure 2.13.) Monitoring the reaction by GC and ^{1}H NMR showed the formation of **222a** and the benzyl lactam **229**. However, continued heating showed the disappearance of **222a** and the formation of **230a** by NMR. There was no evidence for the formation of the exo-cyclic diene product **228** which was believed to be an intermediate in the synthesis of **229**. However, the crude reaction mixture contained many inseparable impurities, believed to be piperidine by-products which formed *via* a 6-endo-trig cyclisation. Trost reported a similar reaction in the cyclisation of 1,6-dienes to carbocycles which also gave 5- and 6-membered ring products[109]. Using only 1eq of PhI was tried, but this gave a very complex mixture of products. The reaction was also tried in THF and MeCN, but on both occasions failed.

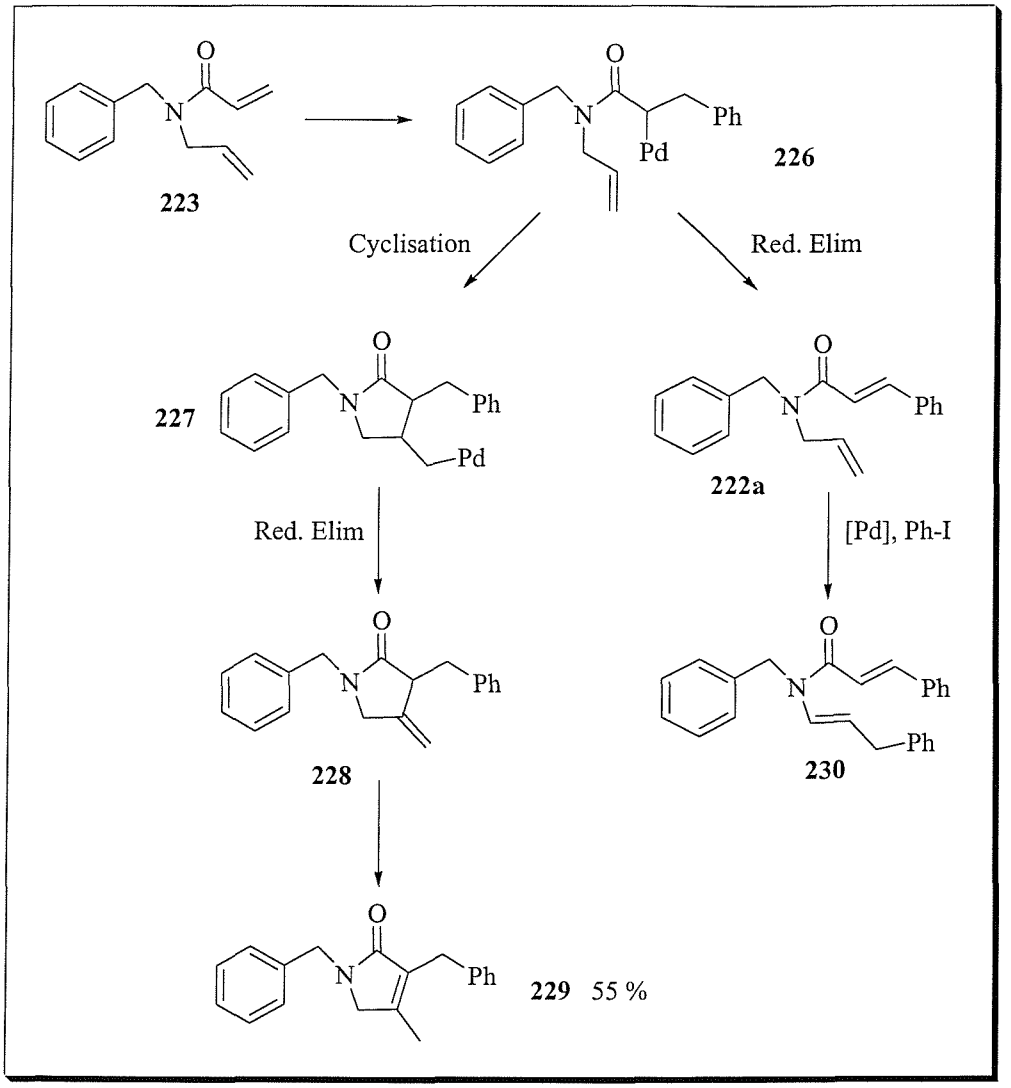


Figure 2.13 - Mechanism of 3-benzyl lactam synthesis

It was felt that if the reductive-elimination step could be impeded, then this reaction could provide a one-pot procedure for the formation of cyclic lactams with varying aromatic groups. Lu reported a similar cyclisation for enynes[110] and in the formation of lactones[111] and showed that Pd-H reductive-elimination could be inhibited by the presence of chloride ions. The addition of 30 equivalents of LiCl to the reaction mixture indeed failed to form **222a** and gave **229** in an isolated yield of 55 %.

2.2.3. Diene Synthesis: Method 2 Using Cinnamic Acids.

It was felt that a different approach would be needed for the synthesis of **222a**. Disconnection of **222a** across the amide bond gave rise to the simple coupling of **224** with synthetically and commercially available cinnamic acid **225a**. Five cinnamic acids **225a-e** were selected, and either obtained commercially or synthesised *via* a Knoevenagel condensation. The cinnamic acids **225a-e** were converted to their acid chlorides by reaction with oxalyl chloride and catalytic DMF, followed by addition of allylamine in aqueous NaOH to give the corresponding *N*-allyl cinnamides. (Figure 2.14.) All secondary amides **231a-e** were recrystallised from ethanol in moderate to high yield. The secondary amides were benzylated to give **222a-e** using NaH and benzyl bromide in moderate to high yield. Carbonyl reduction was initially tried by reaction of **222a** with $LiAlH_4$ and DIBAL-H. In both instances, the reactions failed to give **220a** cleanly. A literature search indicated that similar reductions of cinnamic fragments had been undertaken successfully using AlH_3[112-114]. The AlH_3 was generated using the procedure by Yoon in which a saturated solution of $LiAlH_4$ in THF was reacted with concentrated H_2SO_4[112] (CARE: EXOTHERMIC REACTION!). Reduction of amides **222a-e** with 1.3 equivalents of AlH_3 in THF gave the corresponding *bis*-allylic amines **220a-e** in moderate yields.

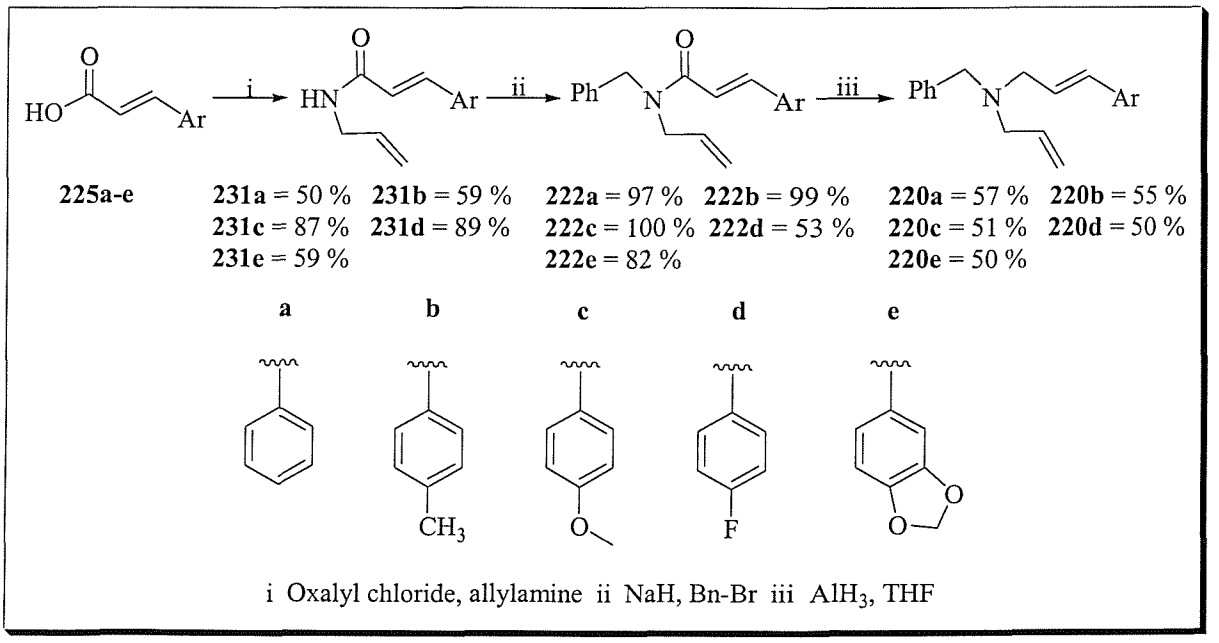


Figure 2.14 - Synthetic approach to cyclisation precursors

2.2.4. Stoichiometric Zirconium Mediated Cyclisations

Dienes **220a-e** were cyclised using Negishi's reagent. Treatment of **220a** with 1 eq of Negishi's reagent led to approximately 90 % conversion by GC to the cyclic product after hydrolytic quench. Using 1.2 eq of Negishi's reagent, **220a**, **220b** and **220d** were completely cyclised to the desired pyrrolidines. (Figure 2.15.) Dienes **220c** and **220e** were found to cyclise incompletely with 1.2 eq of Negishi's reagent. However, addition of 2 eq of Negishi's reagent led to complete cyclisation.

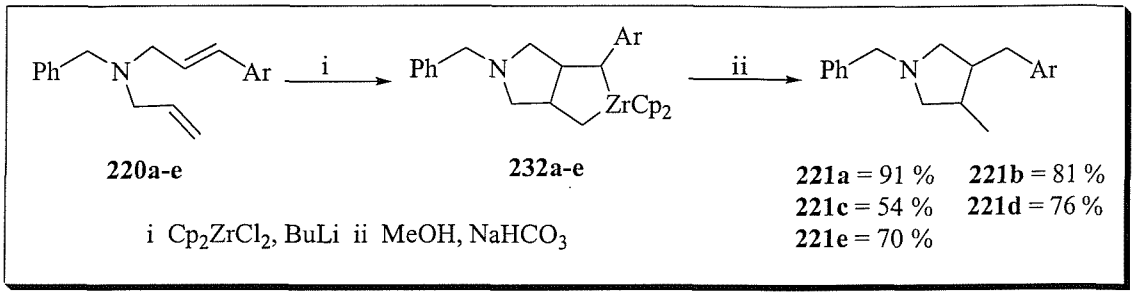


Figure 2.15 - Zirconium mediated synthesis of 3-benzyl pyrrolidines

The diastereoselectivity of the resulting pyrrolidines **221** was dependent on how long zirconacycle **232** was left before being quenched with MeOH and $NaHCO_3$. After 1 hour, the *trans* to *cis* ratio was approximately 1:1. However, leaving **232a-e** for 8 hours gave a 5:1 *trans* to *cis* ratio of pyrrolidine diastereoisomers after protonation. It was hoped that refluxing zirconacycle **232a** would favour the thermodynamically more favourable *trans* isomer. However, the reaction mixture was found to consist of many by-products.

As part of our studies into the cyclisation of cinnamyl derived amines, diene **233** was synthesised from the reaction of cinnamyl bromide and benzyl amine in 85 % yield. We were pleased to find that the hindered diene **233** cyclised cleanly to **234** to give an 11:1 ratio of *trans* to *cis* diastereoisomers. (Figure 2.16.)

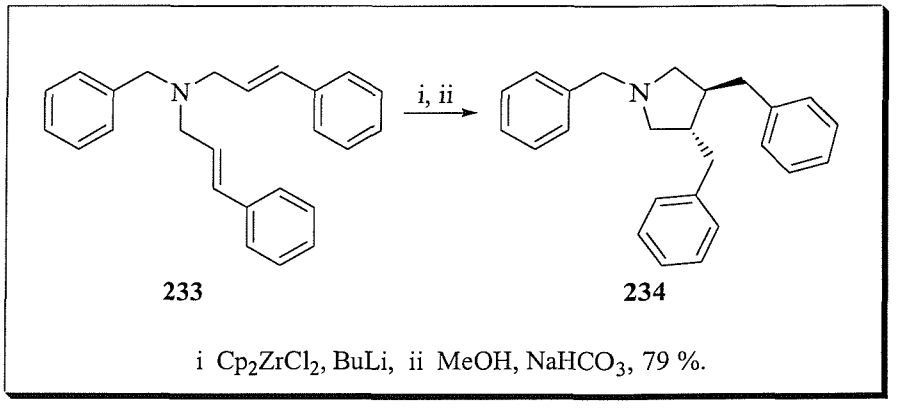


Figure 2.16 - Zirconium mediated synthesis of 3,4-dibenzyl pyrrolidines

2.2.5. Sub-stoichiometric Zirconium Mediated Cyclisations

Since its earliest report[32], considerable research has been undertaken into the cyclisation of diene systems using sub-stoichiometric Cp_2ZrCl_2 and Grignard reagents. In particular, Waymouth had shown that diene **235** could be cyclised to the *bis*-Grignard reagent **236** using 10 mol% of Cp_2ZrCl_2 and 4 eq of BuMgCl[33]. After protonation, **237** was obtained as a 2:1 ratio of *cis* to *trans* pyrrolidines. (Figure 2.17.)

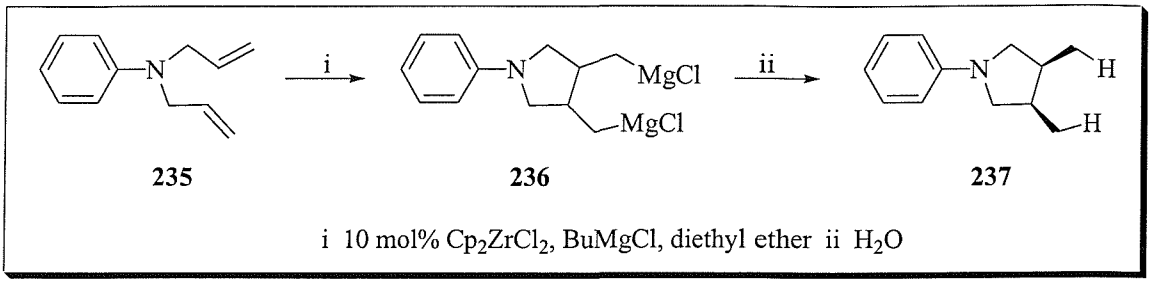


Figure 2.17 - Waymouth's sub-stoichiometric cyclisation

Mori had also shown that the hindered diene **238** could be cyclised to the *bis*-Grignard reagent **239** which gave pyrrolidine **240** after hydrolysis[34]. (Figure 2.18.)

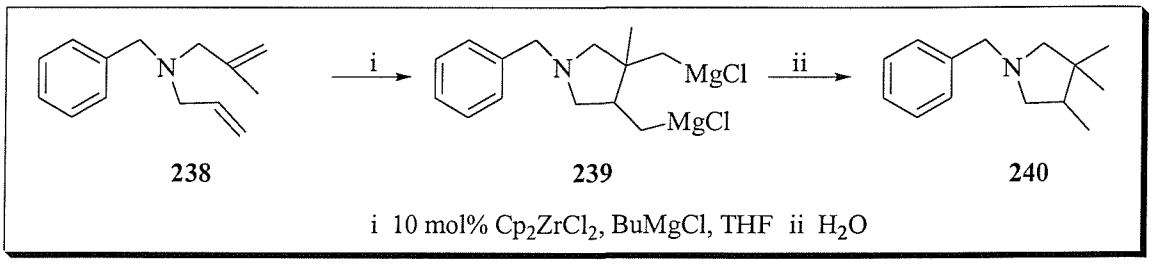


Figure 2.18 - Mori's cyclisation

It was hoped that a set of cyclisation conditions could be developed for the cyclisation of dienes **220** to the *bis*-Grignard **241**. (Figure 2.19.) This would give pyrrolidine **221** after hydrolysis. Pyrrolidines **221a-e** had been synthesised using Negishi's reagent, so by monitoring the reactions by G.C we hoped to develop a set of conditions to cyclise dienes **220a-e** using sub-stoichiometric amounts of Cp_2ZrCl_2.

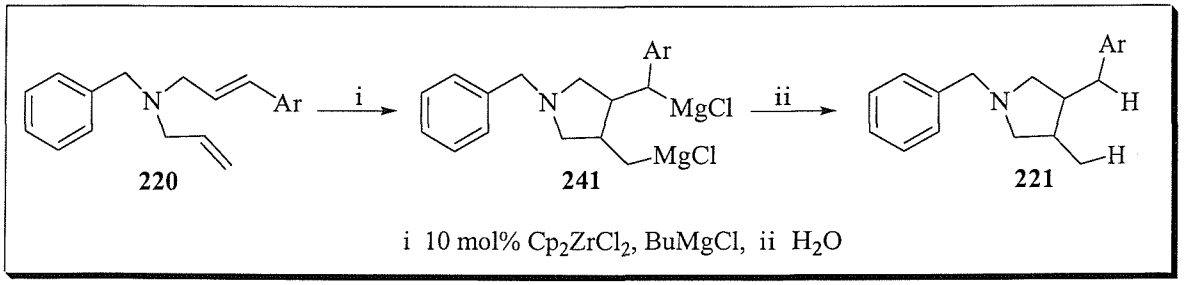


Figure 2.19 - Sub-stoichiometric zirconium mediated cyclisation

However, using the mechanism outlined by Waymouth, it was also possible for the *mono*-Grignard **243** to form during the reaction[115]. (Figure 2.20.)

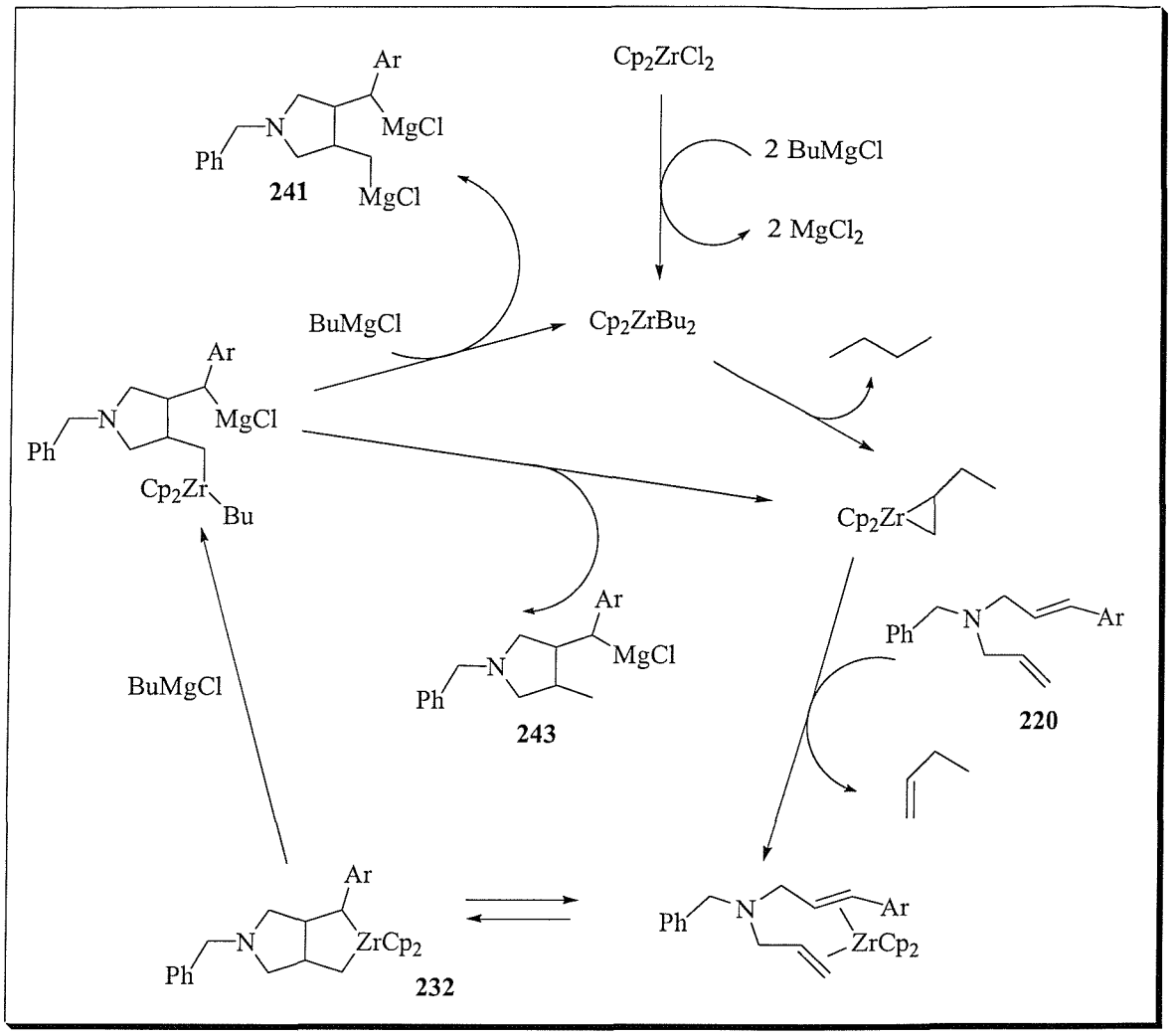


Figure 2.20 - Mechanism of sub-stoichiometric zirconium mediated cyclisation

To determine whether **241** and **243** were forming, the reaction was quenched with D_2O. (Figure 2.21.)

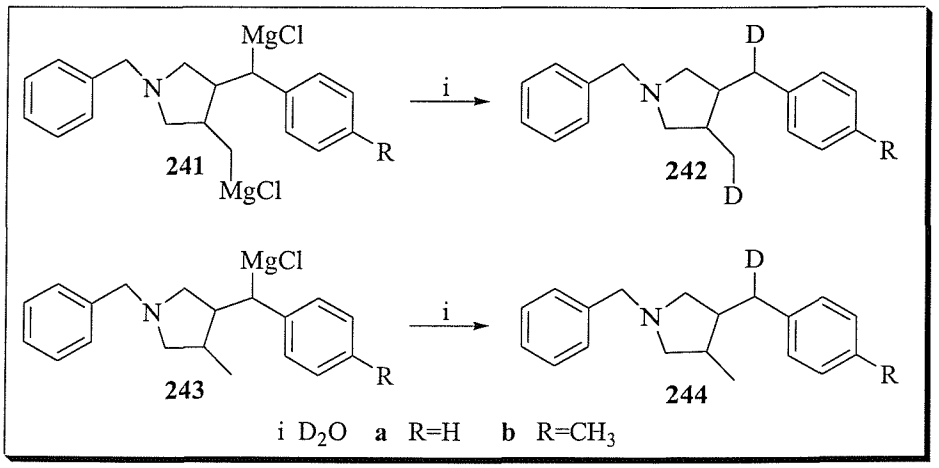


Figure 2.21 - Deuterium quench product

A set of reaction conditions were chosen for the cyclisation of **220a** to **221a** and the reactions monitored by GC. The results are summarised in table 2.22.

Eq of BuMgCl	Solvent	Temperature	Time / hrs	% **220a**	% *cis* **221a**	% *trans* **221a**
4	DEE	Reflux	3	100	0	0
4	DEE	Reflux	23	92	4	4
4	DEE	Reflux	48	63	19	18
8	DEE	Reflux	24	60	20	19
8	DEE	Reflux	48	43	28	29
8	DEE	Reflux	72	19	30	30
8	DBE	Reflux	1	0	30	51
8	DBE	70 °C	15	0	36	24
4	THF	Reflux	22	3	61	29
8	THF	Reflux	22	0	74	26

Table 2.22 - Cyclisation reaction conditions

Performing the reactions in DEE always gave approximately a 1:1 ratio of *cis* to *trans* diastereoisomers, whilst DBE gave a preference for the *trans* isomer, although the reaction contained a significant amount of unknown impurtities. Performing the reactions in THF gave excellent conversion to the desired pyrrolidines, with a preference for the *cis* isomer. Thus, cyclisation of diene **220b** was attempted by refluxing the reaction with 10 mol% of Cp_2ZrCl_2 and 8 eq of BuMgCl in THF. The reaction was quenched with D_2O and analysis of the crude deuterated products indicated **242b** had formed as a 2:1 ratio of *cis* to *trans* diastereoisomers. Although these reaction conditions gave the greatest conversion to product, **242b** could not be isolated pure as it was contaminated with small amounts of impurities. See δ_H 3.35-3.65 ppm of ^1H NMR in figure 2.23.

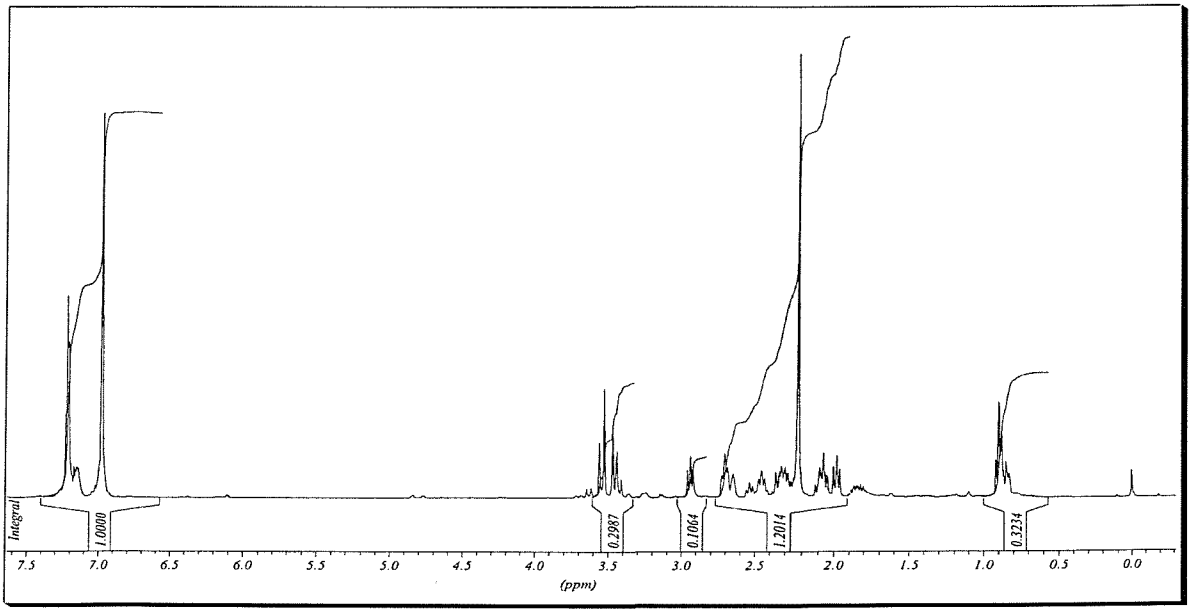


Figure 2.23 - ^1H NMR of purified deuterated pyrrolidine mixture of **242b**

Negishi reported the cyclisation of diene **245** and the carbocyclic diene **248**[116]. It was reported that although the major compound isolated was the expected cyclised products **246** and **249**, the double bond-isomers **247**, **250** and **251** were generated in both cases. (Figure 2.24.) It's possible that the impurities could be exo-cyclic methylene products.

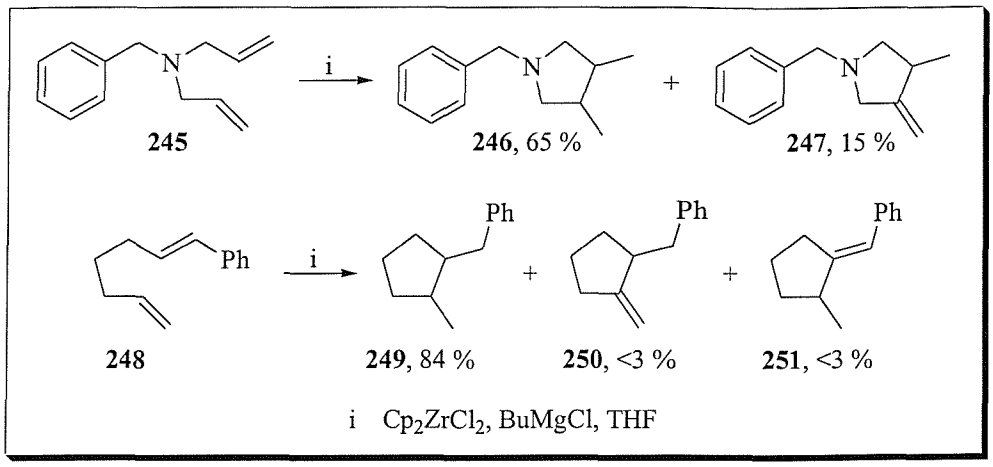


Figure 2.24 - Formation of exo-cyclic methylene products

Having quenched the reaction with D_2O, pyrrolidine **244b** did form *via* β-H abstraction and was estimated to be present as a 1:3 ratio to that of **242b**. This was determined in two ways. Firstly, the ratio of the $\underline{C}HCH_2D$ ^{13}C signal of *cis* **242b** (34.38 ppm) was compared to that of the $\underline{C}HCH_3$ ^{13}C signal of *cis* **244b** (34.47 ppm). (Figure 2.25.)

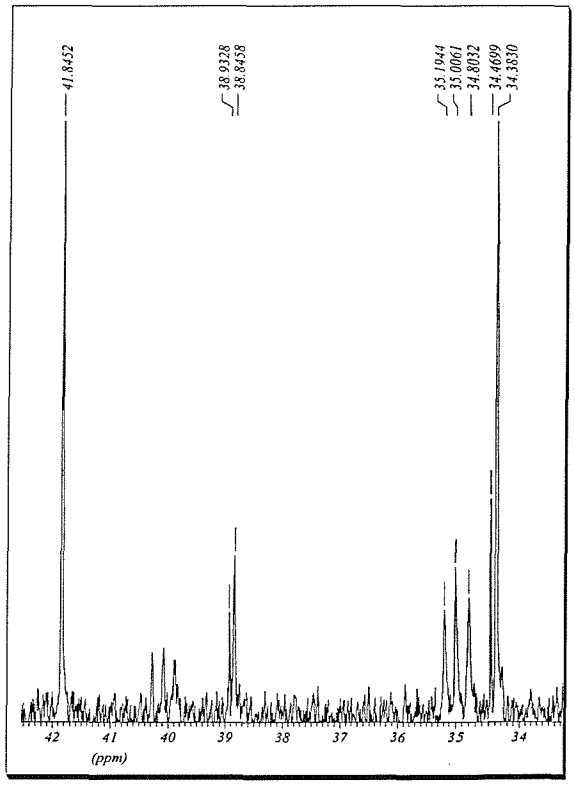


Figure 2.25 - ^{13}C NMR expansion of purified deuterated pyrrolidine mixture

Secondly, the $\underline{C}H_2D$ signal of **242b** (14.89 ppm, t, J=19.5 Hz) was compared to the $\underline{C}H_3$ signal of **244b** (15.19 ppm). (Figure 2.26.)

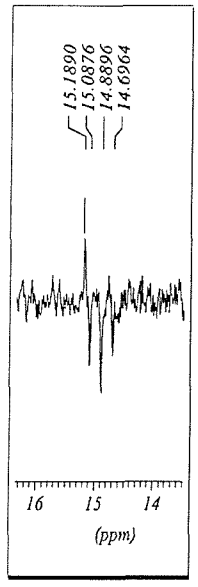


Figure 2.26 - ^{13}C DEPT expansion of purified deuterated pyrrolidine mixture

However, it must be remembered that these ratios are only estimates as ^{13}C integration is an unreliable method for quantitative analysis due to the diffreneces in relaxation times of the carbon nuclei. Ideally, the use of ^{1}H NMR integration would be used, but as there are no clear signals to compare, then only a crude estimate can be obtained.

Unfortunately, the complete optimisation of this reaction was never achieved due to a lack of time towards the end of the project. However, the conversion of diene to pyrrolidine is high which should enable the optimisation to be achieved relatively quickly in the future.

2.2.6. Palladium Mediated Cyclisations

As dienes were successively synthesised and cyclised, the possibility of extending the methodology to enyne systems was briefly explored. Amide **252** was synthesised and subsequently reduced to **253** using AlH_3. (Figure 2.27.) This was fortuitous as it was believed that the acetylene triple bond may have been at risk at being reduced. However, using the procedure outlined by Trost[117], the cyclisation of **253** was not as clean as was hoped. NMR analysis of the crude indicated the formation of **254**, but even after column chromatography, **254** was more impure than before the attempted purification. This was probably due to **254** isomerising on the SiO_2 column to the pyrrole, which then underwent polymerisation.

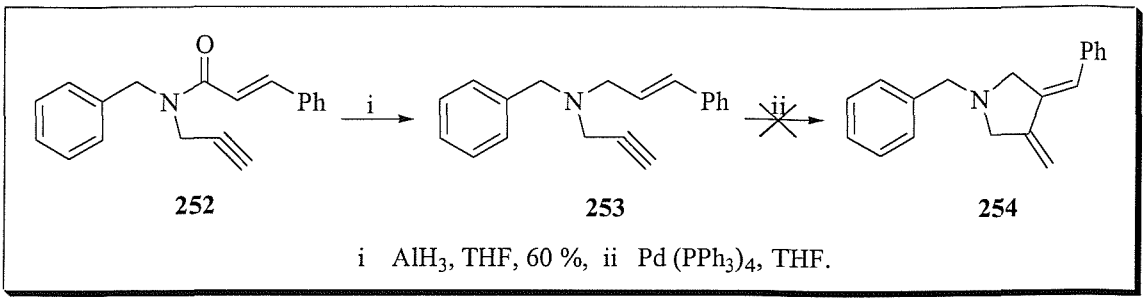


Figure 2.27 - Catalytic palladium mediated cyclisation

Having demonstrated that it was possible to convert the acyclic diene **223** to the novel cyclic lactam **229** in one step, we hoped that it may be possible to convert amide **222a** to **229** using Pd-H catalysis. However, both conditions failed to yield **229** and left only unreacted **222a**. (Figure 2.28.)

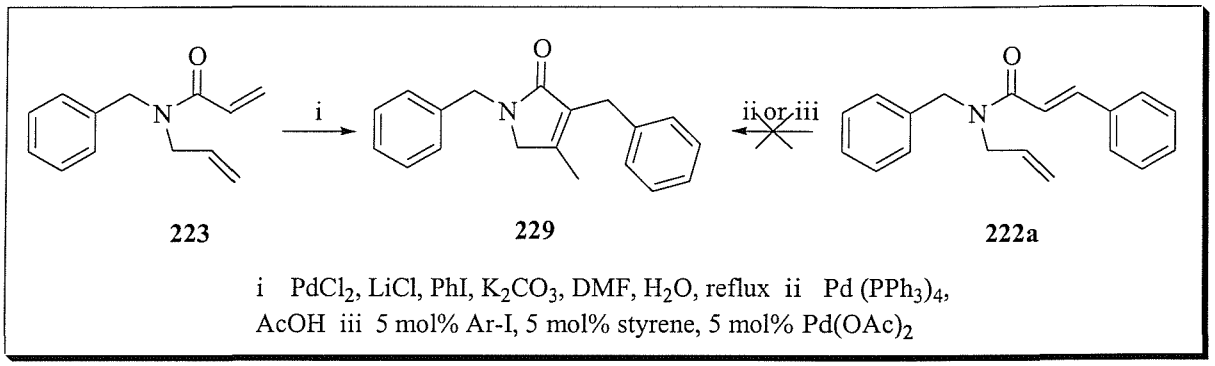


Figure 2.28 - Catalytic palladium mediated cyclisation

2.2.7. Titanium Mediated Cyclisations

Due to the similar chemistry of Zr and Ti, we hoped that that it may have been possible to cyclise the diene systems with Ti(IV). Sato showed that it was possible to cyclise enyne **255** using stoichiometric Ti(IV) to pyrrolidine **247**[118] and we hoped that this could be extended to our pyrrolidines synthesis. (Figure 2.29.)

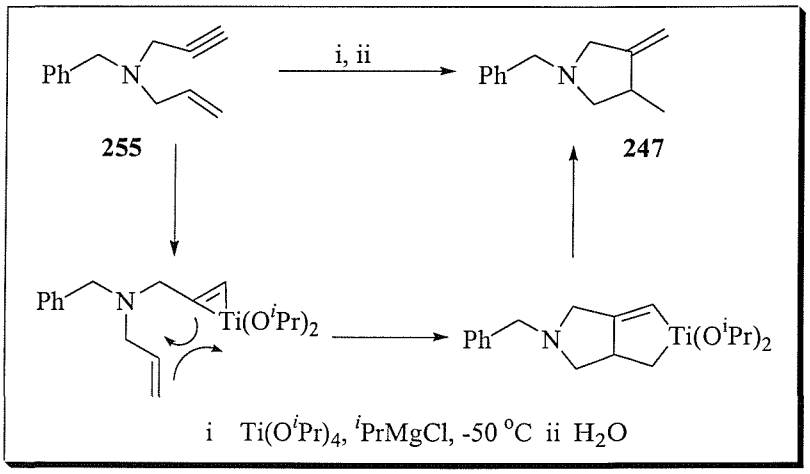


Figure 2.29 - Catalytic titanium mediated cyclisation

Cyclisation of **245** gave a 9:1 ratio of *cis* to *trans* isomers of **246** in 69 % yield. (Figure 2.30.) However, cyclisation of **220a** failed to give **221a**, leaving only unreacted **220a**. The cyclisation conditions were also applied to amide **222a** to make **256a**, but only generated a complex mixture of inseparable compounds, including deallylated product.

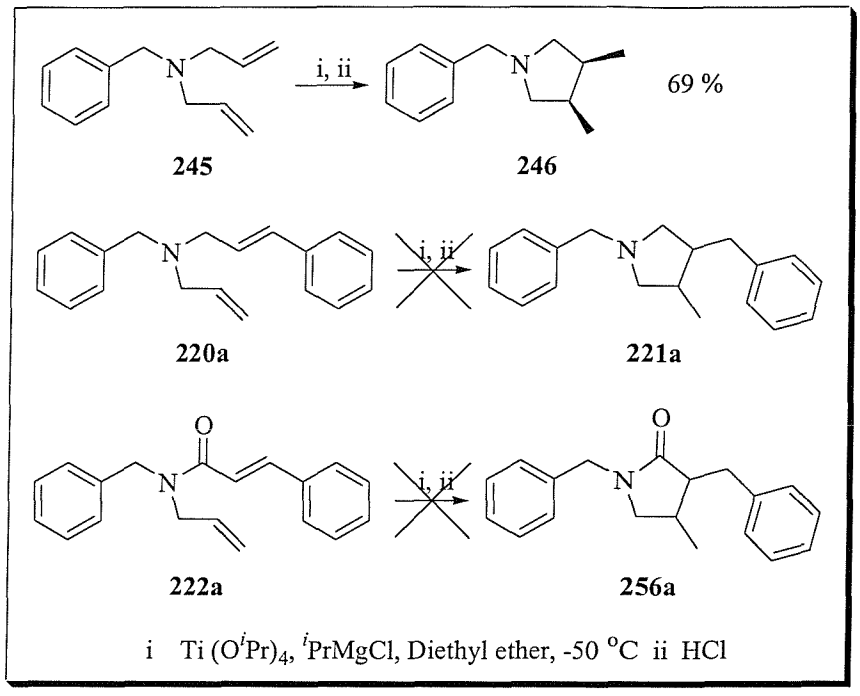


Figure 2.30 - Catalytic titanium mediated cyclisation

2.3. Future Work

For the continuation of the research into the synthesis of 3-benzyl pyrrolidines, it will be necessary to optimise the "one-pot" lactam formation from diene **223** to lactam **257**. (Figure 2.31.) This reaction is of synthetic interest due to the reported biological applications of 3-benzyl lactams.

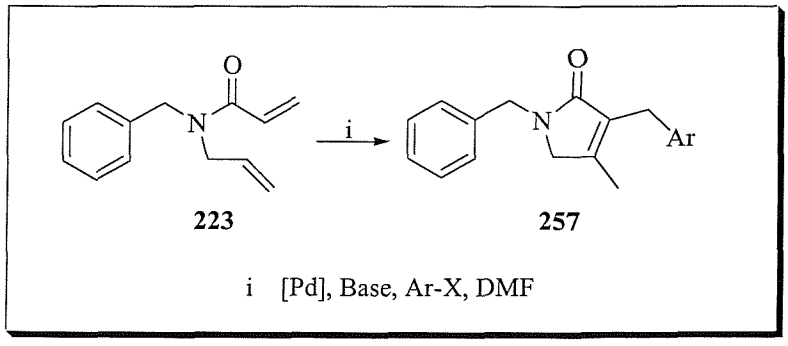


Figure 2.31 - Future optimisation of tandem "one-pot" cyclisation

It will also be necessary to optimise the sub-stoichiometric zirconium mediated cyclisation of dienes **220a-e**, and to quench with a range of electrophiles to give pyrrolidines **258**. (Figure 2.32.) One of the key factors to vary will be the reaction solvent as this has been shown to be critical in determining whether the reaction proceeds, as well as its diastereoselectivity.

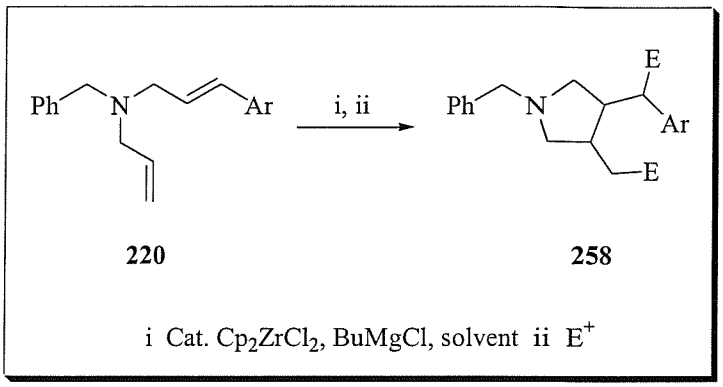


Figure 2.32 - Future optimisation of sub-stoichiometric zirconium mediated cyclisation

2.4. Conclusions

The preceeding chapter has discussed the synthesis of the 3-benzyl pyrrolidine pharmacophore. Initial investigation into the formation of diene **222a** led to the discovery of a novel cyclisation to lactam **229** involving a tandem Heck-coupling and cyclisation.

The use of AlH_3 has enabled the cyclisation precursors **220a-e** and **248** to be synthesised from readily available cinnamic acids. Cyclisation of dienes **220a-e** using stoichiometric Negishi's reagent and hydrolysis quench gave the novel pyrrolidines **221a-e** in good yield and as a 5:1 mixture of *trans:cis* diastereoisomers.

Cyclisation of **220** using sub-stoichiometric Cp_2ZrCl_2 has begun to be investigated. Initial studies have shown that the diene **220b** could be cyclised to give a 1:2 ratio of *trans* to *cis* diastereoisomers and as a 1:3 mixture of *mono-* to *bis*-deuterated pyrrolidines. Unfortunately, small amounts of impurities contaminated the pyrrolidine mixture and so the final *mono-* and *bis*-deuterated pyrrolidines could not be fully characterised.

Cyclisation of the dienes and enynes using catalytic palladium and stoichiometric titanium have so far proved unsuccessful. However, with careful tuning of the metal centre, the formation of pyrrolidines using these complexes may finally be realised.

CHAPTER 3

THE COMBINATORIAL SYNTHESIS OF 3-BENZYL PYRROLIDINES

3. The Combinatorial Synthesis of 3-Benzyl Pyrrolidines

3.1. Introduction to Combinatorial Chemistry

Solid phase chemistry has been used for the synthesis of molecules for over 40 years. From its first use in peptide[119,120] and nucleotide[121] synthesis, the development of combinatorial chemistry has become a significant area of research due to the urgent need for rapid compound synthesis for biological screening and testing. An important feature of combinatorial chemistry is the attachment of the molecule to the solid support. This is done using a cleavable linker[122,123] which acts as a 'bifunctional protecting group'. It has the characteristic feature of being attached to the molecule that is synthesised through a bond labile to the cleavage conditions, whilst retained on the polymer matrix through a more stable bond.

There are many criteria to consider when choosing a linker for molecule and library synthesis:

- It would be cheap and readily available
- The attachment of starting material would be readily achieved in high yield
- The linker would be stable to the chemistry used in the synthesis
- Cleavage would be efficient and not damage the target molecule
- The cleavage method should enable the target molecule to be easily purified and not introduce impurities that are difficult to remove

Our aim was to develop a route to 3-benzyl pyrrolidines using combinatorial chemistry. (Figure 3.1.) By choosing an appropriate linker, we wished to introduce the allyl fragment first, followed by a selection of different cinnamyl fragments. After cyclising with Negishi's reagent, we hoped to cleave to either the protected pyrrolidine **301** (which could be reduced further to the free secondary pyrrolidine **302** if required), or the free secondary pyrrolidine **302** directly.

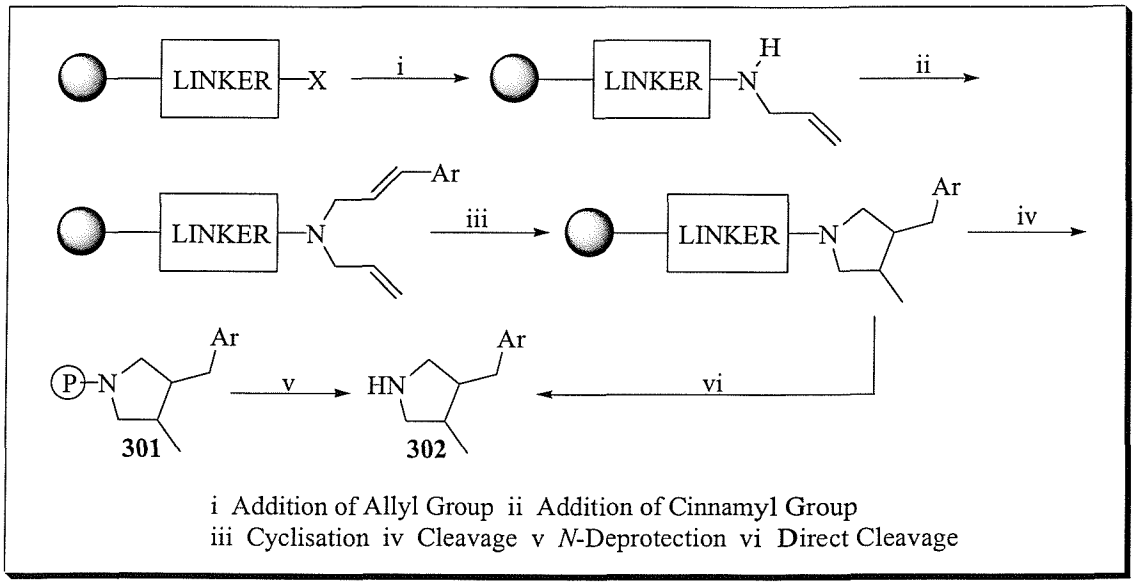


Figure 3.1 - Combinatorial strategy to pyrrolidine target

3.2. Solid-Phase Pyrrolidine Synthesis

The nature of the nitrogen substituent is crucial in allowing the zirconium diene cyclisation to occur. A study of the literature showed that compatible groups include carbamate[124], alkyl[107] and benzyl[14,125]. There have been many methods developed for generating both free amines and protected amines (such as amides and carbamates) from the resin[126-132]. We hoped that one of these would provide a convenient route to our 3-benzyl pyrrolidine targets.

3.2.1. Choice of Linker

We wanted a linker which when cleaved, would easily generate the secondary pyrrolidine **302** directly. Initially, we chose to attach the diene through a carbamate linker, which would liberate the free amine upon reaction with TFA in DCM[127]. (Figure 3.2.) The use of a carbamate linker had the added advantage in that it can also be reduced with $LiAlH_4$ to generate *N*-methyl amines[133].

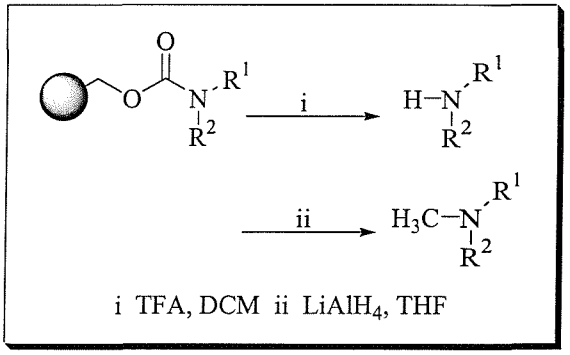


Figure 3.2 - Carbamate cleavage

3.3. Results and Discussion

3.3.1. BOC Linker Approach

Whitby showed that BOC protected piperidines could be synthesised *via* enyne cyclisation using Negishi's reagent[124]. (Figure 3.3.)

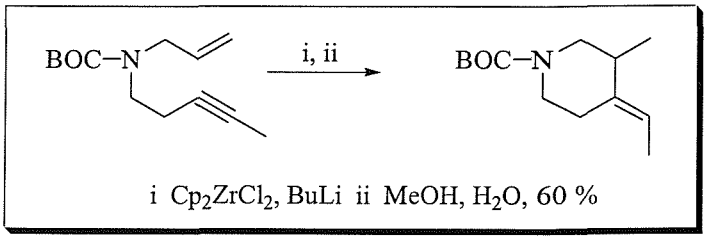


Figure 3.3 - BOC-protected piperidine synthesis

Due to this compatibility, a carbamate linker was chosen for the diene cyclisations. (Figure 3.4.) We hoped to alkylate a carbamate linker using different cinnamyl bromides as our aryl source. After cyclisation, the pyrrolidine could be cleaved from the resin using TFA to generate pyrrolidines **302**.

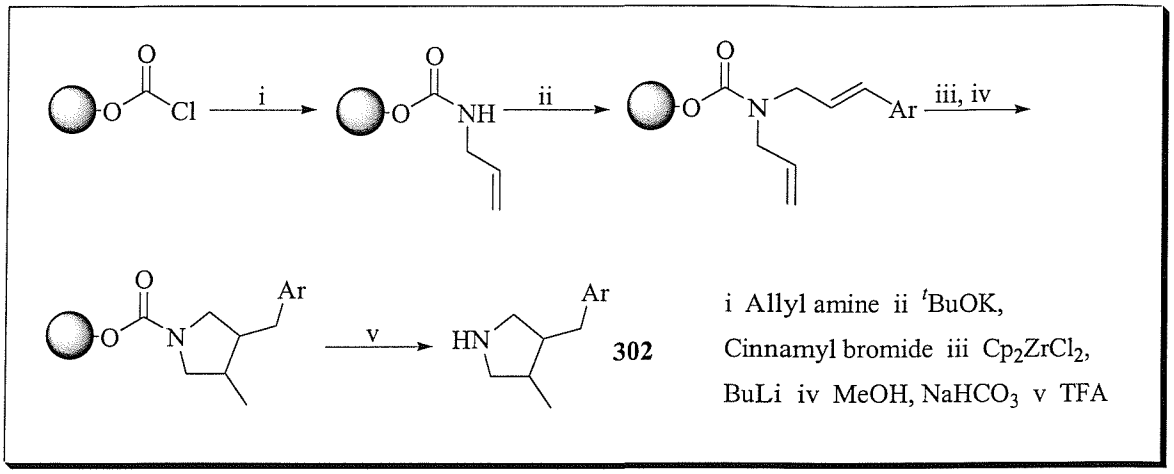


Figure 3.4 - BOC Linker strategy to pyrrolidine target

As a model study, BOC protected dienes **303** and **305** were synthesised and reacted with Negishi's reagent to see if cyclisation would occur to give pyrrolidines **304** and **306**. (Figure 3.5.)

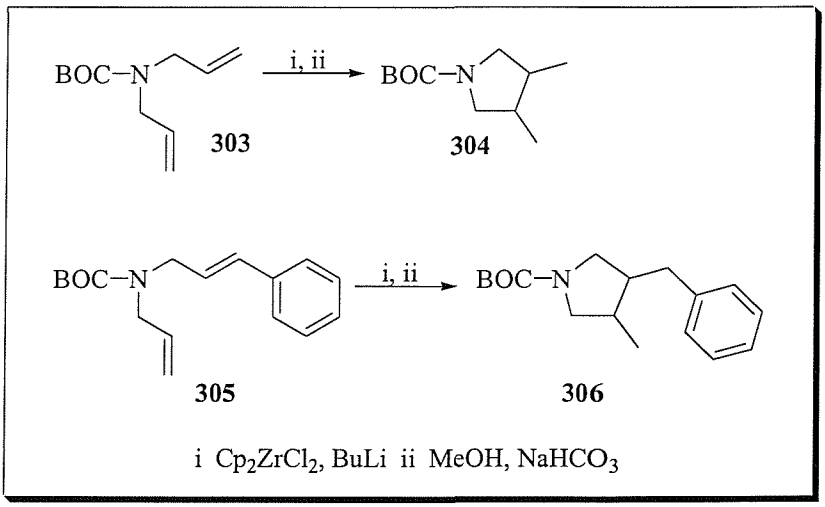


Figure 3.5 - Cyclisation of BOC dienes

Unfortunately, in both cases, the major product obtained from the reaction were the deallylated products **307** and **308** which probably formed *via* the mechanism shown in figure 3.6.

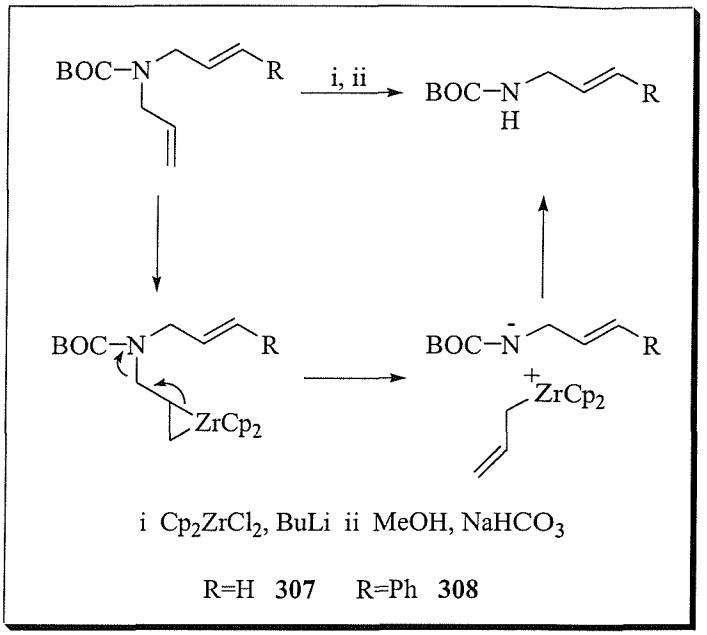


Figure 3.6 - Mechanism of deallylation

3.3.2. Benzyl Linker Approach

It was decided that use of a benzyl linker would be appropriate, as we had established that the cyclisation was compatible from the solution phase models in chapter 2.

There are relatively few methods for the removal of a benzyl group from a resin-bound amine. One particular method was the protocol reported by Leysen, whereby *N*-benzyl tertiary amines could be cleaved from Merrifield, Wang and Sasrin resins cleanly and efficiently, using α-chloroethyl chloroformate (ACE-Cl) to yield secondary amine HCl salts in high yield and purity[134]. (Figure 3.7.) Additionally, all by-products were volatile.

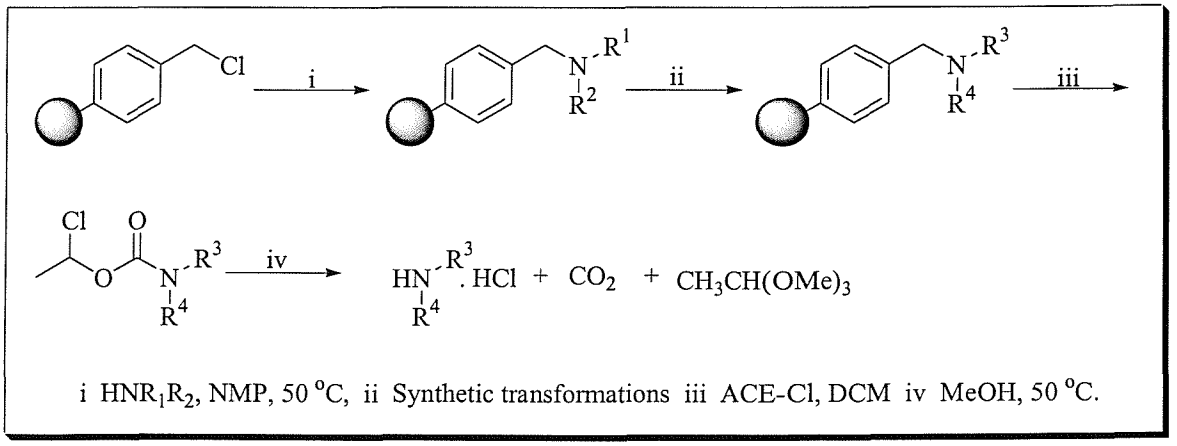


Figure 3.7 - Leysen's debenzylation protocol

Initially, it was hoped that resin **309** could be oxidised to **310**, followed by reaction with allylamine to generate the amide linker resin **311**. (Figure 3.8.) From this, we would be able to add the cinnamyl fragment to the resin to give **312**. Carbonyl reduction of **312** would yield the polymer-supported diene fragment **313**. Cyclisation to **314**, followed by cleavage using the Leysen protocol would furnish our desired 3-benzyl pyrrolidine **302**.

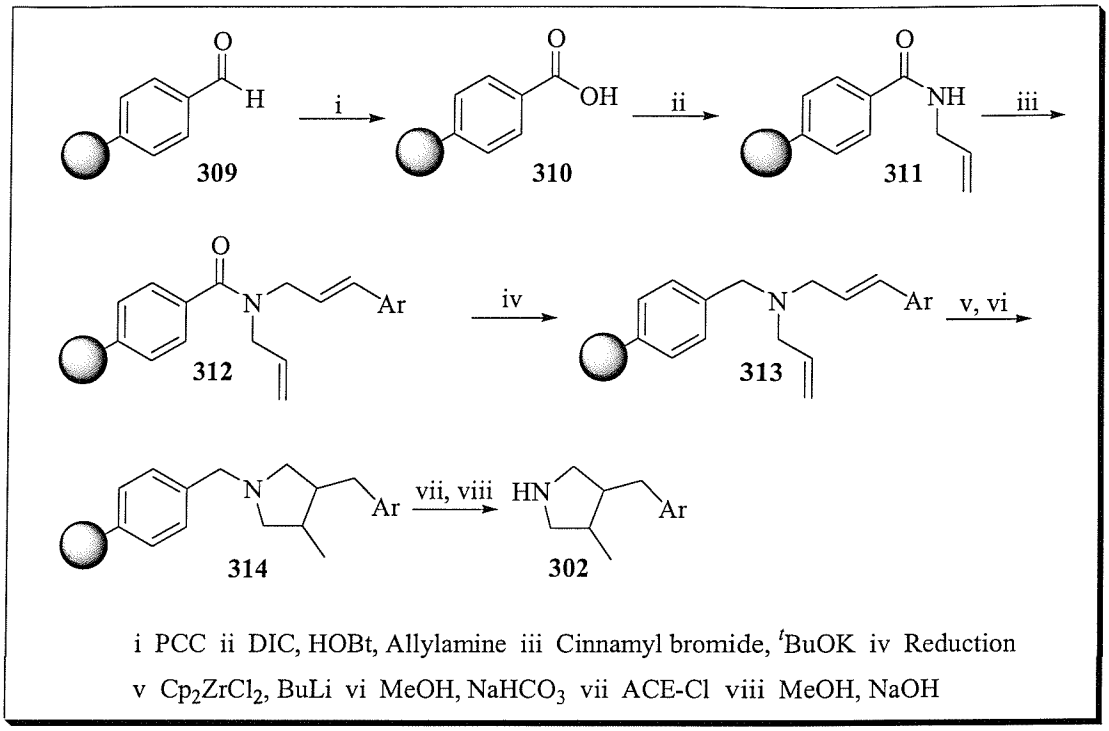


Figure 3.8 - Amide linker approach to pyrrolidines

As a model study, we investigated the carbonyl reduction of amide **315** to amine **220a**. (Figure 3.9.)

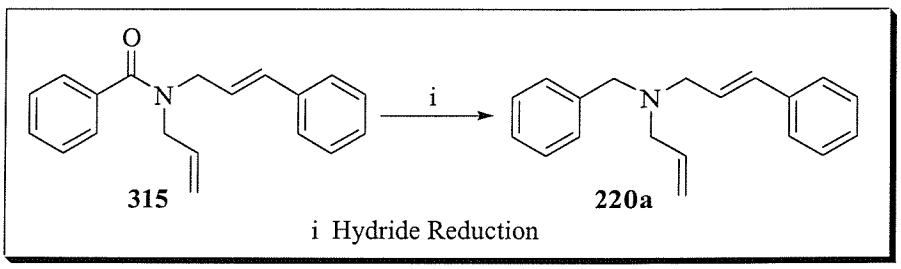


Figure 3.9 - Model study reduction

The reactions were monitored by GC and the conversions from the starting amide **315** to the amine product **220a** are summarised in table 3.10.

Reductant	Temperature / °C	% Remaining of **315**	% Conversion to **220a**
$LiAlH_4$	0	0	10
DIBAL-H	-78	4	69
DIBAL-H	0	5	81
DIBAL-H	20	15	64
DIBAL-H	130	0	60
AlH_3	0	0	100

Table 3.10 - Optimisation of carbonyl reduction

The use of $LiAlH_4$ favoured the rupturing of the amide bond to give *N*-allyl-*N*-cinnamyl amine, rather than the reduced product **220a**. Although DIBAL-H gave good conversions to **220a**, AlH_3 was found to be the most effective reductant as the reaction was very clean and generated no side-products. (Figure 3.11.)

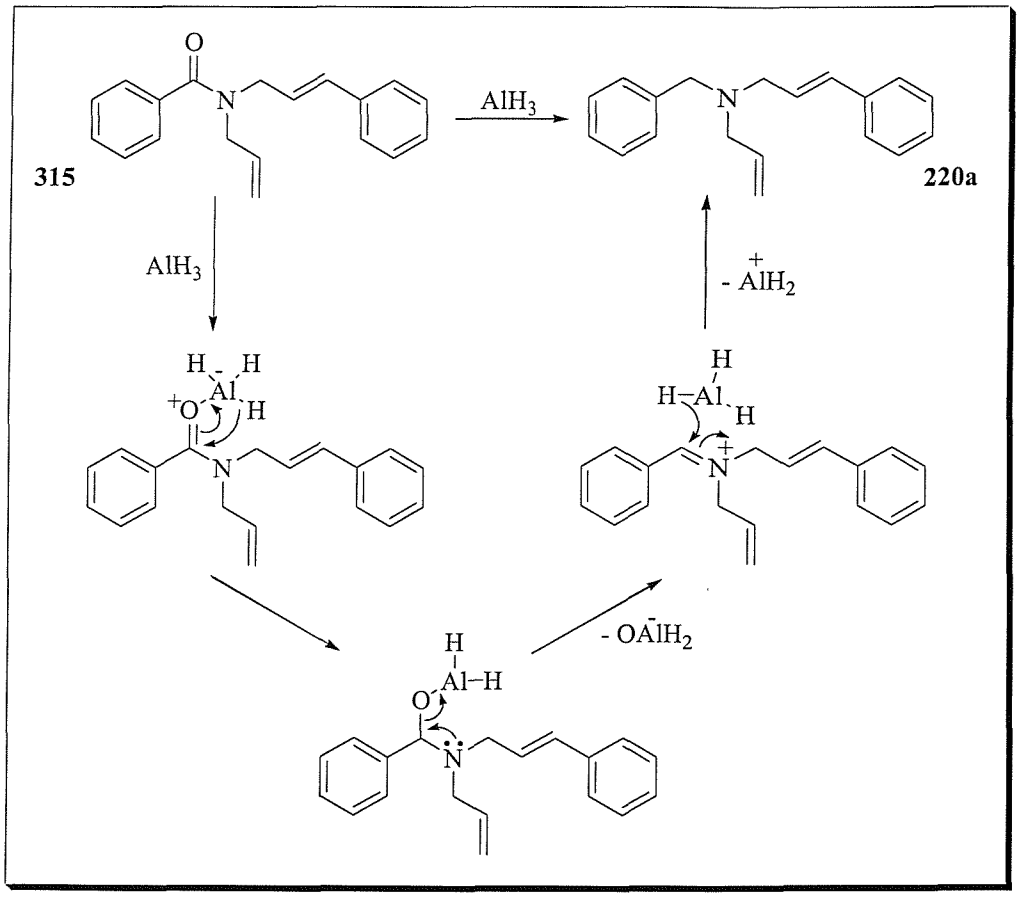


Figure 3.11 - AlH_3 reduction mechanism

We felt that the use of AlH_3 would give us a promising route to our resin-bound diene precursor **313**, as shown in figure 3.8.

The results described in chapter 2 had shown that AlH_3 was the reductant of choice for reducing tertiary cinnamides **222a-e** to dienes **220a-e**. Consequently, it was concluded that the best approach would be to use the same synthetic strategy that was used for **220a-e** in chapter 2. This had the added advantage of allowing the use of commercially available cinnamic acids as our aryl source, rather than requiring the synthesis of a selection of cinnamyl bromides. Thus, our synthetic strategy was to react Merrifield resin with allylamine to generate resin **316**. (Figure 3.12.) After the amide coupling with a variety of cinnamic acids to give **317**, AlH_3 reduction would give the resin-bound amines **313**. Cyclisation of **313** to **314** and subsequent cleavage would provide the 3-benzyl pyrrolidines **302**.

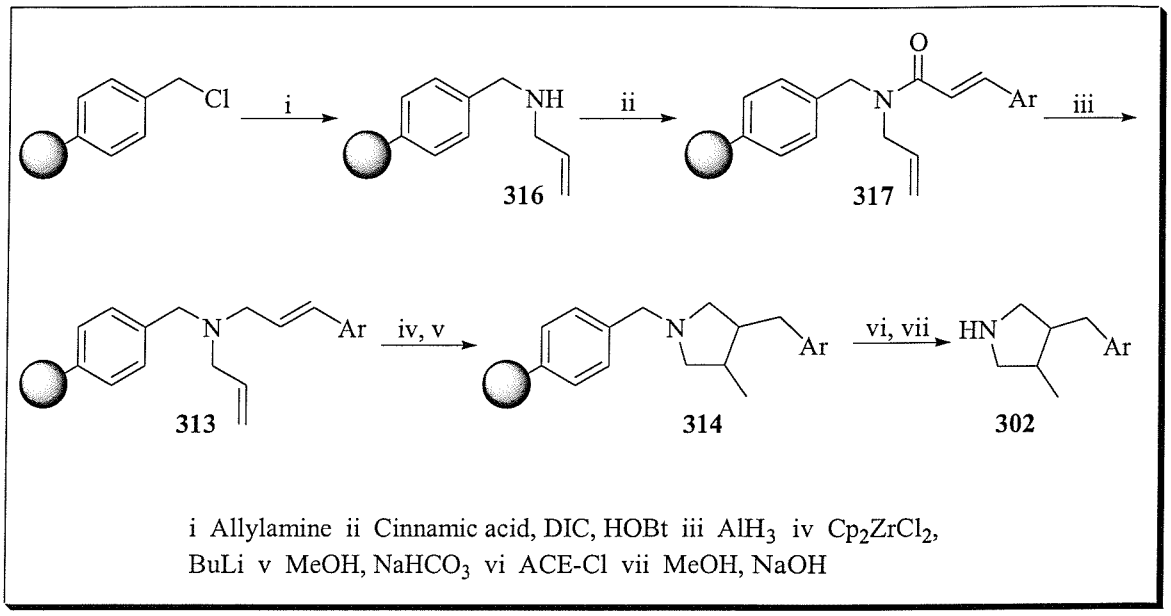


Figure 3.12 - Benzyl linker approach to pyrrolidines

As it had already been shown that AlH_3 would effectively reduce the cinnamic amides (see chapter 2), we looked into the debenzylation of the amine from the resin.

3.3.3. Debenzylation Approaches

Initially, the debenzylation of **221a** to **302a** was attempted in solution using the Leysen protocol to check its viability for resin-bound substrates. (Figure 3.13.)

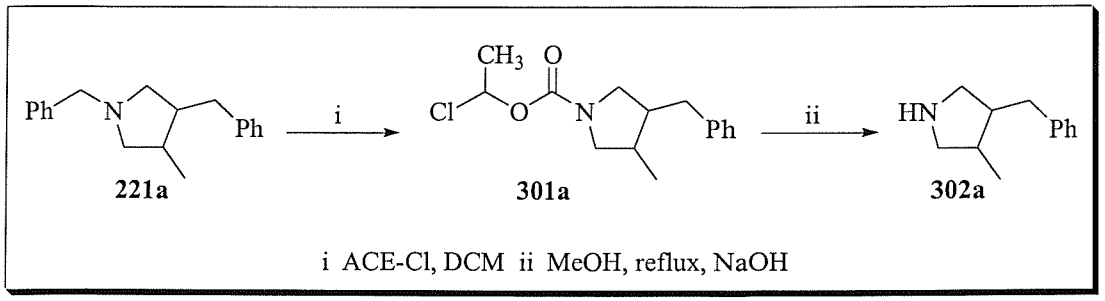


Figure 3.13 - Leysen debenzylation of 3-benzyl pyrrolidines

Pyrrolidine **221a** was treated with ACE-Cl using the procedure by Leysen but gave very poor conversion to carbamate intermediate **301a** and to the secondary pyrrolidine **302a**. We ruled out the possibility of debenzylation using hydrogenation as this has been shown to be an unreliable approach to solid-phase substrates[126]. Consequently, we chose to cleave the amine from the resin by generating an ethyl carbamate based on the procedure by Sasakura[135]. The resulting carbamate could be further reduced to the secondary amine **302** by either acid[127] or base[135] hydrolysis if required.

Initially, the debenzylation of amine **245** by reaction with ethylchloroformate in refluxing DCM was investigated. Although the deprotection worked, deallylation also took place to give a 7:1 ratio of **318** to **319**. (Figure 3.14.) Carbamate **318** was isolated in a 65 % yield.

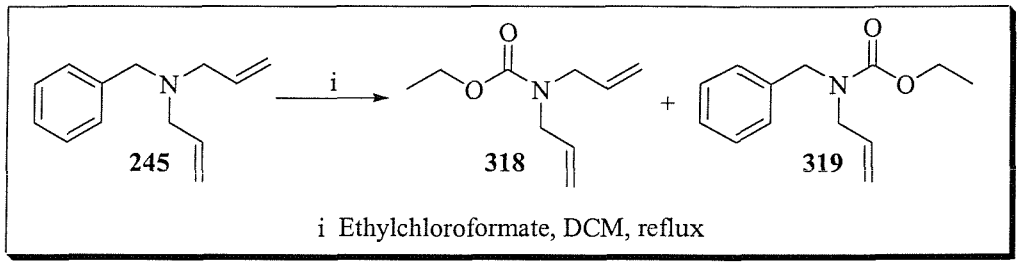


Figure 3.14 - Debenzylation of *N*-benzyl-diallyl amine

Next, the debenzylation of a substituted pyrrolidine was attempted. Pyrrolidine **246** was treated with ethylchloroformate in refluxing DCM to give **320**. However, the reaction conditions also resulted in pyrrolidine ring-opening to yield **321**. (Figure 3.15.) However, it was felt that this debenzylation method on the solid-support would not be too problematic as the amount of ring-opened product was small (5:1 ratio of **320** to **321**) and the unwanted by-product would be immobilized.

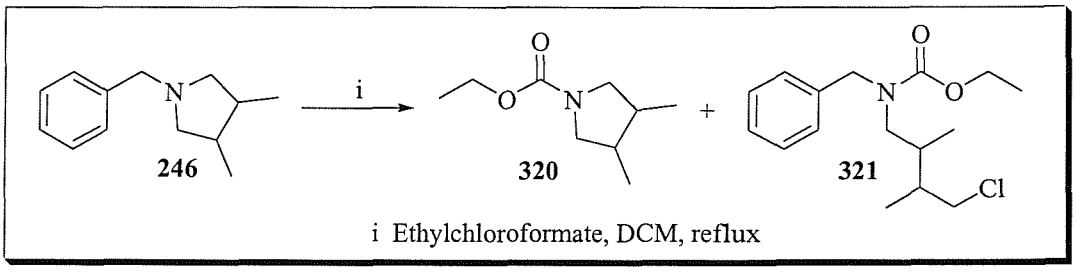


Figure 3.15 - Debenzylation of 1-benzyl-3,4-dimethyl pyrrolidine

Due to the success of the solution phase model, the next step was to test the debenzylation with a resin-bound substrate. Merrifield resin was heated with diallylamine in NMP overnight at 120 °C to yield the immobilized diallyl amine **322**. (Figure 3.16.) The resin was split into three equal batches. The first batch was treated with ethylchloroformate giving **318** cleanly in 82 % yield. The second and third batches of **322** were only washed with freshly distilled THF and placed under high vacuum for an hour to ensure no moisture was present for the zirconium mediated cyclisation. It was felt that it was important not to wash the resin with DCM and MeOH because it was known that both these solvents can react with Negishi's reagent[44,136], hence their absence in the

purification procedure was desirable. For the second batch of **322**, 1 eq of resin-bound diene **322** was suspended in THF at -78 °C before 1 eq of Negishi's reagent was added. The reaction was left for 3 hours to cyclise before MeOH and saturated $NaHCO_3$ solution were added to quench the zirconacycle. Subsequent filtration, washing and ethylchloroformate cleavage of the product from the resin gave a 1:2 mixture of **318** to **320**. For the third batch of **322**, 2 eq of Negishi's reagent were added to 1 eq of resin-bound diene **322** and the reaction was left for 36 hours. After MeOH/$NaHCO_3$ quench and ethylchloroformate cleavage, this gave **320** as a 2:1 ratio of *trans* to *cis* diastereoisomers in an 81 % yield.

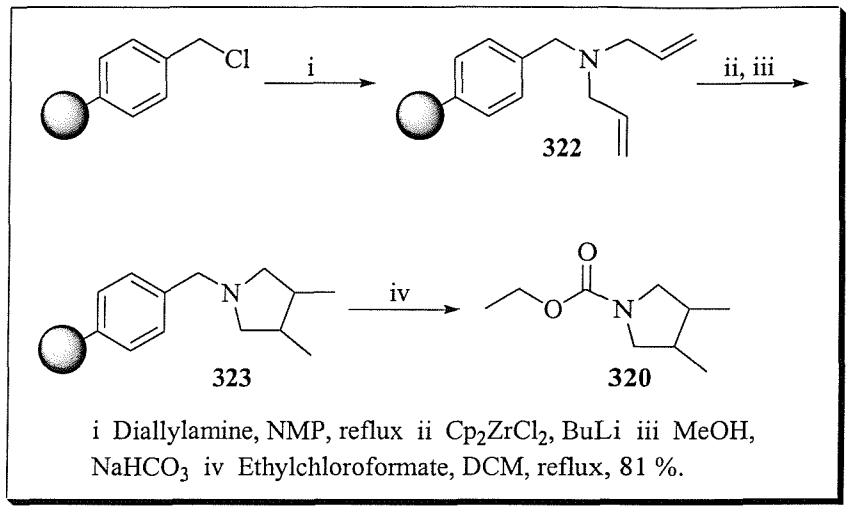


Figure 3.16 - Combinatorial pyrrolidine synthesis

3.3.4. Benzyl Pyrrolidine Synthesis

It was hoped that a small library of benzyl pyrrolidines could be synthesised *via* carbamate formation as the debenzylation step. The debenzylation conditions were applied to pyrrolidines **221a-e** (isolated in chapter 2), to generate carbamates **324a-e** in moderate to high yield. (Figure 3.17.)

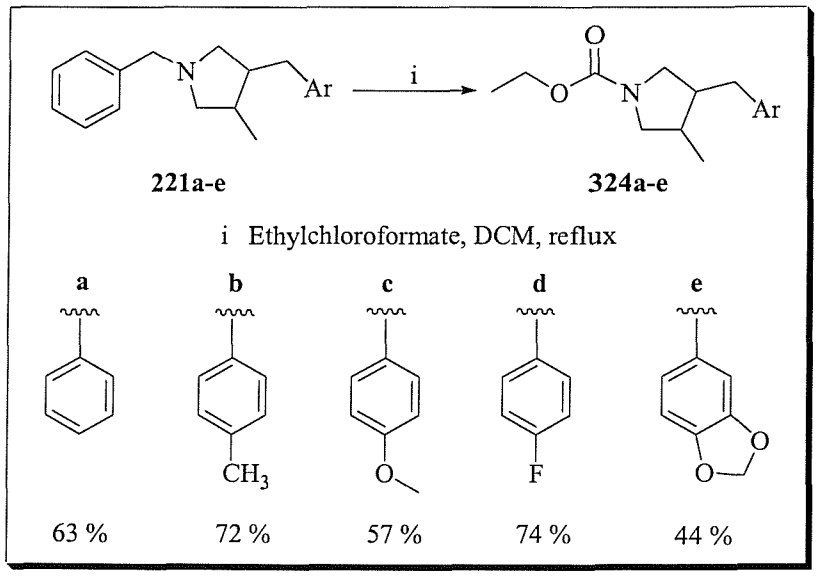


Figure 3.17 - Debenzylation of 3-benzyl pyrrolidines

Encouraged by the good yields of the isolated carbamates **324a-e**, and by the high purity of carbamate **320** isolated after resin cleavage, it was felt that this would be a good approach to the combinatorial synthesis of 3-benzyl pyrrolidines. The methodology was extended to the solid-support using the synthetic strategy in figure 3.18.

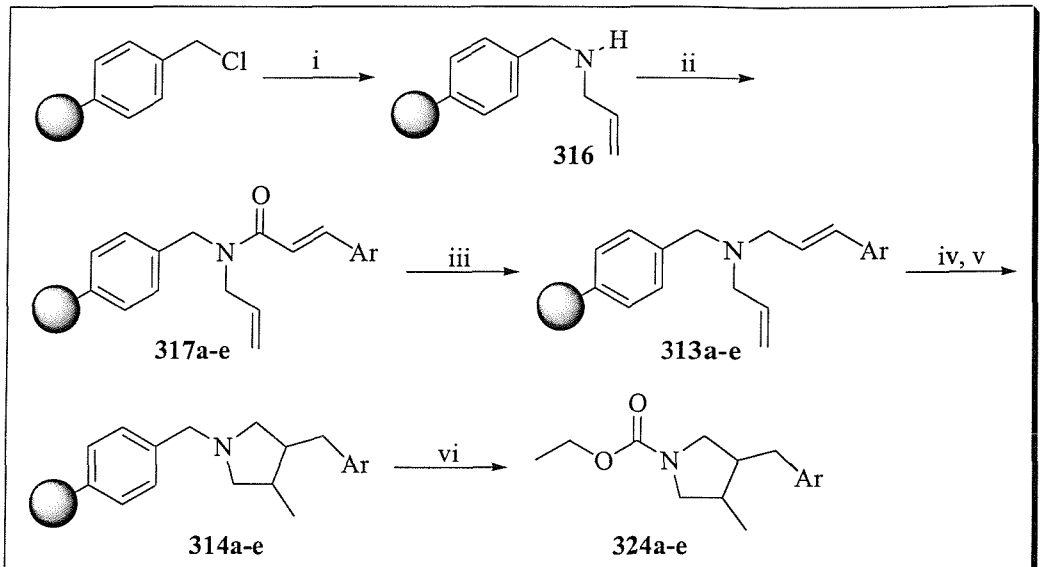


Figure 3.18 - Combinatorial approach to 3-benzyl pyrrolidines

In order to model the synthesis of **316**, the synthesis of **224** was tried in solution. Solution phase models showed that no reaction occurred between benzyl chloride and allylamine by overnight heating in NMP at 120 °C. However, **224** was synthesised by overnight reflux in THF. (Figure 3.19.) Subsequent amide coupling using cinnamic acid was achieved using HOBt / DIC conditions in DCM to give **222a**.

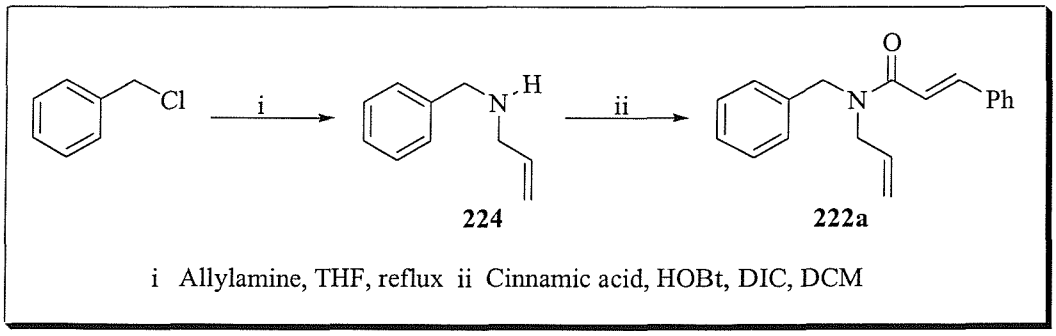


Figure 3.19 - Addition of allyl fragment

Reaction of Merrifield resin with allylamine in refluxing THF generated the resin-bound amine **316** in 94 % yield. This was determined by analysing the resin for residual chloride using elemental analysis. Amide coupling of **316** with cinnamic acids failed to give **317a-e** in DCM (as indicated by the resins giving a positive

chloranil test[137]), but worked in DMF. Resin-bound amides **317a-e** were reduced using AlH_3 to give **313a-e**. Subsequent addition of 3 equivalents of Negishi's reagent, overnight shaking and MeOH/$NaHCO_3$ quench gave resin-bound pyrrolidines **314a-e**. Cleavage from the resin using ethylchloroformate generated carbamates **324a-e** as a 2:1 ratio of *trans* to *cis* isomers in moderate yield (25-57 %) from the resin-bound allyl amine **316**. (Figure 3.20.) The pyrrolidines were obtained in high purity (85-98 % by NMR) and are shown in appendix 8.3.

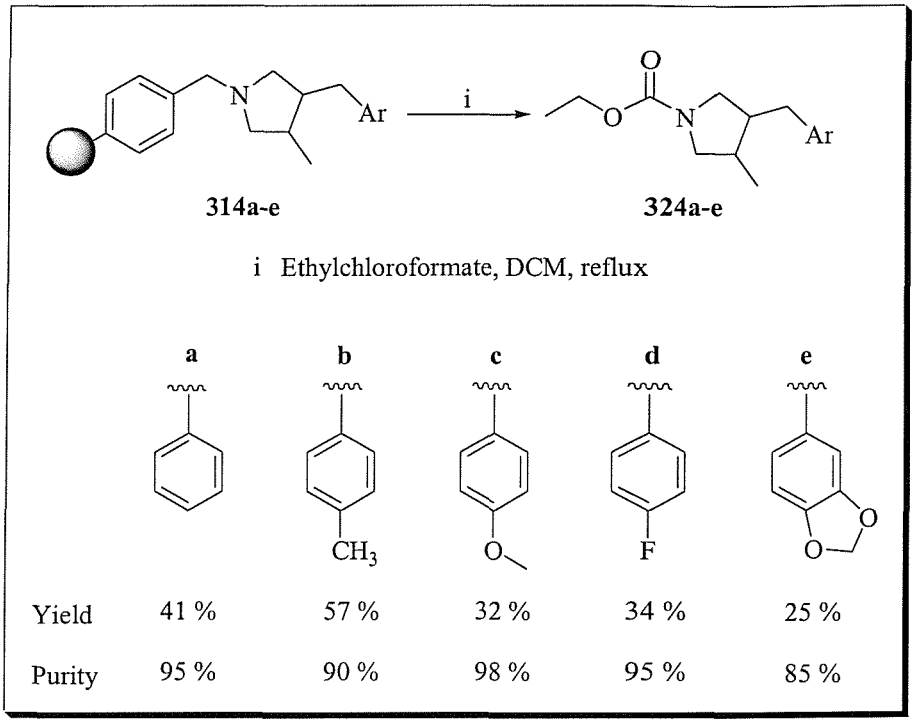


Figure 3.20 - Resin cleavage of 3-benzyl pyrrolidines

The 2:1 *trans* to *cis* diastereoselectivity observed is an interesting result because in chapter 2, **221a-e** which were synthesised in solution were isolated as a 5:1 ratio of pyrrolidines. As both the solution phase and resin-bound zirconacycle intermediates were left for 18 hours, the reason for the difference in diastereoselectivity may be due to the resin environment not allowing the zirconacycle intermediates to adopt their preferred thermodynamic *trans* structure.

3.4. Future Work

Continuation of the research into the combinatorial synthesis of the 3-benzyl pharmacophore would require the synthesis of a library of secondary amines such as **325** *via* addition of (homo)-allyl and -propargyl amine fragments to Merrifield resin. (Figure 3.21.) Subsequent cinnamic acid coupling to give **326** and AlH_3 reduction would furnish a library of cyclisation precursors such as **327**. Cyclisation of **327** to **328** would be achieved by using a range of other metal sources. After cleavage, this would give a library of 3-benzyl pyrrolidine and piperidine pharmacophores such as **329** which could be screened for biological activity.

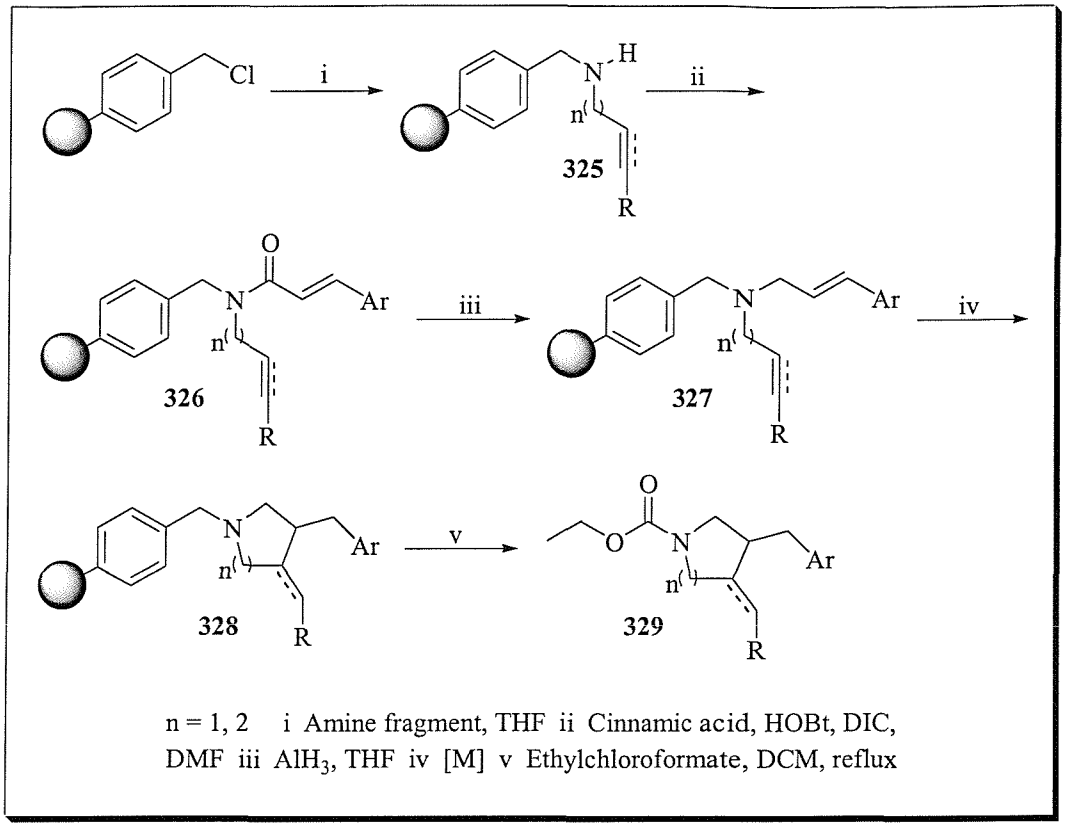


Figure 3.21 - Future combinatorial approach to 3-benzyl pharmacophores

3.5. Conclusions

The preceeding chapter has discussed the combinatorial synthesis of the 3-benzyl pyrrolidine pharmacophore. Starting from the commercially available and inexpensive Merrifield Resin, the amine support **316** was synthesised by reaction with allylamine in THF. Subsequent amide coupling using commercially or synthetically available cinnamic acids generated the resin-bound amides **317a-e**. AlH_3 reduction gave the diene substrates **313a-e**, which after zirconium mediated cyclisation and protonation afforded the resin-bound pyrrolidines **314a-e**. Cleavage using ethylchloroformate generated the novel carbamates **324a-e** as a 2:1 ratio of *trans* to *cis* diastereoisomers, in moderate to good yields (25-57 %) over 3 steps, with high purity (85-98 %).

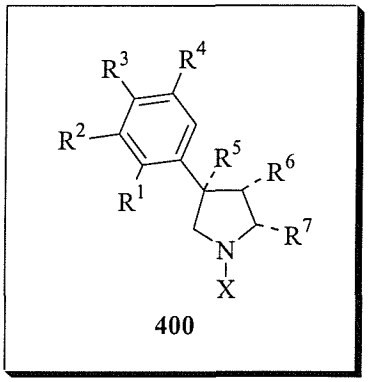
CHAPTER 4

THE SYNTHESIS OF 3-ARYL PYRROLIDINES

4. The Synthesis of 3-Aryl Pyrrolidines

4.1. Introduction to 3-Aryl Pyrrolidines

There has been significant research into the synthesis and pharmacological activity of 5-membered nitrogen heterocycles featuring an aryl group at C_3, as they have shown potent biological activity. (Figure 4.1.)



400

Figure 4.1 - Pyrrolidine target

4.1.1. Activity of 3-Aryl Pyrrolidines

A major area of research is the use of 3-aryl pyrrolidines as receptor antagonists. The CCR5 chemokine receptor is a member of the superfamily of seven-*trans*membrane spanning G-protein coupled receptors[138], and it was shown that the CCR5 receptor acts as a primary co-receptor for certain HIV-1 viral strains[139]. Merck developed the early lead compound **401**[140,141] which with SAR variation[142,143], has led to the more recent compound **402**[144] which exhibited high binding affinities for the CCR5 receptor. (Figure 4.2.)

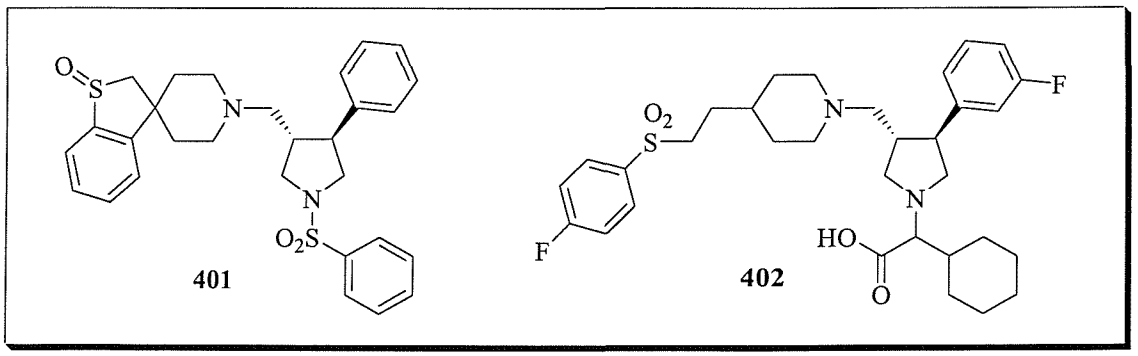
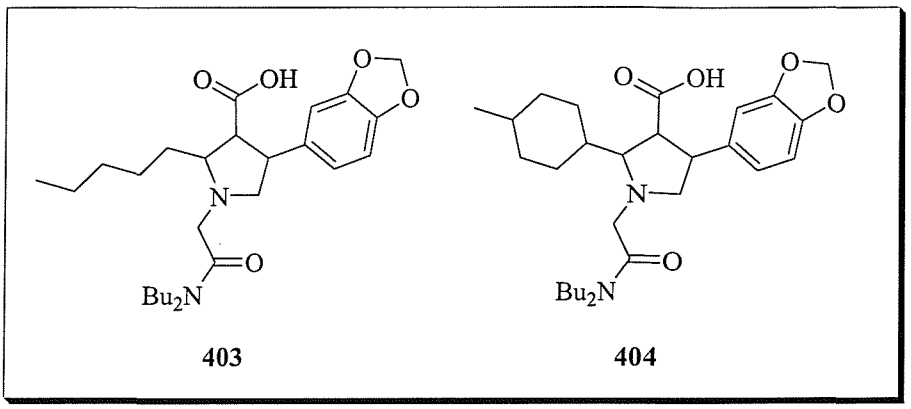


Figure 4.2 - CCR5 Antagonists

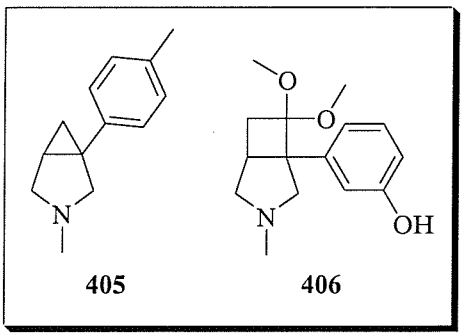
Endothelins ET-1, ET-2 and ET-3 are potent vasoconstricting and mitogenic 21-amino acid bicyclic peptides, which exert their effects upon binding to the ET_A and ET_B receptors[145-147]. Selective antagonists of endothelin receptors may prove useful in determining the role of endothelin in various tissue types and disease states, potentially acting as therapeutic agents for such diseases. Boyd reported the synthesis of endothelin receptor antagonists based on pyrrolidines such as **403** and **404** which showed high levels of potency[148]. (Figure 4.3.)



403 **404**

Figure 4.3 - Endothelin antagonists

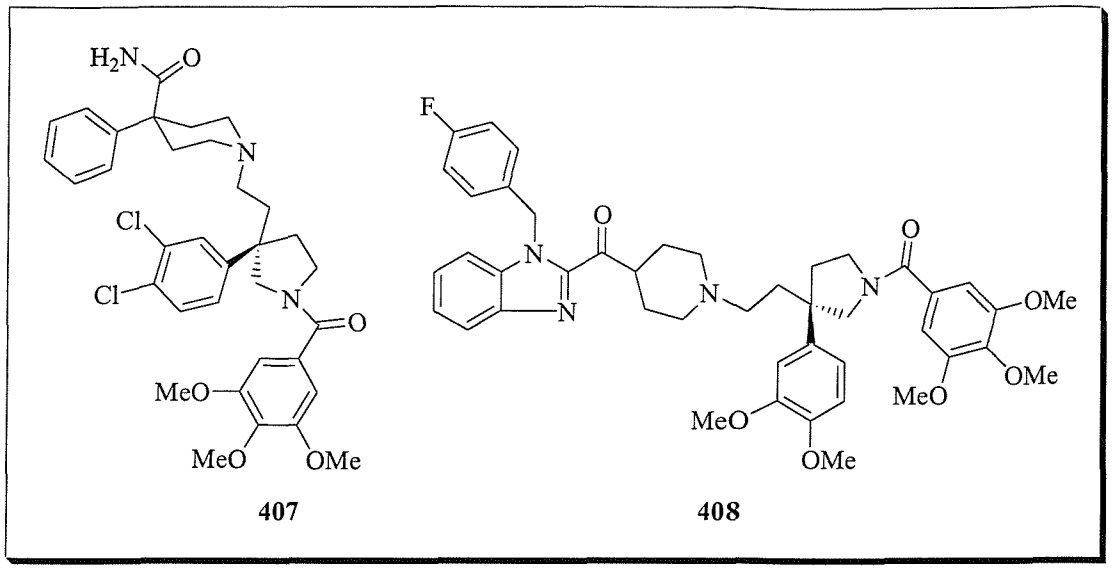
Epstein reported a series of non-narcotic analgesic agents based on a [5,3] ring system[149]. In particular, amine **405** was found to show high levels of analgesic potency. (Figure 4.4.) This was later modified to the [5,4] ring system[150] and compounds such as **406** were shown to have physiological effects identical to those of morphine.



405 **406**

Figure 4.4 - Non-narcotic analgesics

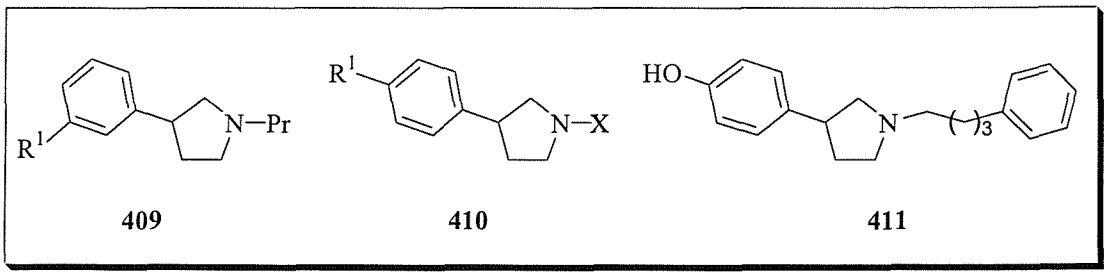
Burkholder reported the synthesis of **407** which was found to have a high affinity for human NK_1 and NK_2 receptors[151,152] which play a key role in vascular regulation[153-155]. (Figure 4.5.) Similarly, Maynard reported the synthesis of **408** which was found to have dual histamine H_1/tachykinin NK_1 receptor antagonist activity[156,157].



407 **408**

Figure 4.5 - NK_1 and NK_2 receptor antagonists

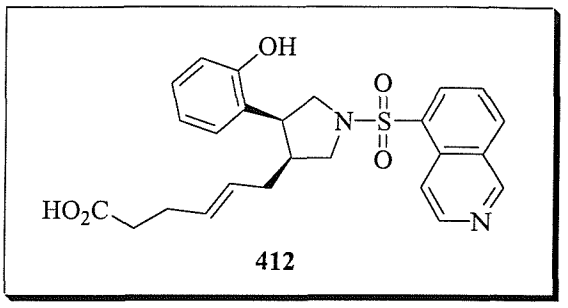
The development of selective and potent ligands for dopamine and serotonin 1A receptor have attracted considerable interest since they are promising drug candidates for the treatment of behaviour, mood and anxiety disorders[158,159]. Sonesson reported the synthesis and activity of 3-aryl pyrrolidines such as **409** with variation of R^1 which were shown to be dopamine autoreceptor antagonists[160]. (Figure 4.6.) Ahn later reported the synthesis of a series of compounds based on **410** with variation of R^1 and X which exhibited potent serotonergic activity[161]. More recently, Guzikowski reported the synthesis and activity of **411** as an *N*-Methyl-D-aspartate (NMDA) receptor antagonist[162], with the potential to treat diseases such as focal ischemia, epilepsy and Parkinson's disease.



409 **410** **411**

Figure 4.6 - Dopamine, serotonin and NMDA receptor antagonists

Thromboxane A_2 has been implicated in the pathogenesis of numerous circulatory disorders[163] and consequently, different structural classes of Thromboxane A_2/Prostaglandin H_2 receptor antagonists have been developed to prevent these disorders[164,165]. Lavielle reported the synthesis of **412** which showed potent activity for receptor binding[166]. (Figure 4.7.)



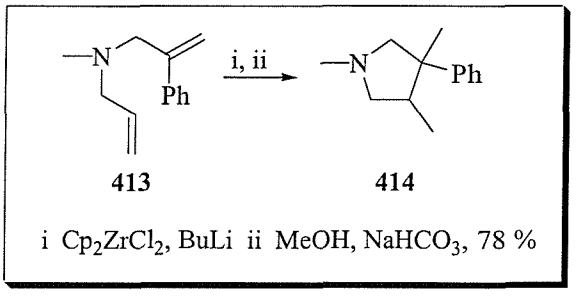
412

Figure 4.7 - Thromboxane A_2/prostaglandin H_2 receptor antagonist

Due to many other biological applications of 3-aryl pyrrolidines[167-174], we felt that these compounds would make interesting biologically active targets for synthesis *via* transition metal mediated diene cyclisation.

4.1.2. Diene Cyclisation to Nitrogen Heterocycles

We initially wanted to focus on the formation of the pyrrolidine ring skeleton using the cyclisation of dienes, as there are fewer methods for cyclising dienes in the literature, in comparison to the number of methods available for enyne and diyne cyclisations. Macfarlane showed that the 2-phenyl-allyl amine **413** cyclised using organo-zirconium chemistry to form the 3-phenyl pyrrolidine **414** in high yield[107]. (Figure 4.8.)

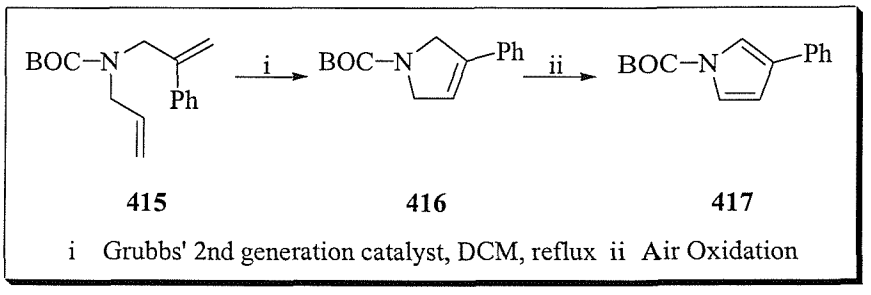


413 **414**

i Cp_2ZrCl_2, BuLi ii MeOH, $NaHCO_3$, 78 %

Figure 4.8 - Zirconium mediated diene cyclisation

There has been precedent for the Ru metathesis of both substituted[175-177] and unsubstituted[178] dienes. Mioskowski showed that the BOC protected diene **415** cyclised to the corresponding dihydropyrrole **416**, before undergoing an unexpected oxidation to form the 3-phenyl pyrrole **417**[179]. (Figure 4.9.)



415 **416** **417**

i Grubbs' 2nd generation catalyst, DCM, reflux ii Air Oxidation

Figure 4.9 - Ruthenium mediated diene cyclisation

It was hoped that these two cyclisation procedures would form the basis of a route to 3-aryl pyrrolidines from diene **415**.

4.2. Results and Discussion

4.2.1. Solution Phase Approach to 3-Phenyl Pyrrolidines

In order to investigate the potential pharmaceutical activity of the phenyl pyrrolidines, it was necessary to develop a route to the cyclisation precursor which would allow easy variation of the aromatic group. With the reported Ru cyclisation of **415** to **417**, it was hoped that **415** would be compatible with the zirconium-mediated cyclisation due to the precedent by Whitby[124]. (Figure 4.10.) However, **415** failed to cyclise to pyrrolidine **418**, giving only the deallylated product **419**.

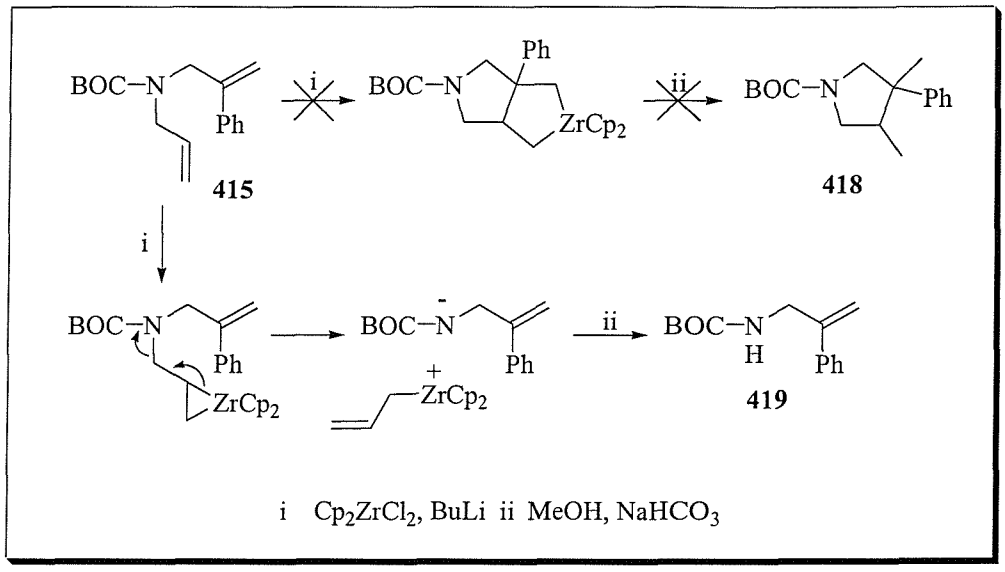


Figure 4.10 - Mechanism of deallylation

Work from the group[107] and results from chapter 2 had indicated that *N*-benzyl dienes were compatible with zirconium mediated cyclisation. Disconnection of the pyrrolidine target **420** gave diene **421** and it was envisaged that **421** could be synthesised *via* a Suzuki cross-coupling of vinyl bromide **422** with $PhB(OH)_2$ using Pd catalysis. (Figure 4.11.)

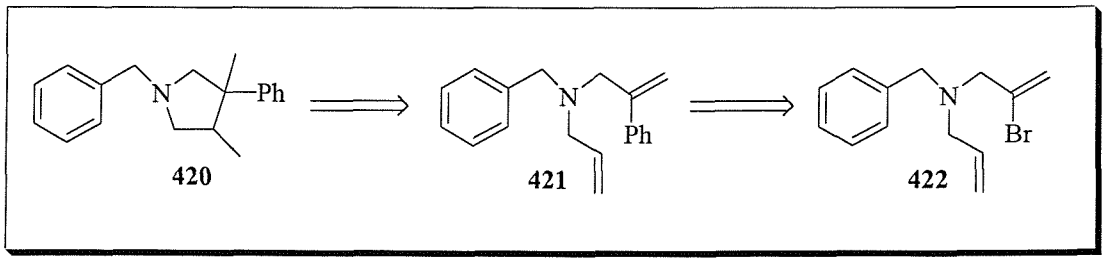


Figure 4.11 - Retrosynthetic analysis of pyrrolidine target

However, the Suzuki coupling failed to work because, after the oxidative addition step occurred, the palladium species **423** rapidly cyclised onto the other allyl group to give **424** before the cross-coupling to **421** could take place. (Figure 4.12.) After cyclisation, **424** reductively eliminated to **425** (before **424** cross-coupled to **427**). Analysis of the crude reaction mixture by ^{1}H NMR indicated that pyrrolidine **425** had isomerised to the thermodynamically more stable 3,4-dimethyl pyrrole **426** under the reaction conditions.

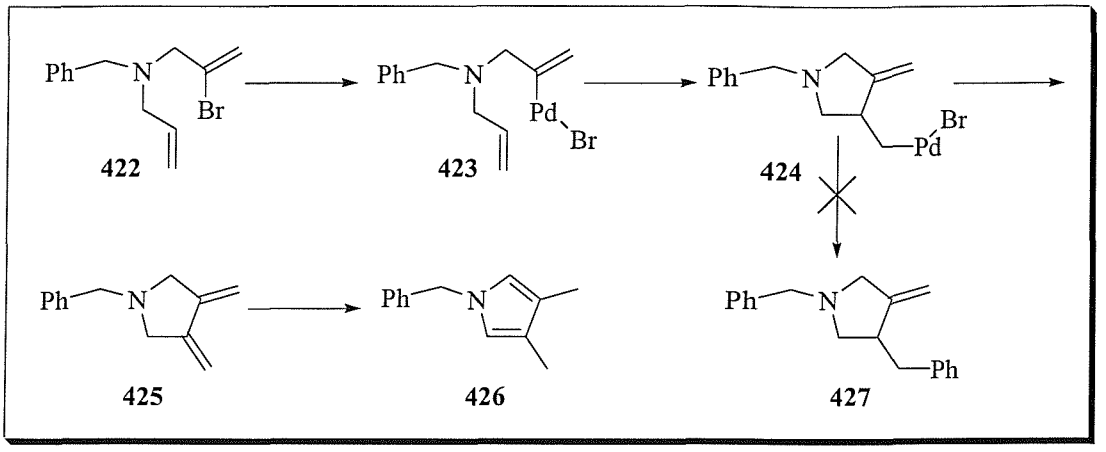


Figure 4.12 - Mechanism of palladium cyclisation

This is consistent with work by Ahn, who reported that diene **428** failed to undergo the expected initial Suzuki coupling, but instead cyclised to the 4-methylene-3-arylmethyl pyrrolidine **430**[180]. (Figure 4.13.) One of the *N*-sulphonyl oxygen atoms was believed to co-ordinatively stabilise the alkylpalladium intermediate **429**, thus preventing the intermediate from β-H elimination and allowing the Suzuki-coupling of **429** to **430** to proceed.

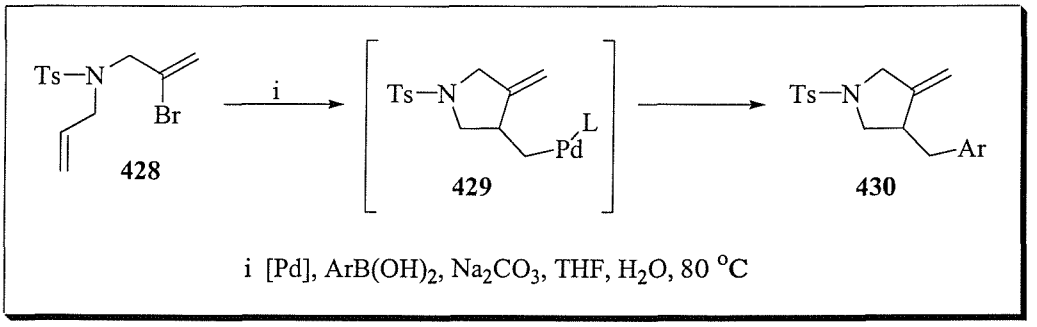


Figure 4.13 - Ahn's palladium mediated cyclisation

A second approach to the diene precursor was attempted *via* AlH_3 reduction of amides using similar chemistry to that of the 3-benzyl pyrrolidines (see chapter 2). Initial disconnection gave amide **432**, which could be synthesised from atropic acid **433**. (Figure 4.14.)

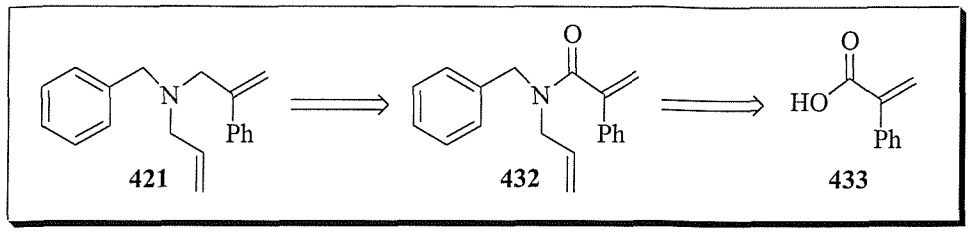


Figure 4.14 - Retrosynthetic analysis of diene precursor

Atropic acid **433** was synthesised under Pd catalysis conditions from CO and phenylacetylene using the procedure described by Scrivanti[181]. This was converted to the acid chloride and trapped as the tertiary amide **432** in 52 % yield by reaction with *N*-benzyl-allyl amine in aqueous NaOH. (Figure 4.15.) However, AlH_3 reduction gave a 3:2 mixture of **421** and the over-reduced product **434** by GC Due to the low yield of acid **433** and the large amount of over-reduced amine **434**, this route towards **421** was discontinued.

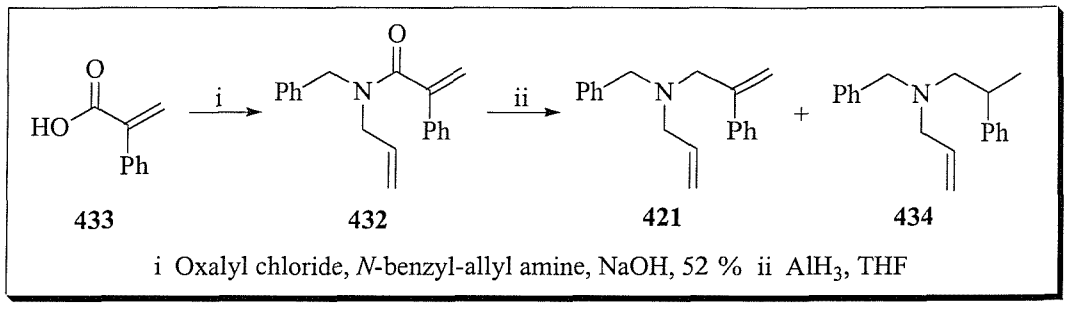


Figure 4.15 - AlH_3 reduction of amide

A second approach towards diene **421** was tried using a Suzuki cross-coupling without the allyl group present. From benzylamine, **435** was synthesised and underwent Suzuki coupling to give **436** in 42 % yield using the procedure described by Organ[182]. (Figure 4.16.) Similarly, acrylamide was converted to **437** in an 8 % yield using procedure reported by Loupy[183]. The low isolated yield was due to the large amount of unreacted acrylamide and the formation of the *bis*-alkylated product as the major product. After Suzuki coupling, **438** was isolated in 44 % yield.

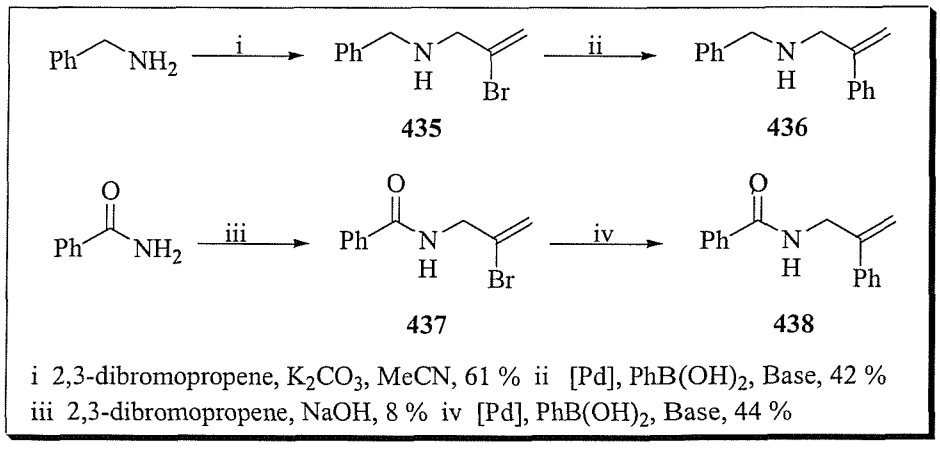
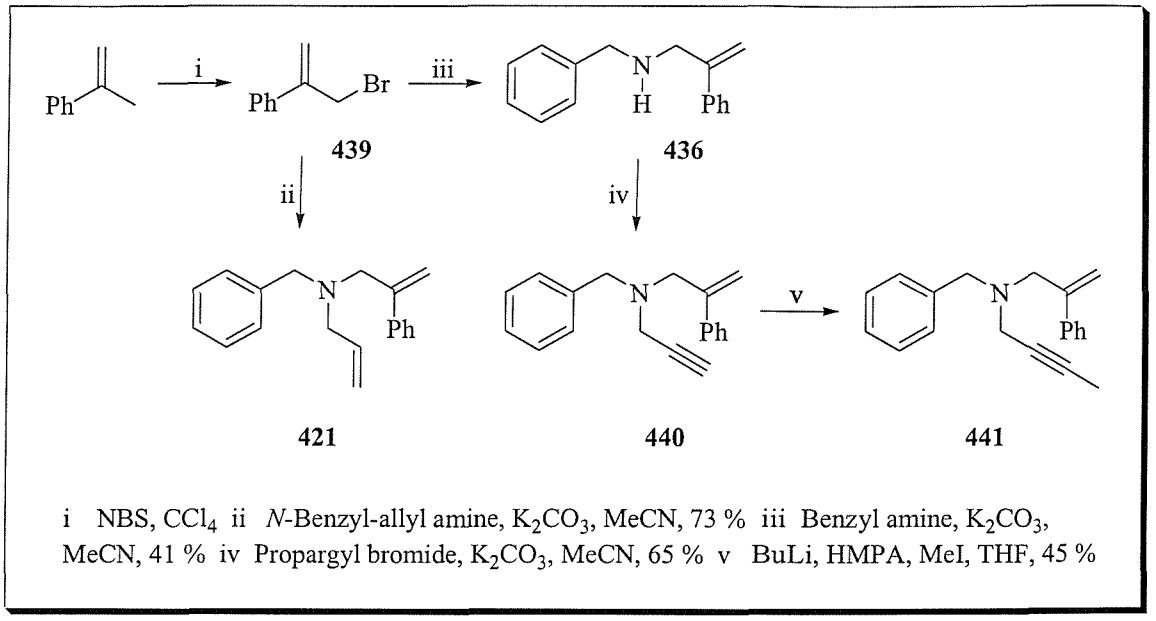


Figure 4.16 - Suzuki coupling route

Although the success of the Suzuki cross-coupling was a useful result, the rather low isolated yields of the arylated products **436** and **438**, and the relatively high expense of commercial boronic acids meant that this route to the cyclisation precursors would not be desirable. However, from a combinatorial approach for future resin work, these routes could become more viable due to the lower reaction scales.

The most desirable route for the synthesis of the solution phase precursors was *via* the radical bromination of α-methyl styrene. After radical bromination, **439** was produced as well as the vinyl bromide regioisomer. Reaction of crude **439** with benzyl amine gave **436** in 41 % yield. (Figure 4.17.) Alkylation of **436** gave the desired enynes **440** and **441**. The use of HMPA in the formation of **441** was found to give better yields of alkylated product due to greater enhancement of the anion nucleophilcity.



i NBS, CCl_4 ii *N*-Benzyl-allyl amine, K_2CO_3, MeCN, 73 % iii Benzyl amine, K_2CO_3, MeCN, 41 % iv Propargyl bromide, K_2CO_3, MeCN, 65 % v BuLi, HMPA, MeI, THF, 45 %

Figure 4.17 - Radical bromination route to dienes and enynes

4.2.2. Zirconium Mediated Diene Cyclisation

Reaction of **421** with Negishi's reagent for 4 hours at r.t. gave the desired pyrrolidine **420**, after hydrolysis quench in 51 % yield. (Figure 4.18.) The reaction time was an important factor as the zirconacycle rearranged after more than 4 hours at r.t. After quench, this gave a mixture of **420** and the acyclic alkene **442**.

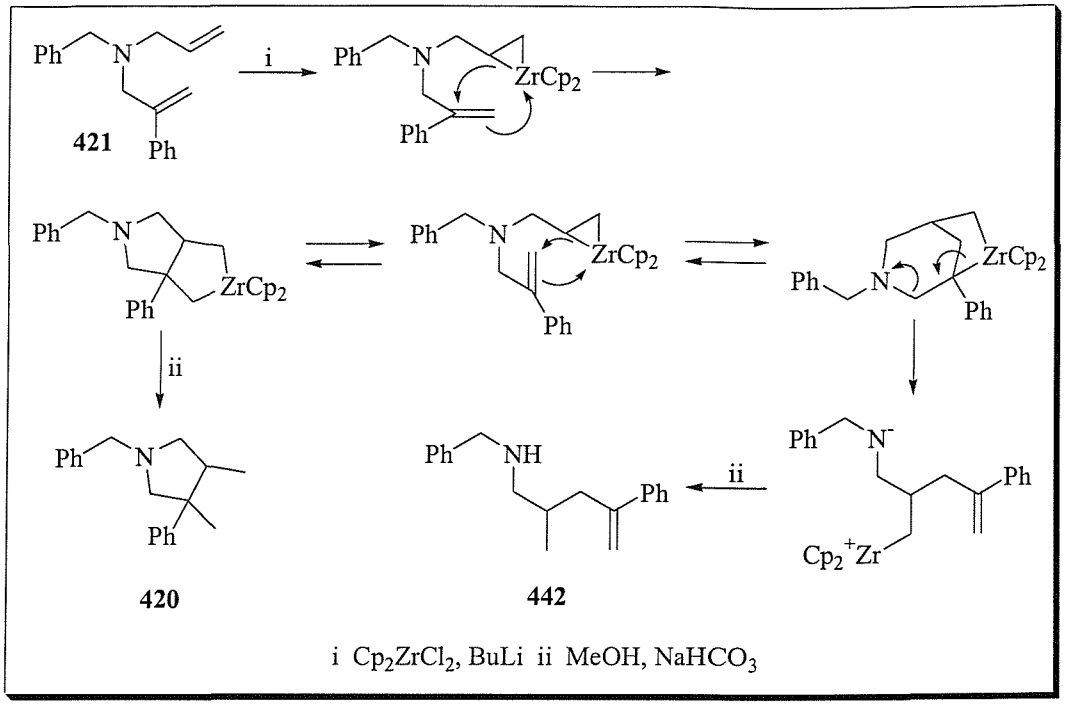


Figure 4.18 - Mechanism of zirconacycle rearrangement

4.2.3 Ruthenium Mediated Diene Cyclisation

It was hoped that diene **421** would cyclise using Grubbs' catalyst to the 3-phenyl pyrrole **444**. (Figure 4.19.) Initially, no reaction was observed in DCM at both r.t. and reflux. This may have been due to the N atom co-ordinating to the Ru metal centre and causing the catalyst to deactivate. However, when diene **421** was refluxed in toluene with Grubbs catalyst under an argon atmosphere, **443** was generated.

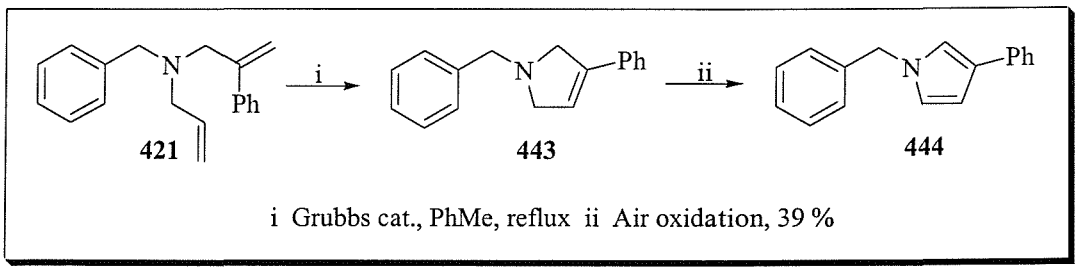


Figure 4.19 - Ruthenium mediated cyclisation to 3-phenyl pyrrole

After aqueous workup in air, examination of the crude by NMR showed that **443** and **444** were present in approximately 1:1 ratio. After purification using column chromatography only **444** was isolated showing that **443** was rapidly oxidising to **444**. Thus, pyrrole **444** was isolated in 39 % yield. This is in agreement with work by Lee who unexpectedly isolated pyrrole **444** rather than the dihydropyrrole after boronic acid cross-coupling[184]. (Figure 4.20.) A mechanism for the unexpected oxidation was not reported but is believed to occur *via* palladium-mediated dehydrogenation[184].

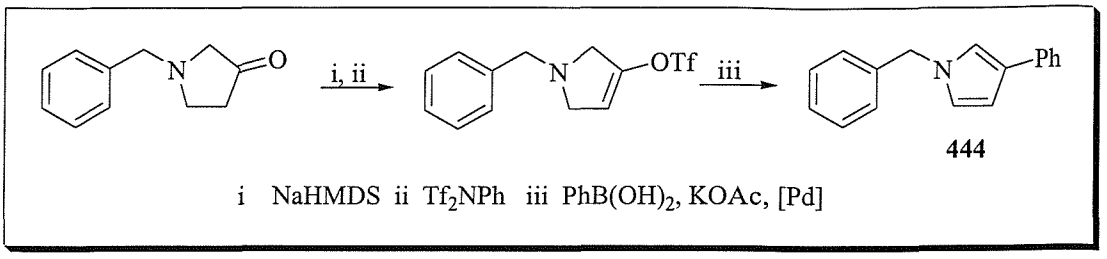


Figure 4.20 - Lee's palladium mediated pyrrole synthesis

It was envisaged that the Ru metathesis reaction would be a useful route to 3-aryl lactams. (Figure 4.21.) Although amide **445** was synthesised, it failed to cyclise to lactam **446**. This may be due to the N and O atoms of **445** chelating to the Ru metal centre and deactivating catalytic turnover.

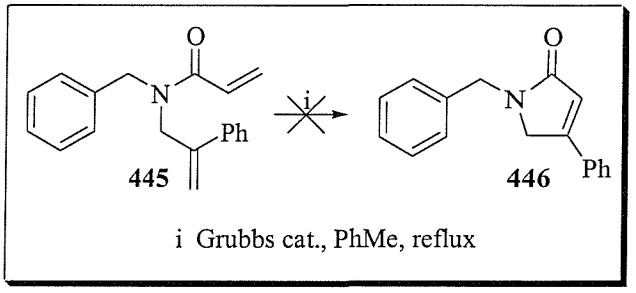


Figure 4.21 - Attempted route to 3-aryl lactams

4.2.4. Zirconium Mediated Enyne Cyclisation

Cyclisation of **441** with Negishi's reagent gave pyrrolidine **447** bearing an exo-cyclic alkene. The geometry of the exo-cyclic double bond is believed to be *trans* as indicted in figure 4.22 due to the stereochemistry of the zirconacycle intermediate. The reaction was quenched after 3 hours to prevent any rearrangement as observed with diene **421**. No attempt was made to deliberately rearrange the zirconacycle due to a shortage of both **441** and time.

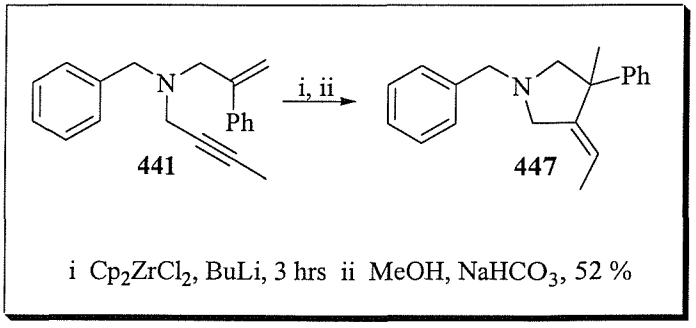


Figure 4.22 - Zirconium mediated enyne cyclisation

4.2.5. Titanium Mediated Enyne Cyclisation

Sato showed that it was possible to cyclise enyne **255** to **247** using stoichiometric Ti(IV)[118]. (Figure 4.23.) It was hoped that this could be extended to the synthesis of 3-aryl pyrrolidines.

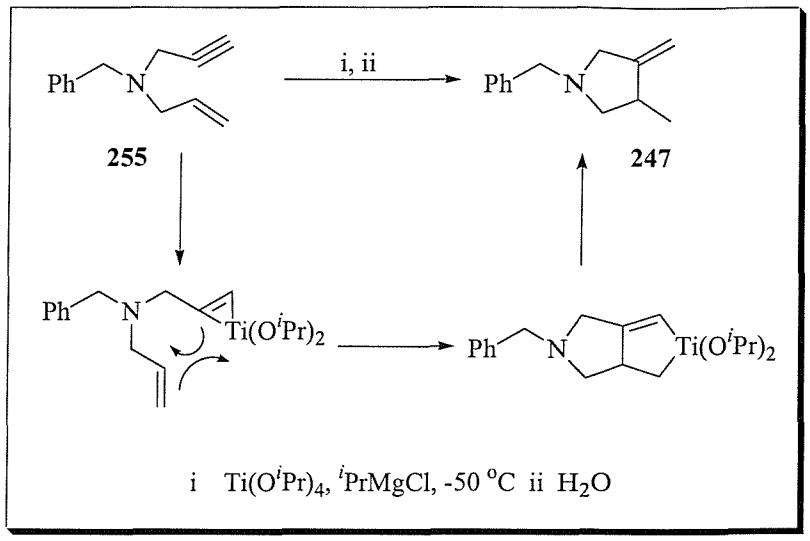


Figure 4.23 - Titanium mediated enyne cyclisation

Using the cyclisation procedure outlined by Sato[118], the cyclisation of **440** to **449** was attempted. (Figure 4.24.) However, titanacycle **448** failed to form. Instead, **436** formed as the major product after protonation. This was believed to occur *via* titanacycle **450** rearranging and depropargylating as shown in figure 4.24.

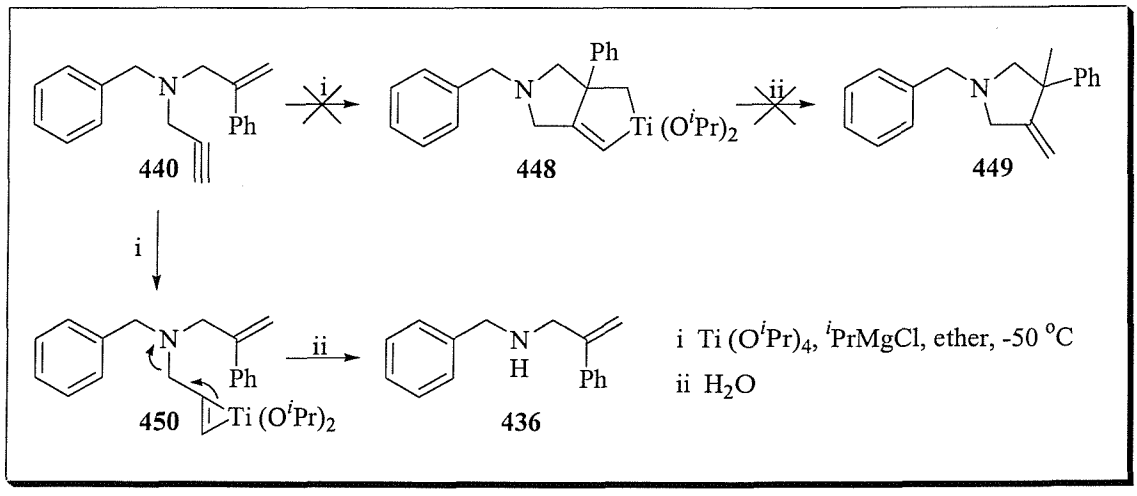


Figure 4.24 - Mechanism of titanium mediated depropargylation

4.3. Combinatorial Approach to 3-Aryl Pyrrolidines

It was hoped that a feasible route to the combinatorial synthesis of 3-phenyl pyrrolidines could be established. Using the successful Suzuki cross-coupling of **437** to **438**, we hoped this could be a potential route to the introduction of the aryl group on the resin. (Figure 4.25.) Amide **451** was reduced to **421** cleanly using AlH_3, as monitored by GC The effective use of AlH_3 on a solid-support has been described in chapter 3.

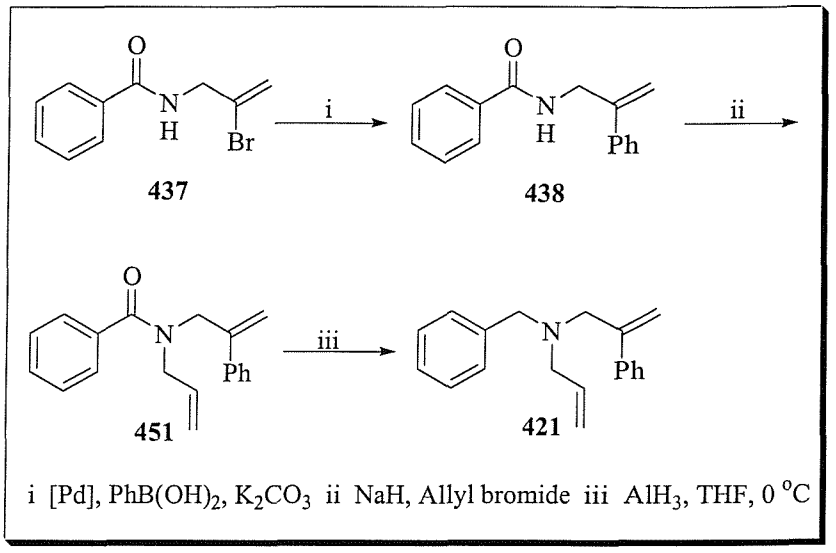


Figure 4.25 - AlH_3 reduction route to diene

After cyclisation of **421** to **420**, we hoped to use Leysen's debenzylation procedure, as it would provide a convenient route to secondary pyrrolidines[134]. Having observed disappointing yields for this debenzylation method in chapter 3, we switched to a Wang resin. It was believed that the cleavage would be more facile due to the greater electron-donating properties of Wang compared to Merrifield resin. Wang resin **452** was prepared using the literature procedure[185], and the secondary amine was anchored to the solid support by heating in NMP to give **453**[134]. (Figure 4.26.) The resin was washed, dried, cyclised with Negishi's reagent and quenched to give **454**. Cleavage was achieved to give **455** in a 29 % yield as a 15:1 mixture of diastereoisomers.

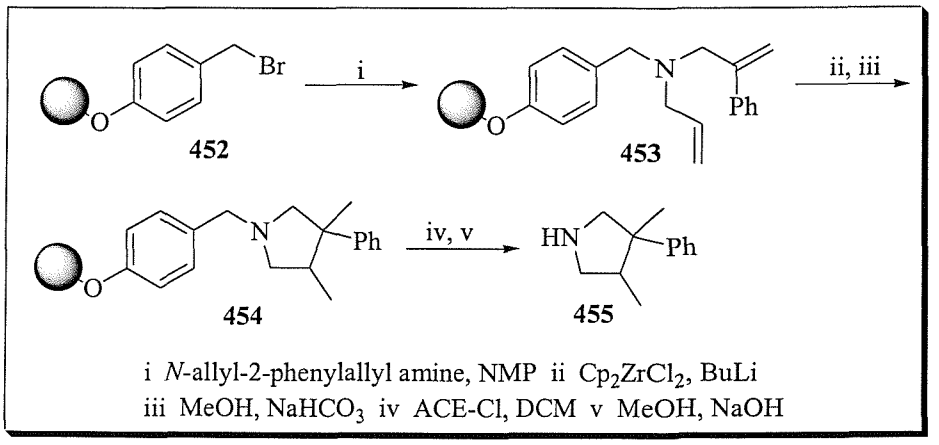


Figure 4.26 - Zirconium mediated diene cyclisation using Wang resin

This is an interesting result in light of the fact that in solution, only one diastereoisomer of **420** was isolated after quench. This is either due to the polymer-matrix environment forcing the zirconacycle intermediate to adopt a particular structural conformation, or because of the different electronic effects of a Wang-derived benzyl group of **453** over a simple benzyl group for **420**.

Due to time constraints, the combinatorial synthesis of 3-aryl pyrrolidines was not finished. A route to the synthesis of 3-phenyl pyrrolidines has been proposed from resin **456**. (Figure 4.27.) The transformations of **456** to **463** have been shown to be possible in solution. The pyrrolidine could then be cleaved by either the formation of carbamate **462** (see chapter 3) or by the Leysen protocol to **463**[134].

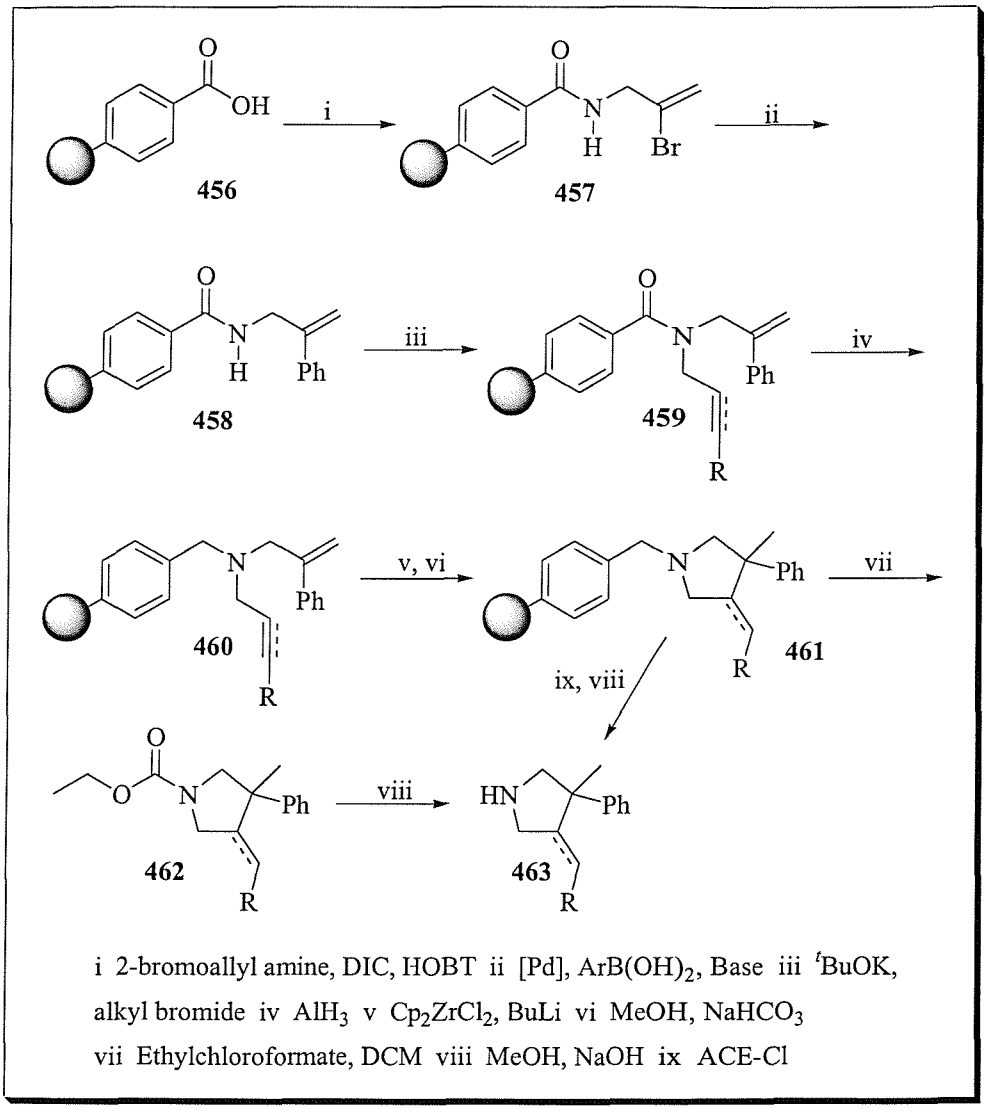


Figure 4.27 - Combinatorial route to 3-aryl pyrrolidines

4.4. Future Work

Continuation of the research into the synthesis of 3-phenyl pyrrolidines would require the synthesis of more dienes and enynes, with varying aromatic groups for cyclisation in the solution phase. The optimum route will be *via* the radical bromination of a selection of α-methyl styrenes **464** to give **465** and subsequent reaction with the appropriate amine source to give **466**. (Figure 4.28.) The diene or enyne would be cyclised with different metal sources to the 3-phenyl pyrrolidine pharmacophore **467**.

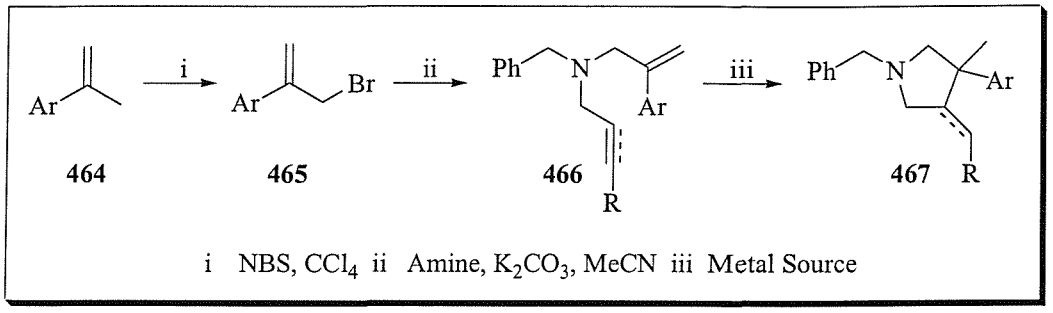


Figure 4.28 - Future solution phase approach to 3-aryl pyrrolidines

Extending this chemistry to the solid-phase would require building the diene or enyne framework on the solid-support by the route shown in figure 4.27.

4.5. Conclusions

The preceeding chapter has discussed the synthesis of the 3-phenyl pyrrolidine pharmacophore. The best route to the solution phase precursors was *via* the radical bromination of α-methyl styrene, and subsequent reaction with the appropriate amine source. This has enabled the synthesis of diene **421** and enyne **441** which were successfully cyclised with Negishi's reagent to afford pyrrolidines **420** and **447** after protonation. Cyclisation of diene **419** with Grubbs' catalyst afforded pyrrole **444** after air oxidation. Initial investigation has shown that the Suzuki cross-coupling of **437** to **438**, the AlH_3 reduction of **451** to **421** and the formation of **455** *via* ACE-Cl debenzylation would be a potential route to the synthesis of 3-aryl pyrrolidines on the solid-support.

CHAPTER 5

THE SYNTHESIS OF 6-MEMBERED PHOSPHACYCLES

5. The Synthesis of 6-Membered Phosphacycles

5.1. Introduction To Aromatic Phosphacycles

The need for phosphorus heterocycles within highly functionalised and elaborate rings systems is a rapidly increasing area of chemistry. Phosphorus compounds have found widespread use in all areas of chemistry due to the element's versatility, and as a consequence, the requirement for efficient synthetic routes to such molecules is a major interest in modern organic chemistry.

Six membered phosphorus aromatic heterocycles can be split into two main classes[186,187]. These are λ^3-phosphinines such as **501**, which behave as fairly classical aromatic systems and the λ^5-phosphinines such as **502** which can be considered either aromatic or as phosphonium ylides. (Figure 5.1.) The λ^3-phosphinines are of particular synthetic interest due to their reported use as ligands in catalysis[188,189].

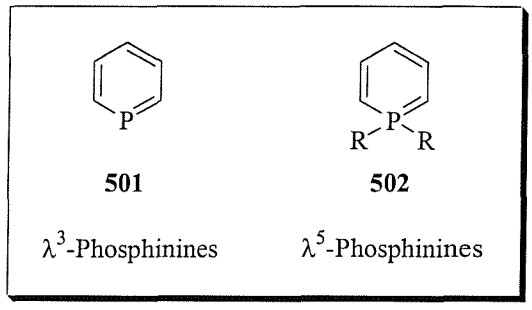


Figure 5.1 - Aromatic 6-membered phosphacycles

5.1.1. λ^3-Phosphinine Syntheses

λ^3-Phosphinines, also known as λ^3-phosphorins and λ^3-phosphorbenzenes were first synthesised by Märkl[190] in 1966 from the oxonium ion species **503**. (Figure 5.2.) The synthesis of the stable crystalline 2,4,6-triphenyl-λ^3-phosphinine **504** was the first phosphorus analogue of a pyridine derivative to be isolated.

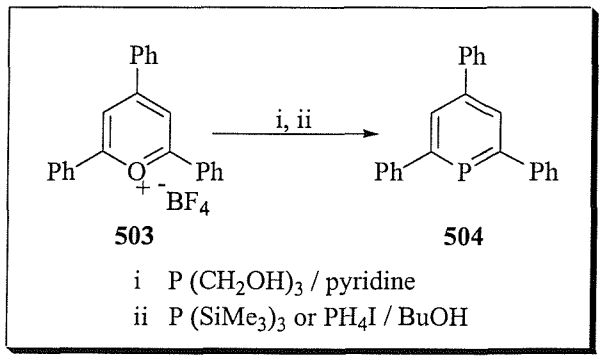


Figure 5.2 - Märkl's synthesis

Later, the parent λ^3-phosphinine **501** was synthesised by Ashe using a stannacycle as an intermediate[191]. (Figure 5.3.) Phosphinine **501** was found to be very air-sensitive and could only be purified by HPLC under an inert atmosphere.

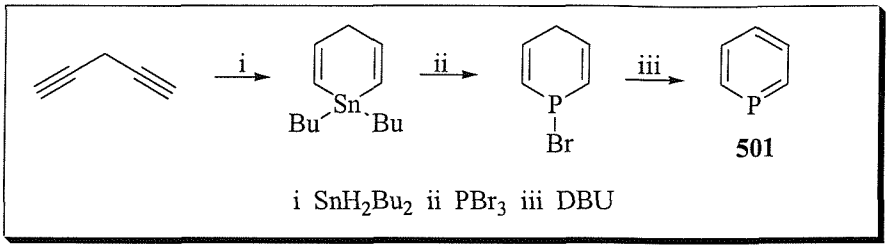


Figure 5.3 - Ashe's synthesis

Märkl developed another synthesis of 4-substituted λ^3-phosphinines such as **505** by initial ring opening of 4-R-4-methoxy-1,1-dibutylstannacyclohexanes with BuLi, addition of PCl_2OBu^n and subsequent reduction with $LiAlH_4$[192]. (Figure 5.4.)

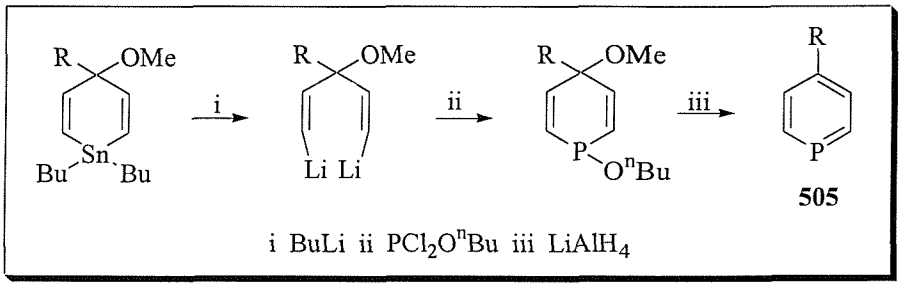


Figure 5.4 - Märkl's synthesis

Märkl later discovered a new synthesis of substituted λ^3-phosphinines such as **506** by 1,4-addition of 1-chloro(α-trimethylsilyl)benzylidenephosphine to α-pyrones[193]. (Figure 5.5.)

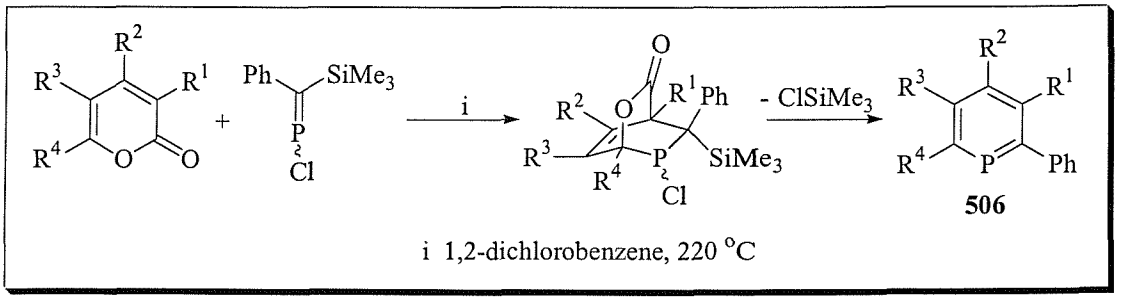


Figure 5.5 - Märkl's synthesis

Thermolytic reactions of 1-^{n}Bu- or 1-^{t}Bu-1,2-dihydrophosphinine derivatives and of 1,1-dibenzyl-λ^5-phosphinines also lead to λ^3-phosphinine derivatives[186] such as **507** and **508**. (Figure 5.6.)

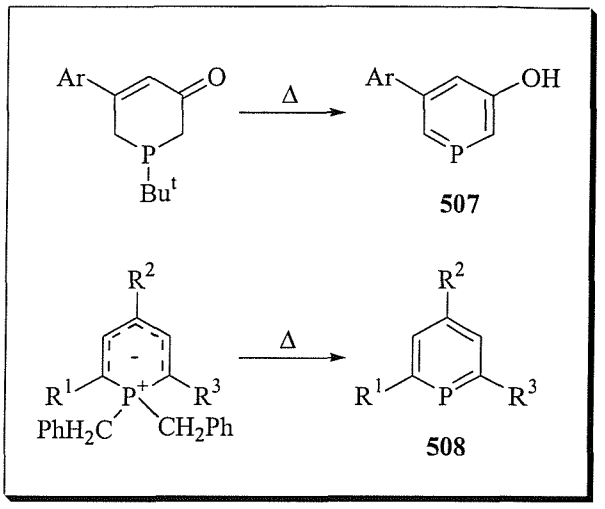


Figure 5.6 - Synthesis via thermolysis

Bickelhaupt and co-workers have studied the λ^3-phosphinine derivatives of benzo annulated rings such as **509**[194]. The final P=C double bond is introduced into the final ring systems by basic elimination of HCl with DBU or other bases. (Figure 5.7.)

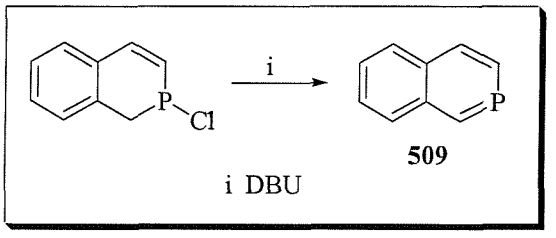


Figure 5.7 - Bickelhaupt's synthesis

5.2. Synthetic Strategy

Following from work within the group and published work from Takahashi[56], it was hoped that a novel route to phosphinines could be developed. Formation of the initial zirconacycle **510**, followed by carbenoid insertion had been shown to give **511**. (Figure 5.8.) It was postulated that treatment of **511** with PCl_3 would induce the metathesis of zirconium to phosphorus, eliminating zirconocene dichloride and trimethylsilylchloride to yield phosphinine **512**. (The metatheses of zirconium to phosphorus and other main-group elements in discussed in chapter 1.) Using this principle, it was hoped that a number of different phosphinines could be synthesised.

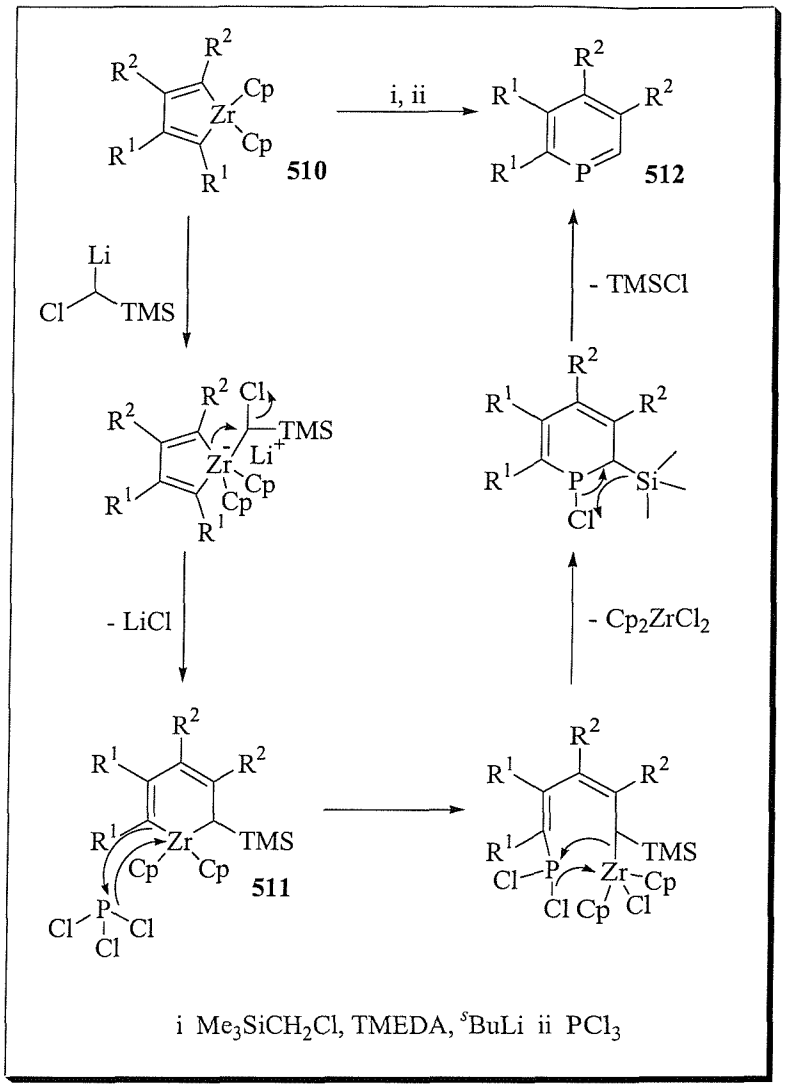


Figure 5.8 - Synthetic strategy and mechanism

5.3. Results And Discussion

5.3.1. Monocyclic λ^3-Phosphinine Synthesis

Zirconacycle **510a** was synthesised and ring expanded to the 6-membered zirconacycle **511a** using Takahashi's protocol[56]. (Figure 5.9.) Monitoring the reaction by GC indicated the allylic isomerisation which had been reported by Takahashi. Reaction of **511a** with PCl_3 at -78 °C gave the desired phosphinine **512a**, with elimination of trimethylsilyl chloride and zirconocene dichloride.

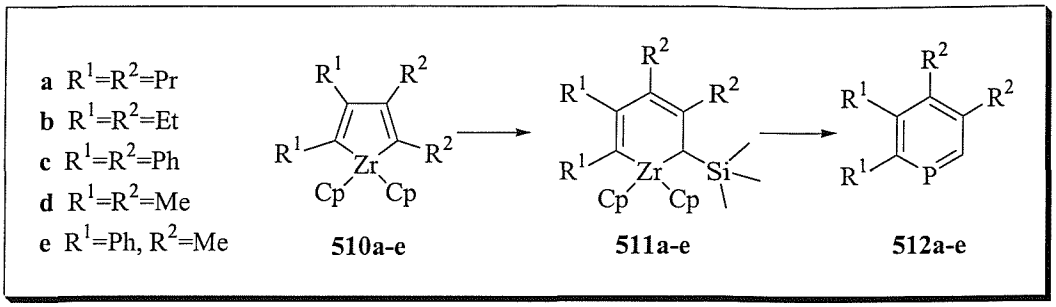


Figure 5.9 - Phosphinine synthesis

However, purification of phosphinine **512a** was difficult due to its sensitivity to air and moisture. Reported methods for the purification of phosphinines have included distillation[195], recrystallisation[190] and column chromatography[196]. Phosphinine **512a** could not be distilled due to its high molecular weight, and would not crystallise due to the propyl chains present. Column chromatography of **512a** using dry silica, dry solvents and under an argon atmosphere was shown to give purer **512a**, but decomposition occurred when left on the column for more than 10 minutes. Crude **512a** was columned quickly on neutral, activated alumina, but ^{1}H NMR analysis showed that decomposition of **512a** occurred during chromatography and thus was not isolated pure. It was therefore decided to purify **512a** by filtration as the chief impurity present was the regenerated zirconocene dichloride. Washing the crude reaction mixture several times with hexane, followed by filtration through a pad of celite under an argon atmosphere afforded a yellow residue which was 55 % pure, with a yield of 37 % of pure **512a**. The residue was contaminated with a small amount of zirconocene dichloride.

Phosphinine **512b** was synthesised from 3-hexyne and purified under identical conditions to **512a**. This gave **512b** in 60 % purity, 33 % yield.

Synthesis of **512c** was attempted as it was hoped that a crystalline phosphinine could be synthesised. Zirconacycle **510c** was generated by the co-cyclisation of two equivalents of diphenylacetylene. However **511c** did not form as the carbenoid insertion failed. This was due to the phenyl rings providing steric bulk which prevented carbenoid insertion.

Synthesis of **512d** was also attempted, but its extreme volatility meant that its isolation from the THF reaction solvent was never achieved.

It was decided that **512e** could be made by synthesising a mixed zirconacycle from two alkyne components using the synthetic strategy outlined by Livinghouse[197]. The advantage of using diphenylacetylene and 2-butyne was that if small amounts of **510c** did form, the carbenoid would not insert and **512c** would not be made. However, if small amounts of **512d** were made then the phosphinine would be too volatile to isolate. Thus, **512e** would be the only phosphinine to be isolated.

The mixed zirconacycle **510e** was prepared and carbenoid insertion was selective into the less sterically hindered methyl side to give **511e**. However, after PCl_3 metathesis, a 1:1 mixture of **512e** and **513e** were formed. (Figure 5.10.) The unexpected formation of **513e** was initially attributed to the basic nature of DMAP inducing HCl, rather than TMSCl elimination. However, it was found that varying the DMAP concentration did not alter the relative amounts of **512e** and **513e**. Even performing the PCl_3 quench with an excess of diethylamine, a stronger base, did not lead to **513e** exclusively. Also adding DMAP to **511b** before PCl_3 addition failed to give any of the HCl eliminated product **513b**.

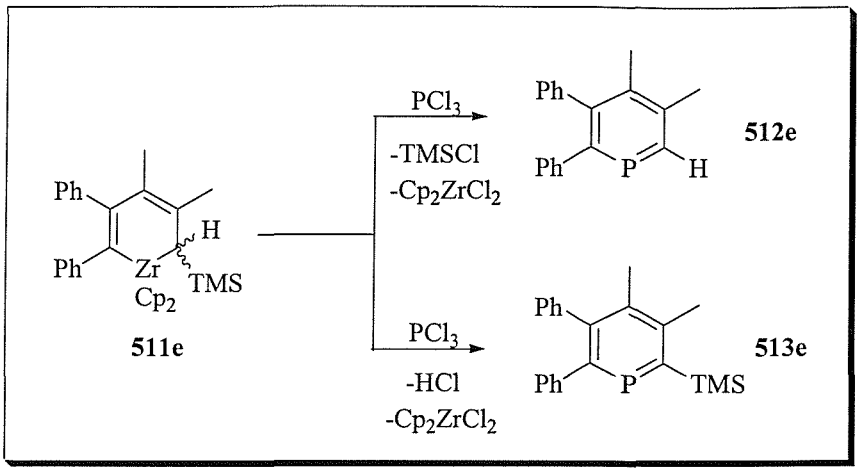


Figure 5.10 - Unexpected HCl elimination

5.3.2. Bicyclic λ^3-Phosphinine Synthesis

With the reported ease with which diynes can be cyclised, it was hoped that bicyclic phosphinines could be synthesised. (Figure 5.11.)

Zirconacycle **514a** was synthesised as it was hoped that the carbenoid would insert into the less sterically hindered propyl side (R^2). When zirconacycle **514a** was reacted with lithiated chloromethyltrimethylsilane the carbenoid insertion to **515a** and PCl_3 quench to **518a** was not clean. GCMS examination of crude **518a** showed two chief impurities besides unreacted **514a** and **515a**. These were shown to be the *bis*-inserted product **508a** and subsequent PCl_3/ TMSCl eliminated product **518a**. ^1H NMR of the crude reaction mixture showed the characteristic ^2J(P-H) coupling of 39.0 Hz correlating to the α proton of **516a**. However, **516a** was heavily contaminated with impurities and subsequently, no further synthesis of **516a** was attempted.

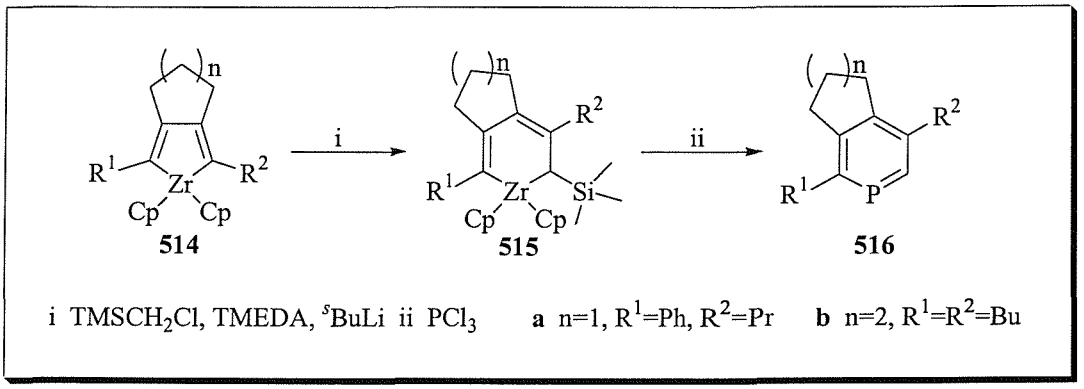


Figure 5.11 - Bicyclic phosphinine strategy

Zirconacycle **514b** was synthesised as it was hoped that by selecting R^1=R^2=butyl, the carbenoid could attack either carbon-zirconium bond to give only one product of **515b**. Zirconacycle **514b** was ring-expanded to **515b**, but carbenoid insertion proved not to be clean and the *bis*-inserted product **517b** was observed. (Figure 5.12.) ^{1}H NMR examination showed the characteristic ^2J(P-H) coupling of 36.8 Hz, but **516b** was contaminated. This reaction was repeated several times, but it was found that **516b** could not be isolated cleanly and therefore was abandoned.

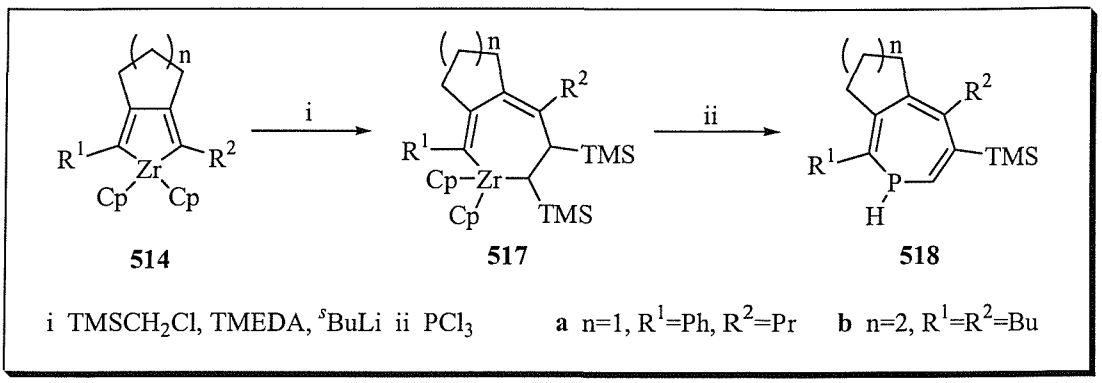


Figure 5.12 - *Bis*-insertion products

5.3.3. Benzo Annulated Phosphinines (Phosphinolines)

Erker showed that it was possible to form the bicyclic zirconaindene **519**[36]. Using this, it was hoped that it would be possible to form either the *iso*-phosphinoline **521** or the phosphinoline **523** depending on the regiochemistry of carbenoid insertion. (Figure 5.13.)

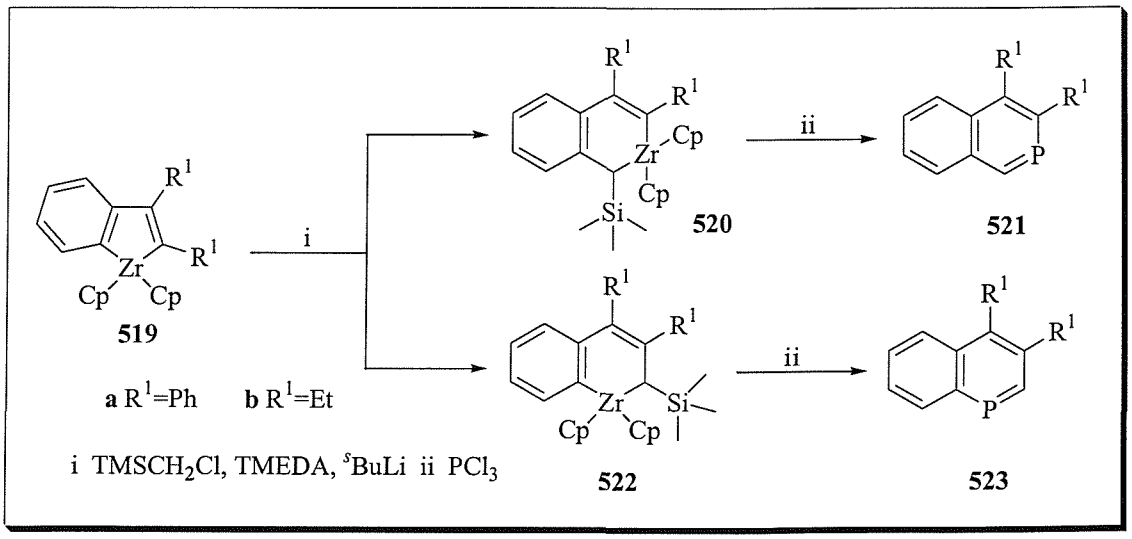


Figure 5.13 - Synthetic route to phosphinolines and *iso*-phosphinolines

It was necessary to determine the regiochemistry of insertion of lithium chloromethyltrimethylsilane into zirconacycle **519**. Zirconacycle **519a** was synthesised as it was hoped that the bulky phenyl rings would force the carbenoid to insert into the less hindered side to form **520a**. Unfortunately, the carbenoid failed to insert

into either carbon-zirconium bonds, probably due to both sides being too sterically hindered to allow insertion to occur. Consequently, the less hindered zirconacycle **519b** was synthesised and reacted with the lithium chloromethyltrimethylsilane to generate **522b**. Insertion of the carbenoid was not clean and gave two main products. The minor component was the *mono*-inserted product **522b** which formed as a racemic mixture, and the major component was the bis-inserted product **524**. (Figure 5.14.) By adding the carbenoid slowly to **519b**, it was hoped that **522b** would be selectively formed. Even with the slow addition of half an equivalent of carbenoid to **519b**, the major product was **524**. As we were unable to selectively form **522b**, the route to phosphinoline **523b** was abandoned.

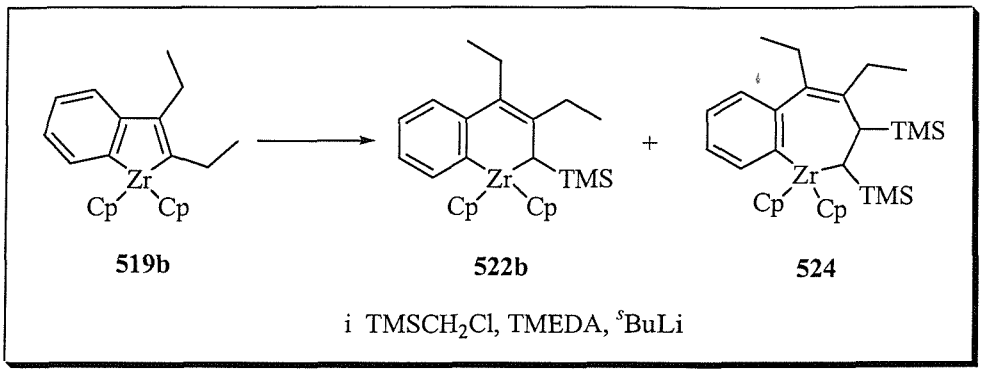


Figure 5.14 - *Bis*-insertion of carbenoid

5.3.4. Synthesis of Chromium Pentacarbonyl Complexes

As it was difficult to obtain the phosphinines pure, it was believed that it would be worthwhile isolating them as a more stable derivative. Group VI transition metal pentacarbonyl complexes have been shown to form phosphinine complexes[198,199]. The chromium pentacarbonyl derivative **525** was synthesised from **512a** using the literature procedure[198]. (Figure 5.15.) However, the compound was not crystalline, probably due to the propyl chains present which meant that an X-ray of **525** could not be obtained. Also, it was found that the phosphinine-Cr adduct **525** decomposed in chloroform and did not give satisfactory mass spectrometry data. Therefore, a different means of derivatisation was sought.

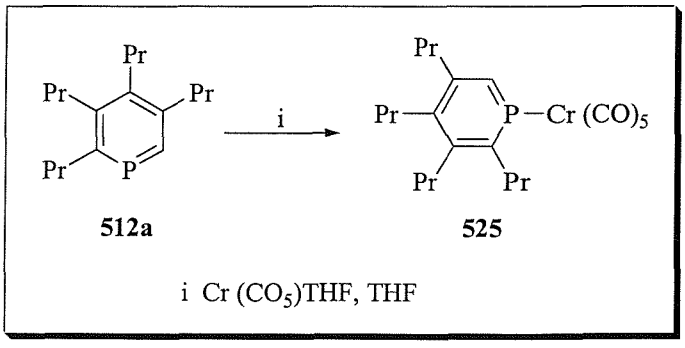


Figure 5.15 - Cr $(CO)_5$-phosphinine complex formation

5.3.5. Synthesis of Diels-Alder Adducts

Mathey had shown that it was possible to make phosphinine Diels-Alder adducts[200,201]. This was advantageous as both the phosphorus atom and phosphorus-carbon double bond in **512** would become protected during the reaction. The adduct can also undergo a retro-Diels-Alder reaction by addition of PBu_3 to regenerate the free phosphinine **512** if required[200,201]. Therefore, by forming the Diels-Alder adducts **526** of the crude phosphinines, more detailed characterisation of the adducts could be completed. (Figure 5.16.)

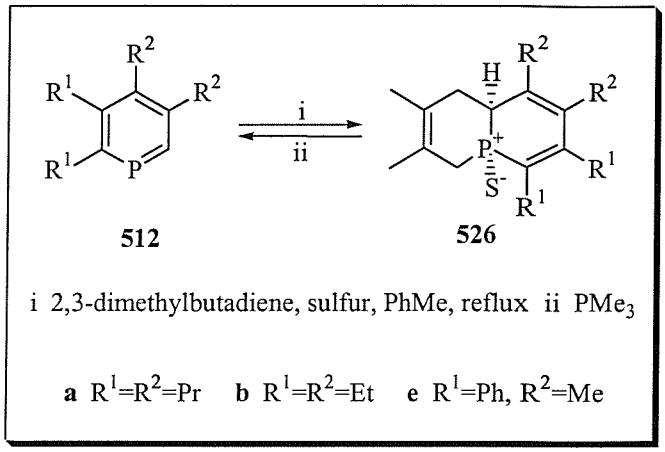
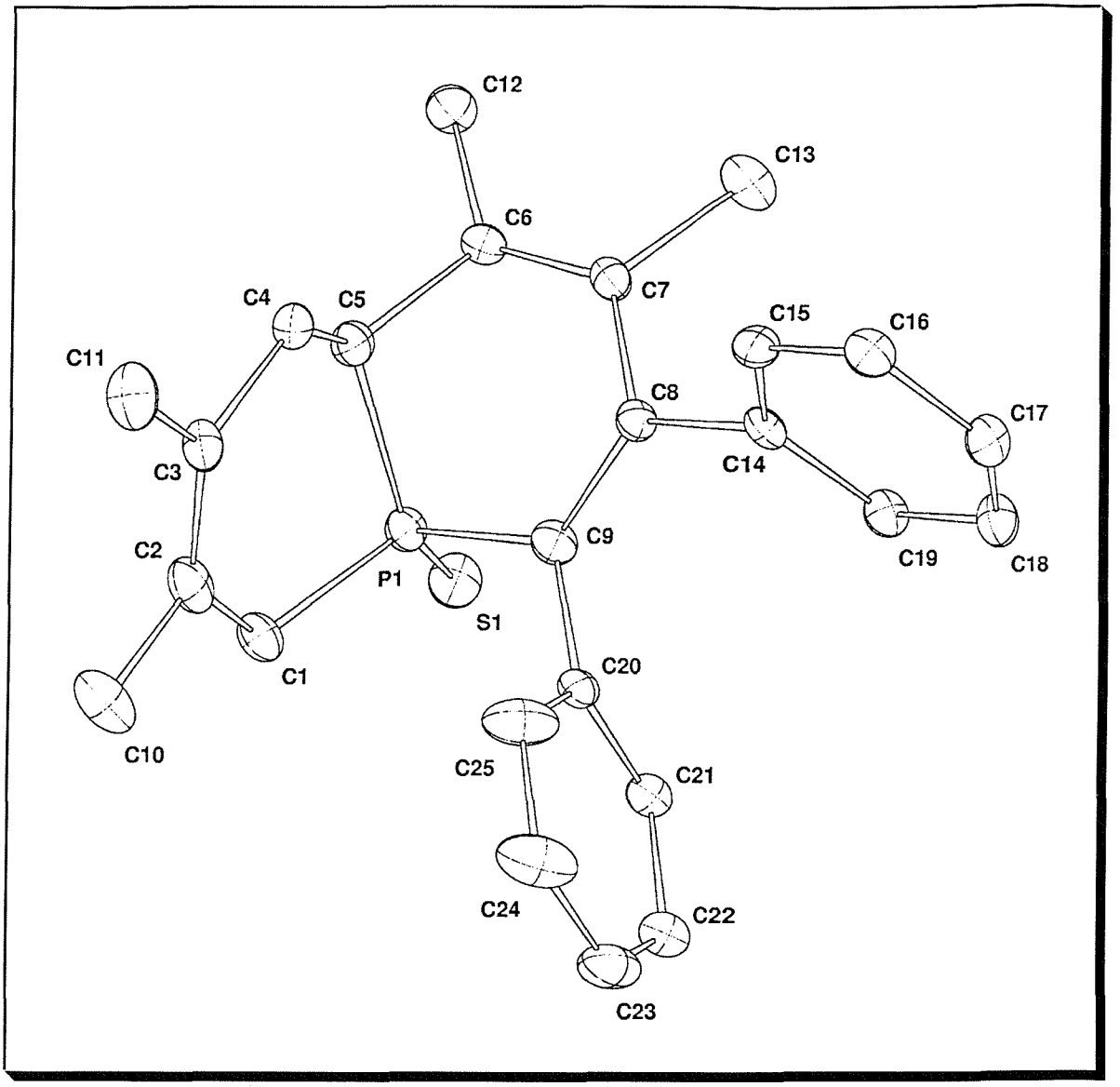


Figure 5.16- Diels-Alder adduct formation

Using the procedure outlined by Mathey[200], the Diels-Alder adducts **526a** and **526b** were isolated in 9 % and 20 % yield respectively, over 4 steps from Cp_2ZrCl_2, by reaction of the phosphinine with sulphur and 2,3-dimethylbutadiene in refluxing toluene. Although phosphinine **512e** was a mixture with phosphinine **513e**, the Diels-Alder adduct of **513e** did not form. Thus, **526e** was isolated as a yellow crystalline solid after column chromatography in 13 % yield. The regiochemistry of carbenoid insertion into zirconacycle **510e** was confirmed by X-ray crystallography. (X-ray 5.17.) The X-ray clearly shows the carbon from the carbenoid insertion stage (C_5) being adjacent to the methyl substituted carbon (C_6). The X-ray also confirms the expected *cis* geometry of S_1 and the hydrogen atom adjacent to C_5.



X-Ray 5.17- Diels-Alder adduct of **526e**

5.4. Phosphinic Acids

Phosphinic acid compounds (phosphinates) are derivatives of phosphinic acid $H_2P(O)(OH)$. The phosphinic moiety is usually present as an alkyl or aryl derivative R_1-P(O)(OH)-R_2. Phosphinic acid peptides (phosphinic pseudopeptides) have been found to be a convenient mimic of the substrate transition state for at least two classes of hydrolytic enzymes. For this reason, they are of wide spread interest in biology, biochemistry and medicine[202].

5.4.1. Phosphinic Acid Syntheses

Many synthetic strategies have been employed to introduce the phosphinic moiety into final heterocyclic systems. Lambert used an Arbusov-Michaelis phosphorylation, intramolecular cyclisation followed by acid hydrolysis to make the parent 6-membered phosphinic acid **527**[203]. (Figure 5.18.)

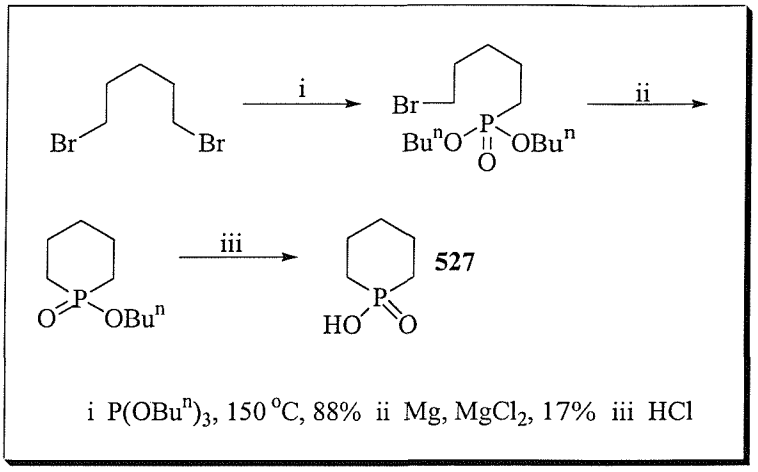


Figure 5.18 - Lambert's phosphinic acid synthesis

An alternative synthesis for phosphinic acids provided by Sommer involved introducing the reactive phosphorus-chlorine bond by refluxing phenylphosporinane with PCl_3[204]. (Figure 5.19.) Hydrogen peroxide oxidised P^{III} to P^{V} to give **527**.

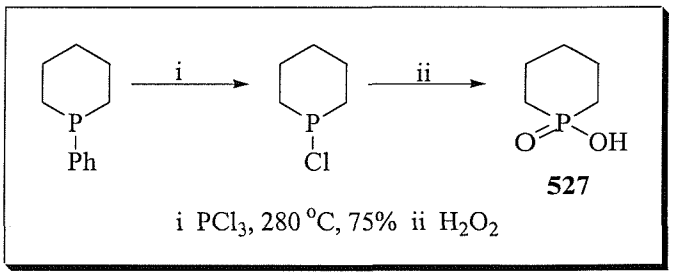


Figure 5.19 - Sommer's phosphinic acid synthesis

Swan formed the benzo annulated phosphinic acid **528** from 3-phenylpropyldichlorophosphine using $AlCl_3$, followed by HCl quench[205]. (Figure 5.20.)

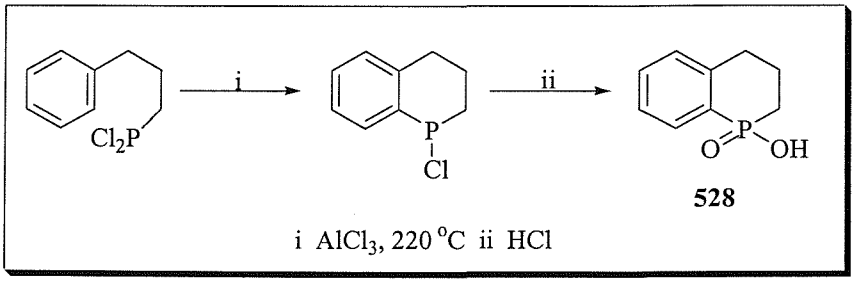


Figure 5.20 - Swan's phosphinic acid synthesis

Lebedeva made the novel bicyclic phosphinic acid by ring-opening the tetracyclic phosphine oxide with refluxing NaOH[206]. (Figure 5.21.)

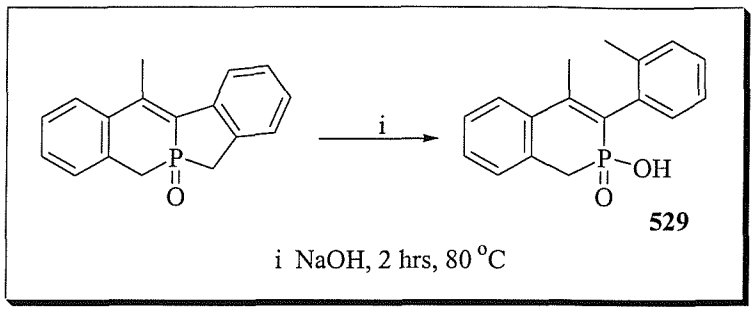


Figure 5.21 - Lebedeva's phosphinic acid synthesis

5.5. Synthetic Strategy

Ring expansion of zirconacycle **530** by carbenoid insertion was expected to result in zirconacyclohexane **531**. (Figure 5.22.) PCl_3 metathesis would allow the introduction of phosphorus to generate the 6-membered phosphacycle **532**. Providing TMSCl wasn't eliminated, subsequent reaction of the phosphorus-chlorine bond with H_2O_2 would give the phosphinic acid **533**.

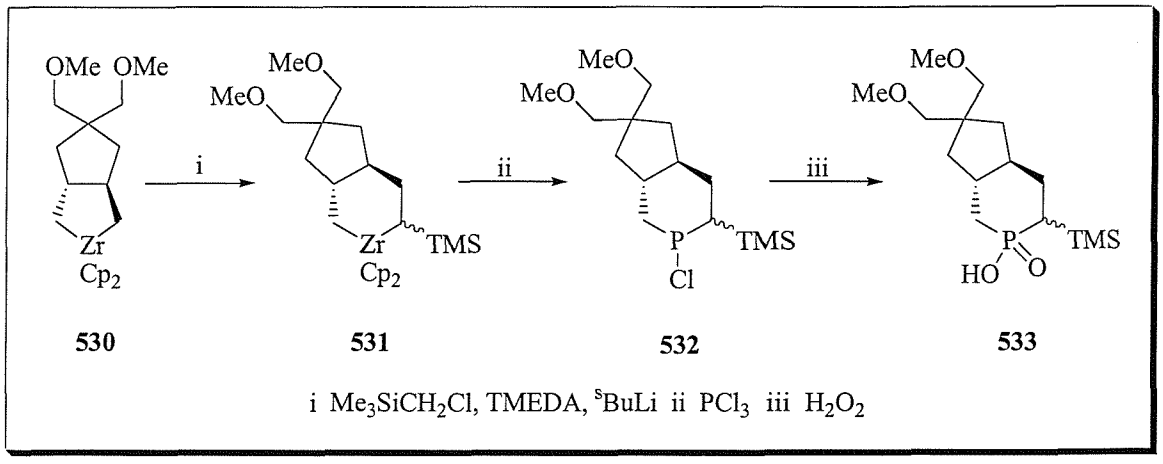


Figure 5.22 - Phosphinic acid synthetic strategy

5.6. Results And Discussion

Zirconacycle **530** formed as the *trans* diastereoisomer and ring expansion to **531** was achieved *via* insertion of lithium-chloromethyltrimethylsilane. PCl_3 was added and stirred at room temperature overnight. ^1H NMR examination showed that the although the initial metathesis was very fast, complete cyclisation took 6 days at room temperature. (Figure 5.23.) Interestingly, the elimination of TMSCl was not observed (as had been demonstrated in the synthesis of phosphinines **512**). Presumably there was no gain in stability for **532** to eliminate TMSCl, compared to the gain in stability provided by aromaticity in the case of **512**. Reaction of **532**

with H_2O_2 generated the phosphinic acid **533** in 36 % yield. Attempts to accelerate the reaction by heating at reflux were not successful.

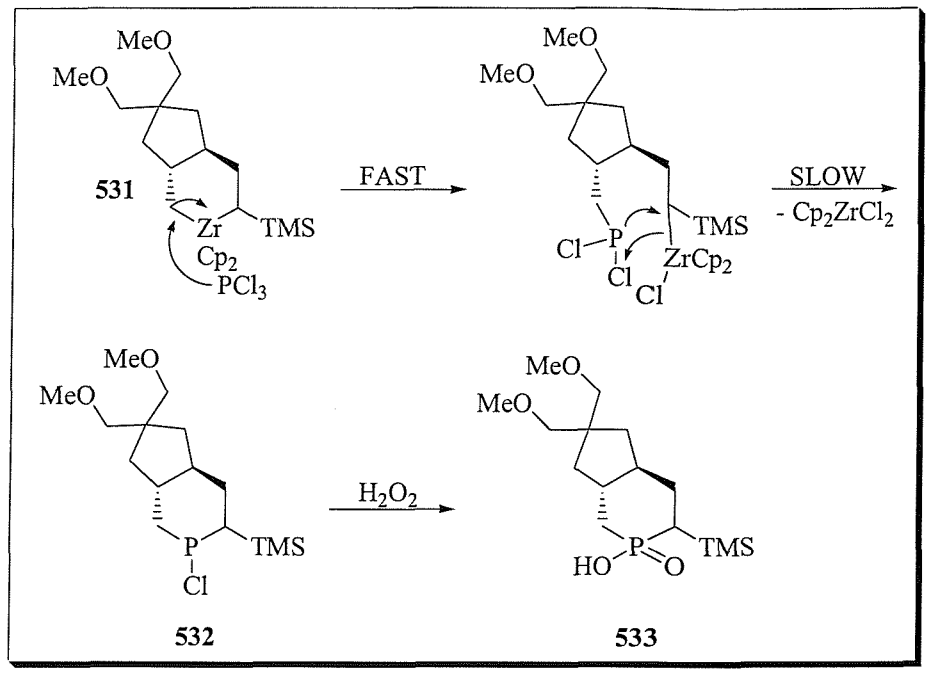


Figure 5.23 - Mechanism of phosphinic acid synthesis

We hoped to remove the α-stereocentre of **533** as this would make diastereomerically pure **534**. (Figure 5.24.) However, reactions with TBAF in THF, TBAF in water, HF in pyridine and conc. HCl all failed to desilylate **533** possibly due to the TMS group being too unactivated.

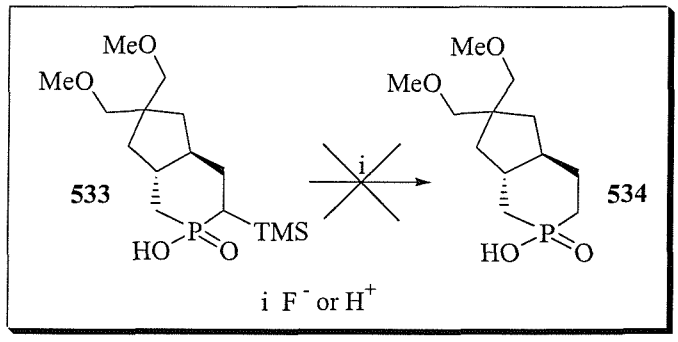


Figure 5.24 - Attempted desilylation

5.7. Future Work

Livinghouse has shown that it is possible to form the thio-ether substituted monozirconapentadiene **535** with high regioselectivity[197]. (Figure 5.25.) It is possible that this could be used to make functionalised phosphinines such as **536** which could be further elaborated.

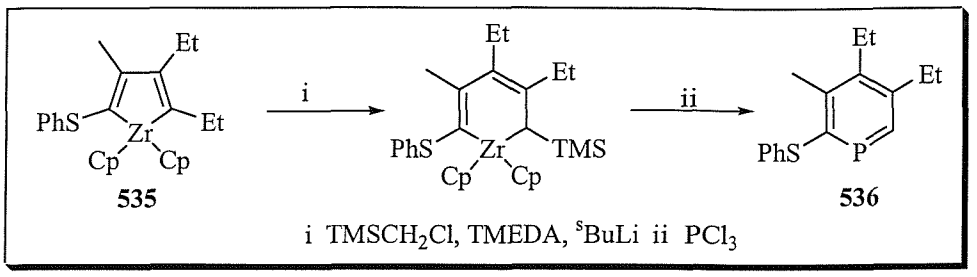


Figure 5.25 - Functionalised phosphinines

Work from within the group has shown that other carbenoids (R=Ph, OEt, SPh, P(O)OEt) will insert into zirconacyclopentanes[57,207]. (Figure 5.26.) It is possible that this route could be used to make other substituted phosphinic acids such as **537**.

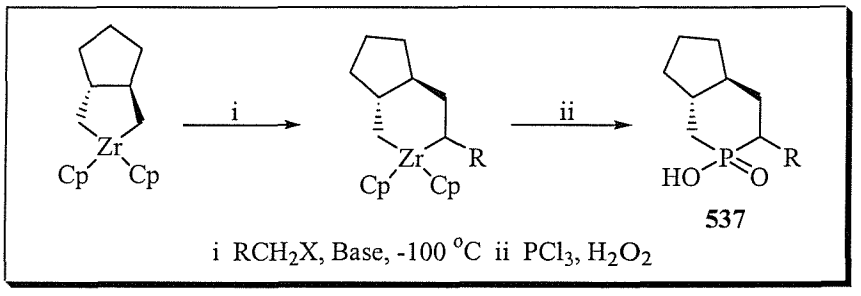


Figure 5.26 - Variation of carbenoid

5.8. Conclusions

The chemistry developed has shown that zirconacyclohexadienes can be used as intermediates in the syntheses of tetrasubstituted monocyclic phosphinines. Although the yields are not as high as would be desired, the phosphinines have been purified and protected as their Diels-Alder adducts. The Diels-Alder adducts can be deprotected in a retro-Diels-Alder fashion as a later stage if required. However, this route to phosphinines has also highlighted some drawbacks. The phosphinines synthesised only have alkyl groups attached, so there is no "handle" on the molecule to enable elaboration at a later stage. At present, only lithiated chloromethyltrimethylsilane has been found to insert into zirconacyclopentadienes which limits the scope for synthesising different phosphinines. Finally, the carbenoid *bis*-inserted into both alkyl and aromatic bicyclic zirconacyclopentadienes which has meant that this route has only be applied to the synthesis of monocyclic phosphinines. However, the carbenoid did not *bis*-insert into the zirconacyclopentane **530**. This enabled the bicyclic zirconacyclohexane **531** to be elaborated to give the reactive phosphorus heterocycle **532**, which upon oxidation with hydrogen peroxide gave the novel phosphinic acid **533** in 36 % over 4 steps.

CHAPTER 6

EXPERIMENTAL

6. Experimental

6.1. General notes

6.1.1. Air and moisture sensitive compounds

All reactions involving organometallic intermediates or other air/moisture sensitive compounds were carried out under an argon atmosphere using standard Schlenk and syringe techniques. The argon was pre-dried by passage over 4 Å molecular sieves and dry silica gel. All apparatus was dried in a hot oven (150 °C, >12 Hrs) before either cooling in a sealed dessicator over silica gel, or assembling while hot and cooling under vacuum (0.1 mm Hg).

6.1.2. Spectroscopic Instrumentation

NMR spectra (both ^{1}H NMR and ^{13}C NMR) were recorded on either Bruker AM300 (300 MHz proton, 75 MHz carbon) or Bruker DPX400 (400 MHz proton, 100 MHz carbon) Fourier transform spectrometers. Unless otherwise specified all spectra were recorded in $CDCl_3$ (stored over K_2CO_3) and referenced to the residual chloroform peak at 7.27 ppm (^{1}H NMR) and 77.27 (^{13}C NMR). Chemical shifts are given in units of ppm on the δ scale and coupling constants (*J*) are given in Hertz (Hz). When quoting proton NMR the following abbreviations are used to denote multiplicity and signal morphology: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; fs, fine splitting; m, multiplet. Carbon NMR, unless otherwise stated, were run proton decoupled and are quoted as: C, quaternary; CH, tertiary carbon; CH_2, secondary carbon; CH_3, primary carbon. The number of attached protons being determined using DEPT (Distortionless Enhancement by Polarisation Transfer) NMR experiments. Additionally 2D correlation experiments, were recorded on either the Bruker AM300 or Bruker DPX400, and were used to conclusively assign complex spectra. These have not been recorded individually in this section. Each signal in the proton NMR is assigned in the following manner: chemical shift (number of protons, coupling constant, proton assignment). The numbers quoted for the molecule's proton assignment are for NMR identification purposes only and do not necessarily correspond to the molecules IUPAC name. Each signal in the carbon NMR is assigned in the following manner: chemical shift (multiplicity, carbon assignment). When diastereoisomers are quoted and each are distinguishable by carbon NMR these are quoted as major and minor isomers, unless otherwise stated these were not isolated as distinct compounds.

Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR instrument, carried out as neat films (for oils) or as solutions in dichloromethane. Absorptions are given in wavenumber (cm^{-1}) and are reported as follows: s, strong; m, medium; br broad; w, weak.

Low Resolution Mass Spectrometry (LRMS) was recorded on a Micromass platform quadrupole mass analyser using an electrospray ion source. The instrument was calibrated with a mixture of sodium and caesium carbonate. High Resolution Mass Spectrometry (HRMS) was recorded on a VG Analytical 70-250-SE double focusing mass spectrometer. Perfluoroketone was used to calibrate the mass spectrometer before high

resolution electron ionisation analysis. Data acquired by mass spectrometry (*m/z*) are reported in atomic mass units followed by the observed peak and assignments where obvious.

X- Ray analysis was carried out at Southampton University by the EPSRC National Crystallography Service using Enraf Nonius KappaCCD area detector and SHELXS86 to solve the structure.

Melting points were recorded using Griffin melting point apparatus and the figures are uncorrected. Microanalysis was carried out by Medac Ltd. All compounds named in this thesis were named using ACD labs software using standard IUPAC nomenclature

6.1.3. Reagent purification

Unless otherwise stated materials were obtained from commercial suppliers, the purity being checked by NMR prior to use, then used without further purification. THF and diethyl ether were distilled from sodium/benzophenone and petroleum ether (b.p 40-60 °C) was distilled through a Vigreaux column prior to use. HMPA and chlorinated solvents were distilled from calcium hydride and stored under argon. Prior to use the magnesium was stirred, under argon, vigorously for 12 hours. Phosphorus trichloride was obtained commercially, distilled and stored under argon.

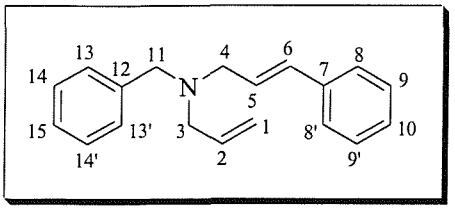
6.1.4. Chromatography

Thin layer chromatography (t.l.c.) was carried out on 0.25 mm Kieselgel 60 G UV_{254} precoated aluminium foil or plastic plates and visualised with a 254 nm UV lamp followed by Iodine dip (55 g iodine in 50 g silica), phosphomolybdic acid (12 g, in 150 mL EtOH) or sulphuric acid (5 %, v/v in MeOH). Column chromatography on silica used Kieselgel 60 (230-400 mesh) silica gel, columns were packed and run under light pressure. Amines underwent t.l.c by pre-running the plate in 2% Et_3N, 98 % petrol, followed by the eluant indicated in the experimental section.

GC analysis was carried out using the following programme conditions: 1 μL was injected at 80 °C increasing by 25 °C per minute until 250 °C using an HP-5 silicon column operating on an HP Gas chromatography machine.

6.2. Experimental For Chapter 2

6.2.1. *N-Allyl-N-benzyl-N-[(2E)-3-phenylprop-2-enyl]amine*, **220a**



AlH_3 in THF (0.68 M, 1.3 eq, 14.3 mmol, 21 mL) in THF (55 mL) was cooled to 0 °C before (2E)-*N*-Allyl-*N*-benzyl-3-phenylacrylamide (11 mmol, 3.05 g) in THF (55 mL) were added slowly. The reaction was stirred for 30 mins at 0 °C. The reaction was quenched by addition of water (5 mL) at 0 °C. 2M NaOH (50 mL) and ether (100 mL) were added and the organic layer was washed with water (3 X 30 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The amine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 1 % Et_3N, 99 % petrol, R_f=0.3). The amine was distilled at 0.1 mm Hg, 180 °C to give the title compound as a pale yellow oil, 1.7 g, 57 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.32-7.10 (10H, m, Ar-*H*), 6.44 (1H, d, *J*=15.9 Hz, C_6-*H*), 6.19 (1H, dt, *J*=15.9 Hz, *J*=6.5 Hz, C_5-*H*), 5.84 (1H, ddt, *J*=17.3 Hz, *J*=10.3 Hz, *J*=6.3 Hz, C_2-*H*), 5.13 (1H, d, *J*=17.3 Hz, C_1-*H* (*trans*)), 5.08 (1H, d, *J*=10.3 Hz, C_1-*H* (*cis*)), 3.55 (2H, s, C_{11}-H_2), 3.16 (2H, d, *J*=6.5 Hz, C_4-H_2), 3.06 (2H, d, *J*=6.3 Hz, C_3-H_2).

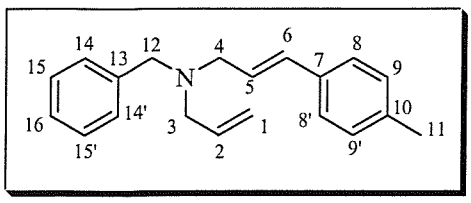
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 139.61 (C, C_{12}), 137.41 (C, C_7), 136.10 (CH, C_2), 132.66 (CH, C_5), 129.11 (CH, C_{13}, $C_{13'}$), 128.70 (CH, C_9, $C_{9'}$), 128.39 (CH, C_{14}, $C_{14'}$), 127.87 (CH, C_6), 127.48 (CH, C_{10}), 127.03 (CH, C_{15}), 126.45 (CH, C_8, $C_{8'}$), 117.64 (CH_2, C_1), 57.96 (CH_2, C_{11}), 56.80 (CH_2, C_3), 56.03 (CH_2, C_4).

IR (cm^{-1}): 2360 (w), 2341 (w), 1494 (m), 1448 (m), 1364 (m), 1120 (m), 965 (m), 734 (s)

LRMS (EI): *m/z* 263 (M, 39 %), 222 (M-allyl, 44 %), 186 (M-Ph, 8 %), 172 (M-CH-Ph, 73 %).

HRMS (ES+): $C_{19}H_{22}N^+$ requires m/z 264.1747, found 264.1745.

6.2.2. *N-Allyl-N-benzyl-N-[(2E)-3-(4-methylphenyl)prop-2-enyl]amine*, **220b**



AlH_3 in THF (0.68 M, 1.3 eq, 13 mmol, 19 mL) in THF (50 mL) was cooled to 0 °C before (2E)-*N*-Allyl-*N*-benzyl-3-(4-methylphenyl)acrylamide (10 mmol, 2.91 g) in THF (50 mL) were added slowly. The reaction was stirred for 30 mins at 0 °C. The reaction was quenched by addition of water (5 mL) at 0 °C. 2M NaOH (50 mL) and ether (100 mL) were added and the organic layer was washed with water (3 X 30 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The amine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 1 % Et_3N, 99 % petrol, R_f=0.3). The amine was distilled at 0.1 mm Hg, 190 °C to give the title compound as a pale yellow oil, 1.5 g, 55 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.46-7.29 (7H, m, Ar-*H*), 7.19 (2H, d, *J*=8.0 Hz, C_{9}-*H*, $C_{9'}$-*H*), 6.56 (1H, d, *J*=15.8 Hz, C_6-*H*), 6.31 (1H, dt, *J*=15.8 Hz, *J*=6.5 Hz, C_5-*H*), 6.00 (1H, ddt, *J*=17.3 Hz, *J*=10.5 Hz, *J*=6.3 Hz, C_2-*H*), 5.29 (1H, d, *J*=17.3 Hz, C_1-*H* (*trans*)), 5.24 (1H, d, *J*=10.5 Hz, C_1-*H* (*cis*)), 3.70 (2H, s, C_{12}-H_2), 3.31 (2H, d, *J*=6.5 Hz, C_4-H_2), 3.21 (2H, d, *J*=6.3 Hz, C_3-H_2), 2.41 (3H, s, C_{11}-H_3).

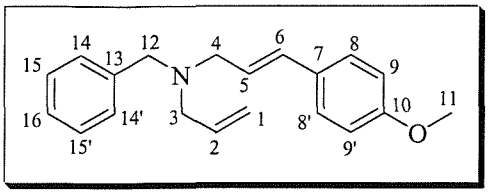
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 139.64 (C, C_{10}), 137.25 (C, C_{13}), 136.13 (CH, C_2), 134.62 (C, C_7), 132.57 (CH, C_5), 129.39 (CH, C_9, $C_{9'}$), 129.12 (CH, C_{14}, $C_{14'}$), 128.36 (CH, C_{15}, $C_{15'}$), 127.00 (CH, C_{16}), 126.74 (CH, C_6), 126.34 (CH, C_8, $C_{8'}$), 117.59 (CH_2, C_1), 57.91 (CH_2, C_{12}), 56.76 (CH_2, C_3), 56.07 (CH_2, C_4), 21.33 (CH_3, C_{11}).

IR (cm^{-1}): 1642 (w), 1512 (w), 1447 (w), 1367 (m), 977 (s), 958 (m), 737 (s).

LRMS (EI): *m/z* 277 (M, 16 %), 236 (M-allyl, 14 %), 186 (M-Ph-CH_3, 13 %), 172 (M-CH-Ph-CH_3, 36 %).

HRMS (ES+): $C_{20}H_{24}N^+$ requires m/z 278.1903, found 278.1904.

6.2.3. *N-Allyl-N-benzyl-N-[(2E)-3-(4-methoxyphenyl)prop-2-enyl]amine*, **220c**



AlH_3 in THF (0.68 M, 1.3 eq, 13 mmol, 19 mL) in THF (50 mL) was cooled to 0 °C before (2E)-*N*-Allyl-*N*-benzyl-3-(4-methoxyphenyl)acrylamide (10 mmol, 3.07 g) in THF (50 mL) were added slowly. The reaction was stirred for 30 mins at 0 °C. The reaction was quenched by addition of water (5 mL) at 0 °C. 2M NaOH (50 mL) and ether (100 mL) were added and the organic layer was washed with water (3 X 30 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The amine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 2 % Et_3N, 98 % petrol, R_f=0.3). The amine was distilled at 0.1 mm Hg, 195 °C to give the title compound as a colourless oil, 1.5 g, 51 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.44-7.27 (7H, m, Ar-H), 6.91 (2H, d, *J*=8.8 Hz, $C_{9'}$-H, $C_{9'}$-H), 6.52 (1H, d, *J*=15.8 Hz, C_6-H), 6.20 (1H, dt, *J*=15.8 Hz, *J*= 6.5 Hz, C_5-H), 5.99 (1H, ddt, *J*=17.1 Hz, *J*=10.3 Hz, *J*=6.5 Hz, C_2-H), 5.28 (1H, d, *J*=17.1 Hz, C_1-H (*trans*)), 5.22 (1H, d, *J*=10.3 Hz, C_1-H (*cis*)), 3.86 (3H, s, C_{11}-H_3), 3.68 (2H, s, C_{12}-H_2), 3.28 (2H, d, *J*=6.5 Hz, C_4-H_2), 3.20 (2H, d, *J*=6.5 Hz, C_3-H_2).

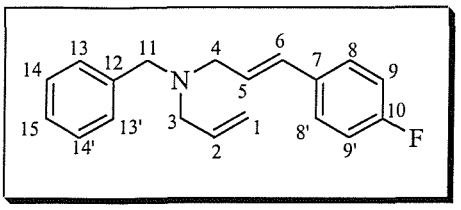
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 159.23 (C, C_{10}), 139.67 (C, C_{13}), 136.15 (CH, C_2), 132.14 (CH, C_5), 130.25 (C, C_7), 129.13 (CH, C_{14}, $C_{14'}$), 128.36 (CH, C_{15}, $C_{15'}$), 127.58 (CH, C_8, $C_{8'}$), 127.00 (CH, C_{16}), 125.54 (CH, C_6), 117.58 (CH_2, C_1), 114.14 (CH, C_9, $C_{9'}$), 57.89 (CH_2, C_{12}), 56.75 (CH_2, C_3), 56.11 (CH_2, C_4), 55.47 (CH_3, C_{11}).

IR (cm^{-1}): 2359 (w), 2342 (w), 1607 (m), 1510 (s), 1453 (w), 1247 (s), 1174 (m), 1035 (m), 967 (m).

LRMS (EI): *m/z* 293 (M, 21 %), 252 (M-allyl, 12 %), 186 (M-Ph-OMe, 6 %), 172 (M-CH-Ph-OMe, 65 %).

HRMS (ES+): $C_{20}H_{24}NO^+$ requires m/z 294.1853, found 294.1854.

6.2.4. *N-Allyl-N-benzyl-N-[(2E)-3-(4-fluorophenyl)prop-2-enyl]amine*, **220d**



AlH_3 in THF (0.68 M, 1.3 eq, 10.4 mmol, 15.3 mL) in THF (40 mL) was cooled to 0 °C before (2E)-*N*-Allyl-*N*-benzyl-3-(4-fluorophenyl)acrylamide (8 mmol, 2.25 g) in THF (40 mL) were added slowly. The reaction was stirred for 30 mins at 0 °C. The reaction was quenched by addition of water (5 mL) at 0 °C. 2M NaOH (50 mL) and ether (100 mL) were added and the organic layer was washed with water (3 X 30 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The amine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 2 % Et_3N, 98 % petrol, R_f=0.5). The amine was distilled at 0.1 mm Hg, 185 °C to give the title compound as a colourless oil, 1.1 g, 50 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.44-7.27 (7H, m, Ar-*H*), 7.05 (2H, dd, *J*=8.6 Hz, *J*=8.6 Hz, $C_{9'}$-*H*, $C_{9'}$-*H*), 6.54 (1H, d, *J*=15.8 Hz, C_6-*H*), 6.24 (1H, dt, *J*=15.8 Hz, *J*=6.5 Hz, C_5-*H*), 5.98 (1H, ddt, *J*=17.1 Hz, *J*=10.3 Hz, *J*=6.0 Hz, C_2-*H*), 5.28 (1H, d, *J*=17.1 Hz, C_1-*H* (*trans*)), 5.23 (1H, d, *J*=10.3 Hz, C_1-*H* (*cis*)), 3.68 (2H, s, C_{11}-H_2), 3.28 (2H, d, *J*=6.5 Hz, C_4-H_2), 3.19 (2H, d, *J*=6.0 Hz, C_3-H_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 162.35 (C, J_{CF}=245.9 Hz, C_{10}), 139.59 (C, C_{12}), 136.05 (CH, C_2), 133.57 (C, J_{CF}=2.9 Hz, C_7), 131.40 (CH, C_5), 129.09 (CH, C_{13}, $C_{13'}$), 128.40 (CH, C_{14}, $C_{14'}$), 127.89 (CH, J_{CF}=7.8 Hz, C_8, $C_{8'}$), 127.68 (CH, J_{CF}=2.4 Hz, C_6), 127.05 (CH, C_{15}), 117.66 (CH_2, C_1), 115.57 (CH, J_{CF}=21.8 Hz, C_9, $C_{9'}$), 58.00 (CH_2, C_{11}), 56.84 (CH_2, C_3), 55.99 (CH_2, C_4).

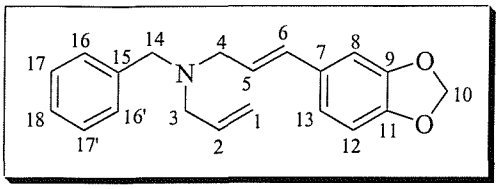
^{19}F NMR (100 MHz, $CDCl_3$): δ / ppm 46.85

IR (cm^{-1}): 2359 (w), 2341 (w), 1601 (m), 1508 (s), 1453 (m), 1364 (w), 1227 (s), 1157 (m), 1121 (m).

LRMS (EI): *m/z* 281 (M, 20 %), 240 (M-allyl, 35 %), 172 (M-CH-Ph-F, 43 %).

HRMS (ES+): $C_{19}H_{21}FN^+$ requires m/z 282.1653, found 282.1652.

6.2.5. *N-Allyl-N-[(2E)-3-(1,3-benzodioxol-5-yl)prop-2-enyl]-N-benzylamine*, **220e**



AlH_3 in THF (0.68 M, 1.3 eq, 13 mmol, 9.5 mL) in THF (80 mL) was cooled to 0 °C before (2E)-*N*-Allyl-3-(1,3-benzodioxol-5-yl)-*N*-benzylacrylamide (5 mmol, 1.54 g) in THF (20 mL) were added slowly. The reaction was stirred for 30 mins at 0 °C. The reaction was quenched by addition of water (3 mL) at 0 °C. 2M NaOH (50 mL) and ether (50 mL) were added and the organic layer was washed with water (3 X 30 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The amine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 2 % Et_3N, 98 % petrol, R_f=0.2). The amine was distilled at 0.1 mm Hg, 235 °C to give the title compound as a colourless oil, 761 mg, 50 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.30-7.13 (5H, m, C_{16}-*H*, $C_{16'}$-*H*, C_{17}-*H*, $C_{17'}$-*H*, C_{18}-*H*), 6.84 (1H, s, C_8-*H*), 6.74-6.64 (2H, m, C_{12}-*H*, C_{13}-*H*), 6.35 (1H, d, *J*=15.8 Hz, C_6-*H*), 6.03 (1H, dt, *J*=15.8 Hz, *J*=6.4 Hz, C_5-*H*), 5.87 (2H, s, C_{10}-H_2), 5.85 (1H, ddt, *J*=17.3 Hz, *J*=10.5 Hz, *J*=6.0 Hz, C_2-*H*), 5.13 (1H, d, *J*=17.3 Hz, C_1-*H* (*trans*)), 5.08 (1H, d, *J*=10.5 Hz, C_1-*H* (*cis*)), 3.53 (2H, s, C_{14}-H_2), 3.13 (2H, d, *J*=6.4 Hz, C_4-H_2), 3.05 (2H, d, *J*=6.0 Hz, C_3-H_2).

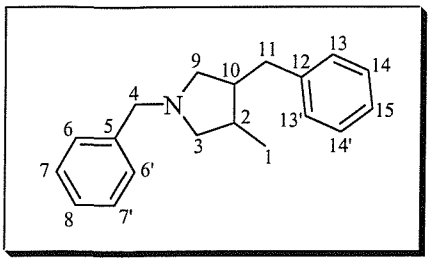
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 148.18 (C, C_9), 147.18 (C, C_{11}), 139.64 (C, C_{15}), 136.12 (CH, C_2), 132.26 (CH, C_5), 131.95 (C, C_7), 129.12 (CH, C_{16}, $C_{16'}$), 128.38 (CH, C_{17}, $C_{17'}$), 127.03 (CH, C_6), 126.05 (CH, C_{18}), 120.93 (CH, C_{13}), 117.62 (CH_2, C_1), 108.42 (CH, C_{12}), 105.86 (CH, C_8), 101.19 (CH_2, C_{10}), 59.93 (CH_2, C_{14}), 56.78 (CH_2, C_3), 55.99 (CH_2, C_4).

IR (cm^{-1}): 3064 (w), 2975 (w), 1642 (w), 1503 (m), 1489 (s), 1248 (s), 1071 (w), 965 (m), 736 (s).

LRMS (EI): *m/z* 307 (M, 11 %), 266 (M-allyl, 10 %), 146 (M-allyl-$C_6H_5O_2$, 13 %), 91 ($PhCH_2$, 100 %).

HRMS (ES+): $C_{20}H_{22}NO_2$ requires m/z 308.1645, found 308.1641

6.2.6. *1,3-Dibenzyl-4-methylpyrrolidine*, **221a**



Cp_2ZrCl_2 (1.2 mmol, 350 mg) in THF (5 mL) was cooled to -78 °C before BuLi (2.4 mmol, 0.96 mL) was added slowly. The reaction was stirred for 20 mins at -78 °C before *N*-allyl-benzyl-((E)-3-phenyl-allyl)-amine (1 mmol, 263 mg) in THF (5 mL) was added slowly. The reaction was warmed to r.t. and stirred for 24 hours. 5 mL of the resulting red solution was removed via syringe and transferred to a dry Schlenk flask. MeOH (5 mL) and $NaHCO_3$ solution (5 mL) were added to the zirconacycle solution and stirred overnight. Ether (40 mL) and water (40 mL) were added. The organic layer was washed with water (3 X 30 mL). The aqueous layer was washed with ether (3 X 30 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The pyrrolidine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 1 % Et_3N, 99 % petrol, R_f=0.3). This gave a 5:1 inseparable mixture of *trans* to *cis* diastereoisomers as a colourless oil, 119 mg, 90 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.27-7.02 (20H, m, Ar-*H* (*cis* and *trans*)), 3.57-3.51 (2H, m, C_4-*H* (*trans*), C_4-*H* (*cis*)), 3.48-3.40 (2H, m, C_4-*H* (*cis*), C_4-*H* (*trans*)), 2.97-2.89 (1H, m, C_3-*H* (*cis*)), 2.75-2.65 (4H, m, C_9-*H* (*cis*), C_3-*H* (*trans*), C_2-*H* (*cis*), C_{10}-*H* (*cis*)), 2.58-2.25 (6H, m, C_9-H_2 (*trans*), C_{11}-H_2 (*cis*), C_{11}-H_2 (*trans*)), 2.13-2.06 (2H, m, C_9-*H* (*cis*), C_3-*H* (*trans*)), 2.03-1.97 (1H, m, C_3-*H* (*cis*)), 1.94-1.77 (2H, m, C_2-*H* (*trans*), C_{10}-*H* (*trans*)), 0.91 (3H, d, *J*=7.0 Hz, C_1-H_3 (*cis*)), 0.84 (3H, d, *J*=6.5 Hz, C_1-H_3 (*trans*)).

^{13}C NMR (75 MHz, $CDCl_3$): ***Trans*** **Isomer:** δ / ppm 141.47 (C, C_{12}), 139.41 (C, C_5), 128.94 (CH, C_{13}, $C_{13'}$), 128.89 (CH, C_6, $C_{6'}$), 128.41 (CH, C_{14}, $C_{14'}$), 128.32 (CH, C_7, $C_{7'}$), 126.96 (CH, C_8), 125.95 (CH, C_{15}), 62.29 (CH_2, C_3), 60.83 (CH_2, C_4), 60.26 (CH_2, C_9), 47.91 (CH, C_{10}), 40.90 (CH_2, C_{11}), 38.92 (CH, C_2), 19.41 (CH_3, C_1).

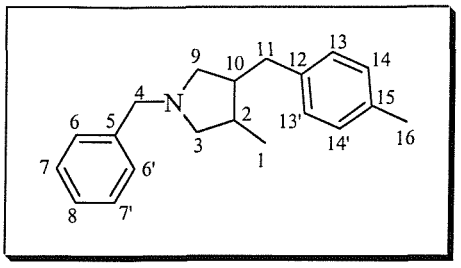
^{13}C NMR (75 MHz, $CDCl_3$): ***Cis*** **Isomer:** δ / ppm 141.73 (C, C_{12}), 139.51 (C, C_5), 128.89 (CH, C_6, $C_{6'}$), 128.78 (CH, C_{13}, $C_{13'}$), 128.45 (CH, C_{14}, $C_{14'}$), 128.32 (CH, C_7, $C_{7'}$), 126.96 (CH, C_8), 125.88 (CH, C_{15}), 62.53 (CH_2, C_3), 61.07 (CH_2, C_4), 59.74 (CH_2, C_9), 41.90 (CH, C_{10}), 35.78 (CH_2, C_{11}), 34.48 (CH, C_2), 15.16 (CH_3, C_1).

IR (cm^{-1}): 3061 (w), 3026 (m), 2910 (m), 2782 (m), 1603 (w), 1494 (m), 1453 (m), 1375 (m), 1028 (m).

LRMS (EI): *m/z* 265 (M, 27 %), 187 (M-Ph, 38 %), 173 (M-$PhCH_2$, 44 %), 158 (M-$PhCH_2$-CH_3, 50 %).

HRMS (ES+): $C_{19}H_{24}N^+$ requires m/z 266.1903, found 266.1902.

6.2.7. *1-Benzyl-3-methyl-4-(4-methylbenzyl)pyrrolidine*, **221b**



Cp_2ZrCl_2 (1.2 mmol, 350 mg) in THF (5 mL) was cooled to -78 °C before BuLi (2.4 mmol, 0.96 mL) was added slowly. The reaction was stirred for 20 mins at -78 °C before *N*-allyl-benzyl-((E)-3-(4-methyl-phenyl)-allyl)-amine (1 mmol, 277 mg) in THF (5 mL) was added slowly. The reaction was warmed to r.t. and stirred for 24 hours. An aliquot of the resulting red solution (5 mL) was removed *via* syringe and transferred to a dry Schlenk flask. MeOH (5 mL) and $NaHCO_3$ solution (5 mL) were added to the zirconacycle solution and stirred overnight. Ether (40 mL) and water (40 mL) were added. The organic layer was washed with water (3 X 30 mL). The aqueous layer was washed with ether (3 X 30 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The pyrrolidine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 1 % Et_3N, 99 % petrol, R_f=0.3). This gave a 5:1 inseparable mixture of *trans* to *cis* diastereoisomers as a colourless oil, 113 mg, 81 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.25-7.10 (10H, m, C_6-*H*, $C_{6'}$-*H*, $C_{7'}$-*H*, $C_{7'}$-*H*, C_8-*H* (*cis* and *trans*), 7.00-6.94 (8H, m, C_{13}-*H*, $C_{13'}$-*H*, C_{14}-*H*, $C_{14'}$-*H* (*cis* and *trans*)), 3.57-3.50 (2H, m, C_4-*H* (*trans*), C_4-*H* (*cis*)), 3.48-3.39 (2H, m, C_4-*H* (*cis*), C_4-*H* (*trans*)), 2.97-2.90 (1H, m, C_3-*H* (*cis*)), 2.75-2.61 (4H, m, C_9-*H* (*cis*), C_3-*H* (*trans*), C_2-*H* (*cis*), C_{10}-*H* (*cis*)), 2.57-2.25 (6H, m, C_9-H_2 (*trans*), C_{11}-H_2 (*cis*), C_{11}-H_2 (*trans*)), 2.22 (6H, s, C_{16}-H_3 (*cis* and *trans*)), 2.13-2.04 (2H, m, C_9-*H* (*cis*), C_3-*H* (*trans*)), 2.02-1.96 (1H, m, C_3-*H* (*cis*)), 1.93-1.76 (2H, m, C_2-*H* (*trans*), C_{10}-*H* (*trans*)), 0.91 (3H, d, *J*=7.3 Hz, C_1-H_3 (*cis*)), 0.85 (3H, d, *J*=6.5 Hz, C_1-H_3 (*trans*)).

^{13}C NMR (75 MHz, $CDCl_3$): *Trans* Isomer: δ / ppm 139.59 (C, C_{12}), 138.42 (C, C_5), 135.33 (C, C_{15}), 129.09 (CH, C_{14}, $C_{14'}$), 128.87 (CH, C_6, $C_{6'}$), 128.82 (CH, C_{13}, $C_{13'}$), 128.31 (CH, C_7, $C_{7'}$), 126.90 (CH, C_8), 62.36 (CH_2, C_3), 60.87 (CH_2, C_4), 60.30 (CH_2, C_9), 48.00 (CH, C_{10}), 40.49 (CH_2, C_{11}), 38.96 (CH, C_2), 21.16 (CH_3, C_{16}), 19.41 (CH_3, C_1).

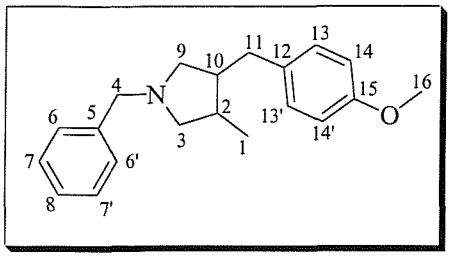
^{13}C NMR (75 MHz, $CDCl_3$): *Cis* Isomer: δ / ppm 139.70 (C, C_{12}), 138.65 (C, C_5), 135.26 (C, C_{15}), 129.14 (CH, C_{14}, $C_{14'}$), 128.87 (CH, C_6, $C_{6'}$), 128.65 (CH, C_{13}, $C_{13'}$), 128.32 (CH, C_7, $C_{7'}$), 126.90 (CH, C_8), 62.62 (CH_2, C_3), 61.12 (CH_2, C_4), 59.84 (CH_2, C_9), 41.95 (CH, C_{10}), 35.35 (CH_2, C_{11}), 34.50 (CH, C_2), 21.16 (CH_3, C_{16}), 15.17 (CH_3, C_1).

IR (cm^{-1}): 3025 (w), 2952 (m), 2915 (m), 2782 (m), 1514 (m), 1453 (s), 1376 (m), 1028 (m).

LRMS (EI): *m/z* 279 (M, 59 %), 187 (M-phenyl-CH_3, 87 %), 173 (M-phenyl-CH_3-CH_2, 76 %), 158 (M-phenyl-CH_3-CH_2-CH_3, 83 %).

HRMS (ES+): $C_{20}H_{26}N^+$ requires m/z 280.2060, found 280.2057.

6.2.8. *1-Benzyl-3-(4-methoxybenzyl)-4-methylpyrrolidine,* **221c**



Cp_2ZrCl_2 (2 mmol, 584 mg) in THF (10 mL) was cooled to -78 °C before BuLi (4 mmol, 1.6 mL) was added slowly. The reaction was stirred for 20 mins at -78 °C before *N*-allyl-benzyl-((E)-3-(4-methoxy-phenyl)-allyl)-amine (1 mmol, 293 mg) in THF (5 mL) was added slowly. The reaction was warmed to r.t. and stirred for 24 hours. MeOH (5 mL) and $NaHCO_3$ solution (5 mL) were added to the red zirconacycle solution and stirred overnight. Ether (40 mL) and water (40 mL) were added. The organic layer was washed with water (3 X 30 mL). The aqueous layer was washed with ether (3 X 30 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The pyrrolidine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 2 % Et_3N, 98 % petrol, R_f=0.3). This gave a 5:1 inseparable mixture of *trans* to *cis* diastereoisomers as a colourless oil, 160 mg, 54 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.26-7.17 (8H, m, C_6-*H*, $C_{6'}$-*H*, C_7-*H*, $C_{7'}$-*H* (*cis* and *trans*)), 7.16-7.11 (2H, m, C_8-*H* (*cis* and *trans*)), 6.99 (2H, d, *J*=8.5 Hz, C_{13}-*H*, $C_{13'}$-*H*, (*cis*)), 6.98 (2H, d, *J*=8.5 Hz, C_{13}-*H*, $C_{13'}$-*H*, (*trans*)), 6.71 (4H, d, *J*=8.5 Hz, C_{14}-*H*, $C_{14'}$-*H*, (*cis* and *trans*)), 3.67 (6H, s, C_{16}-H_3 (*cis* and *trans*)), 3.57-3.50 (2H, m, C_4-*H* (*cis*), C_4-*H* (*trans*)), 3.48-3.39 (2H, m, C_4-*H* (*cis*), C_4-*H* (*trans*)), 2.97-2.90 (1H, m, C_3-*H* (*cis*)), 2.75-2.59 (4H, m, C_9-*H* (*cis*), C_3-*H* (*trans*), C_2-*H* (*cis*), C_{10}-*H* (*cis*)), 2.57-2.23 (6H, m, C_9-H_2 (*trans*), C_{11}-H_2 (*cis*), C_{11}-H_2 (*trans*)), 2.13-2.03 (2H, m, C_9-*H* (*cis*), C_3-*H* (*trans*)), 2.02-1.95 (1H, m, C_3-*H* (*cis*)), 1.90-1.75 (2H, m, C_2-*H* (*trans*), C_{10}-*H* (*trans*)), 0.90 (3H, d *J*=7.0 Hz, C_1-H_3 (*cis*)), 0.84 (3H, d, *J*=6.5 Hz, C_1-H_3 (*trans*)).

^{13}C NMR (75 MHz, $CDCl_3$): ***Trans*** **Isomer:** δ / ppm 157.93 (C, C_{15}), 139.56 (C, C_5), 133.61 (C, C_{12}), 129.81 (CH, C_{13}, $C_{13'}$), 128.87 (CH, C_6, $C_{6'}$), 128.31 (CH, C_7, $C_{7'}$), 126.92 (CH, C_8), 113.83 (CH, C_{14}, $C_{14'}$), 62.37 (CH_2, C_3), 60.87 (CH_2, C_4), 60.28 (CH_2, C_9), 55.37 (CH_3, C_{16}), 48.13 (CH, C_{10}), 40.02 (CH_2, C_{11}), 38.88 (CH, C_2), 19.49 (CH_3, C_1).

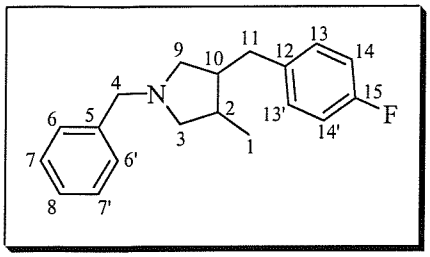
^{13}C NMR (75 MHz, $CDCl_3$): ***Cis*** **Isomer:** δ / ppm 157.86 (C, C_{15}), 139.67 (C, C_5), 133.78 (C, C_{12}), 129.61 (CH, C_{13}, $C_{13'}$), 128.87 (CH, C_6, $C_{6'}$), 128.33 (CH, C_7, $C_{7'}$), 126.92 (CH, C_8), 113.89 (CH, C_{14}, $C_{14'}$), 62.63 (CH_2, C_3), 61.11 (CH_2, C_4), 59.82 (CH_2, C_9), 55.37 (CH_3, C_{16}), 42.08 (CH, C_{10}), 34.86 (CH_2, C_{11}), 34.46 (CH, C_2), 15.15 (CH_3, C_1).

IR (cm^{-1}): 3027 (w), 2953 (m), 2915 (m), 2909 (m), 2784 (w), 2359 (w), 1611 (w), 1511 (s), 1244 (s), 1036 (m).

LRMS (EI): *m/z* 295 (M, 36 %), 187 (M-phenyl-OCH_3, 83 %), 173 (M-phenyl-OCH_3-CH_2, 38 %), 158 (M-phenyl-OCH_3-CH_2-CH_3, 71 %).

HRMS (ES+): $C_{20}H_{26}NO^+$ requires m/z 296.2009, found 296.2009.

6.2.9. *1-Benzyl-3-(4-fluorobenzyl)-4-methylpyrrolidine,* **221d**



Cp_2ZrCl_2 (1.2 mmol, 350 mg) in THF (5 mL) was cooled to -78 °C before BuLi (2.4 mmol, 0.96 mL) was added. The reaction was stirred for 20 mins before *N*-allyl-benzyl-((E)-3-(4-fluoro-phenyl)-allyl)-amine (1 mmol, 281 mg) in THF (5 mL) was added. The reaction was warmed to r.t., stirred for 24 hours and quenched by addition of MeOH (5 mL) and $NaHCO_3$ solution (5 mL). Ether (40 mL) and water (40 mL) were added. The organic layer was washed with water (3 X 30 mL). The aqueous layer was washed with ether (3 X 30 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The pyrrolidine was purified by column chromatography (2 % Et_3N, 98 % petrol, R_f=0.4, 0.3). This gave a 5:1 inseparable mixture of *trans* to *cis* diastereoisomers as a colourless oil, 214 mg, 76 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.25-7.19 (8H, m, C_6-*H*, $C_{6'}$-*H*, C_7-*H*, $C_{7'}$-*H* (*cis* and *trans*)), 7.18-7.11 (2H, m, C_8-*H* (*cis* and *trans*)), 7.02 (4H, dd, *J*=5.9 Hz, *J*=8.5 Hz, C_{13}-*H*, $C_{13'}$-*H* (*cis* and *trans*)), 6.85 (4H, t, *J*=8.5 Hz, C_{14}-*H*, $C_{14'}$-*H* (*cis* and *trans*)), 3.58-3.51 (2H, m, C_4-*H* (*trans*), C_4-*H* (*cis*)), 3.49-3.39 (2H, m, C_4-*H* (*cis*), C_4-*H* (*trans*)), 2.97-2.91 (1H, dd, *J*=7.3 Hz, *J*=9.0 Hz, C_3-*H* (*cis*)), 2.76-2.61 (4H, m, C_9-*H* (*cis*), C_3-*H* (*trans*), C_2-*H* (*cis*), C_{10}-*H* (*cis*)), 2.56-2.25 (6H, m, C_9-H_2 (*trans*), C_{11}-H_2 (*cis*), C_{11}-H_2 (*trans*)), 2.13-1.96 (3H, m, C_9-*H* (*cis*), C_3-*H* (*trans*), C_3-*H* (*cis*)), 1.90-1.75 (2H, m, C_2-*H* (*trans*), C_{10}-*H* (*trans*)), 0.90 (3H, d, *J*=7.0 Hz, C_1-H_3 (*cis*)), 0.84 (3H, d, *J*=6.3 Hz, C_1-H_3 (*trans*)).

^{13}C NMR (75 MHz, $CDCl_3$): *Trans* Isomer: δ / ppm 161.45 (C, J_{CF}=242.5 Hz, C_{15}), 139.52 (C, C_5), 137.13 (C, J_{CF}=3.4 Hz, C_{12}), 130.24 (CH, J_{CF}=7.8 Hz, C_{13}, $C_{13'}$), 128.87 (CH, C_6, $C_{6'}$), 128.34 (CH, C_7, $C_{7'}$), 126.97 (CH, C_8), 115.16 (CH, J_{CF}=21.3 Hz, C_{14}, $C_{14'}$), 62.35 (CH_2, C_3), 60.82 (CH_2, C_4), 60.16 (CH_2, C_9), 48.07 (CH, C_{10}), 40.11 (CH_2, C_{11}), 38.87 (CH, C_2), 19.50 (CH_3, C_1).

^{13}C NMR (75 MHz, $CDCl_3$): *Cis* Isomer: δ / ppm 161.38 (C, J_{CF}=242.5 Hz, C_{15}), 139.63 (C, C_5), 137.35 (C, J_{CF}=3.4 Hz, C_{12}), 130.04 (CH, J_{CF}=7.8 Hz, C_{13}, $C_{13'}$), 128.87 (CH, C_6, $C_{6'}$), 128.35 (CH, C_7, $C_{7'}$), 126.97 (CH, C_8), 115.20 (CH, J_{CF}=21.3 Hz, C_{14}, $C_{14'}$), 62.57 (CH_2, C_3), 61.06 (CH_2, C_4), 59.67 (CH_2, C_9), 42.08 (CH, C_{10}), 34.99 (CH_2, C_{11}), 34.45 (CH, C_2), 15.17 (CH_3, C_1).

^{19}F NMR (100 MHz, $CDCl_3$): *Trans* Isomer: δ / ppm 44.05

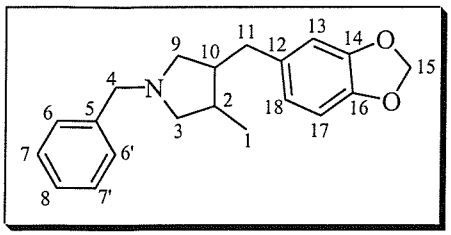
^{19}F NMR (100 MHz, $CDCl_3$): *Cis* Isomer: δ / ppm 43.94

IR (cm^{-1}): 3030 (w), 2953 (m), 2909 (m), 2783 (m), 2361 (w), 2342 (w), 1602 (m), 1508 (s), 1220 (s).

LRMS (EI): *m/z* 283 (M, 53 %), 187 (M-Ph-F, 86%), 173 (M-Ph-F-CH_2, 72%), 158 (M-Ph-F-CH_2CH_3, 69%).

HRMS (ES+): $C_{19}H_{23}FN^+$ requires m/z 284.1809, found 284.1809.

6.2.10. *3-(1,3-benzodioxol-5-ylmethyl)-1-benzyl-4-methylpyrrolidine*, **221e**



Cp_2ZrCl_2 (2 mmol, 584 mg) in THF (10 mL) was cooled to -78 °C before BuLi (4 mmol, 1.6 mL) was added slowly. The reaction was stirred for 20 mins at -78 °C before *N*-allyl-(3-benzo[1,3]dioxol-5-yl-allyl)-benzyl-amine (1 mmol, 307 mg) in THF (5 mL) was added slowly. The reaction was warmed to r.t. and stirred for 24 hours. MeOH (5 mL) and $NaHCO_3$ solution (5 mL) were added to the red zirconacycle solution and stirred overnight. Ether (30 mL) and water (30 mL) were added. The organic layer was washed with water (3 X 10 mL). The aqueous layer was washed with ether (3 X 10 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The pyrrolidine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 2 % Et_3N, 98 % petrol, R_f=0.2). This gave a 5:1 inseparable mixture of *trans* to *cis* diastereoisomers as a colourless oil, 215 mg, 70 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.25-7.13 (10H, m, C_6-*H*, $C_{6'}$-*H*, C_7-*H*, $C_{7'}$-*H*, C_8-*H*, (*cis* and *trans*)), 6.62 (2H, d, *J*=8.0 Hz, C_{17}-*H* (*cis* and *trans*)), 6.58 (2H, s, C_{13}-*H* (*cis* and *trans*)), 6.53 (2H, d, *J*=8.0 Hz, C_{18}-*H* (*cis* and *trans*)), 5.84 (4H, s, C_{15}-H_2 (*cis* and *trans*)), 3.58-3.51 (2H, m, C_4-*H* (*cis*), C_4-*H* (*trans*)), 3.49-3.41 (2H, m, C_4-*H* (*cis*), C_4-*H* (*trans*)), 2.97-2.90 (1H, m, C_3-*H* (*cis*)), 2.75-2.57 (4H, m, C_9-*H* (*cis*), C_3-*H* (*trans*), C_2-*H* (*cis*), C_{10}-*H* (*cis*)), 2.56-2.25 (6H, m, C_9-H_2 (*trans*), C_{11}-H_2 (*cis*), C_{11}-H_2 (*trans*)), 2.13-1.96 (3H, m, C_9-*H* (*cis*), C_3-*H* (*trans*), C_3-*H* (*cis*)), 1.89-1.76 (2H, m, C_2-*H* (*trans*), C_{10}-*H* (*trans*)), 0.90 (3H, d *J*=7.0 Hz, C_1-H_3 (*cis*)), 0.86 (3H, d, *J*=6.5 Hz, C_1-H_3 (*trans*)).

^{13}C NMR (75 MHz, $CDCl_3$): *Trans* Isomer: δ / ppm 147.65 (C, C_{14}), 145.76 (C, C_{16}), 139.59 (C, C_5), 135.42 (C, C_{12}), 128.88 (CH, C_6, $C_{6'}$), 128.33 (CH, C_7, $C_{7'}$), 126.93 (CH, C_8), 121.69 (CH, C_{18}), 109.33 (CH, C_{13}), 108.21 (CH, C_{17}), 100.89 (CH_2, C_{15}), 62.38 (CH_2, C_3), 60.86 (CH_2, C_4), 60.20 (CH_2, C_9), 48.17 (CH, C_{10}), 40.69 (CH_2, C_{11}), 38.86 (CH, C_2), 19.53 (CH_3, C_1).

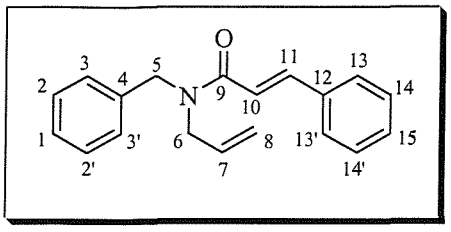
^{13}C NMR (75 MHz, $CDCl_3$): *Cis* Isomer: δ / ppm 147.65 (C, C_{14}), 145.76 (C, C_{16}), 139.71 (C, C_5), 135.61 (C, C_{12}), 128.88 (CH, C_6, $C_{6'}$), 128.33 (CH, C_7, $C_{7'}$), 126.93 (CH, C_8), 121.49 (CH, C_{18}), 109.14 (CH, C_{13}), 108.25 (CH, C_{17}), 100.89 (CH_2, C_{15}), 62.62 (CH_2, C_3), 61.11 (CH_2, C_4), 59.74 (CH_2, C_9), 42.14 (CH, C_{10}), 34.56 (CH_2, C_{11}), 34.47 (CH, C_2), 15.16 (CH_3, C_1).

IR (cm^{-1}): 3026 (w), 2952 (w), 2781 (w), 1607 (w), 1502 (m), 1488 (s), 1334 (w), 1244 (s), 1071 (w), 926 (m).

LRMS (EI): *m/z* 309 (M, 9 %), 187 (M-$C_7H_5O_2$, 14 %), 173 (M-$CH_2C_7H_5O_2$, 42 %), 158 (M-$CH_2C_7H_5O_2$-Me, 34 %), 91 ($PhCH_2$, 100 %).

HRMS (ES+): $C_{20}H_{24}NO_2^+$ requires m/z 310.1802, found 310.1796

6.2.11. *(2E)-N-Allyl-N-benzyl-3-phenylacrylamide*, **222a**



NaH (60% dispersion in mineral oil, 30 mmol, 1.2 g) was washed with petrol (30 mL) under argon and the petrol was removed *via* syringe. THF (20 mL) was added and the reaction flask was cooled to 0 °C. (E)-*N*-Allyl-3-phenyl-acrylamide (20 mmol, 3.74 g) in THF (20 mL) were added and the reaction was stirred for 15 mins. Benzyl bromide (30 mmol, 5.13 g) in THF (10 mL) were then added slowly and the reaction was warmed to r.t. and stirred overnight. The reaction was cooled to 0 °C and the reaction was quenched with water (30 mL). Ether (50 mL) was added. The organic phase was washed with water (3 X 20 mL). The aqueous phase was washed with ether (3 X 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (SiO_2, 1:1 ether to petrol, R_f=0.6) to give the title compound as a yellow oil, 5.4 g, 97%.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.71 (2H, d, *J*=15.6 Hz, C_{11}-*H* (major and minor rotamers)), 7.48-7.12 (20H, m, Ar-*H* (major and minor rotamers)), 6.76 (2H, d, *J*=15.6 Hz, C_{10}-*H* (major and minor rotamers)), 5.83-5.66 (2H, m, C_7-*H* (major and minor rotamers)), 5.24-5.03 (4H, m, C_8-*H* (major and minor rotamers)), 4.64 (2H, s, C_5-H_2 (major rotamer)), 4.57 (2H, s, C_5-H_2 (minor rotamer)), 4.04 (2H, d, *J*=5.3 Hz, C_6-H_2 (minor rotamer)), 3.91 (2H, bs, C_6-H_2 (major rotamer))

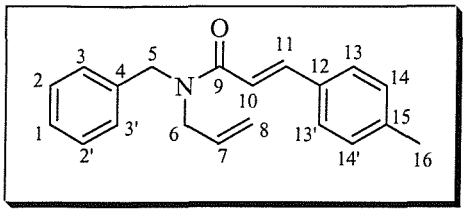
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 167.16 (C, C_9 (major rotamer)), 167.00 (C, C_9 (minor rotamer)), 143.65 (CH, C_{11} (minor rotamer)), 143.42 (CH, C_{11} (major rotamer)), 137.75 (C, C_4 (major rotamer)), 137.15 (C, C_4 (minor rotamer)), 135.48 (C, C_{12} (major rotamer)), 135.37 (C, C_{12} (minor rotamer)), 133.13 (CH, C_7 (major and minor rotamers)), 129.80 (CH, C_{14}, $C_{14'}$ (major and minor rotamers)), 129.11 (CH, C_1 (major rotamer)), 128.94 (CH, C_2, $C_{2'}$ (major rotamer)), 128.75 (CH, C_{15} (major and minor rotamers)), 128.45 (CH, C_3, $C_{3'}$ (major rotamer)), 128.00 (CH, C_{13}, $C_{13'}$ (major and minor rotamers)), 127.82 (CH, C_1 (minor rotamer)), 127.55 (CH, C_2, $C_{2'}$ (minor rotamer)), 126.67 (CH, C_3, $C_{3'}$ (minor rotamer)), 117.85 (CH_2, C_8 (minor rotamer)), 117.67 (CH, C_{10} (major rotamer)), 117.55 (CH, C_{10} (minor rotamer), 117.18 (CH_2, C_8 (major rotamer)), 50.36 (CH_2, C_5 (minor rotamer)), 49.41 (CH_2, C_5 (major rotamer)), 49.25 (CH_2, C_6 (major rotamer)), 48.78 (CH_2, C_6 (minor rotamer)).

IR (cm^{-1}): 1649 (s), 1604 (s), 1578 (w), 1495 (w), 1450 (m), 1413 (s), 1202 (s), 977 (m), 763 (s).

LRMS (EI): *m/z* 277 (M, 12 %), 236 (M-allyl, 7 %), 91 ($PhCH_2$, 29 %).

In agreement with literature[208].

6.2.12. *(2E)-N-Allyl-N-benzyl-3-(4-methylphenyl)acrylamide*, **222b**



NaH (60% dispersion in mineral oil, 30 mmol, 1.2 g) was washed with petrol (30 mL) under argon and the petrol was removed *via* syringe. THF (20 mL) was added and the reaction flask was cooled to 0 °C. (E)-*N*-Allyl-3-(4-methyl-phenyl)-acrylamide (20 mmol, 4.025 g) in THF (20 mL) were added and the reaction was stirred for 15 mins. Benzyl bromide (30 mmol, 5.13 g) in THF (10 mL) were then added slowly and the reaction was warmed to r.t. and stirred overnight. The reaction was cooled to 0 °C and the reaction was quenched with water (30 mL). Ether (50 mL) was added. The organic phase was washed with water (3 X 20 mL). The aqueous phase was washed with ether (3 X 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (SiO_2, 1:1 ether to petrol, R_f=0.5) to give the title compound as a pale yellow oil, 5.7 g, 99%.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.69 (2H, d, *J*=15.6, C_{11}-*H* (major and minor rotamers)), 7.36-7.00 (18H, m, Ar-*H* (major and minor rotamers)), 6.71 (2H, d, *J*=15.6 Hz, C_{10}-*H* (major and minor rotamers)), 5.83-5.65 (2H, m, C_7-*H* (major and minor rotamers)), 5.21-5.01 (4H, m, C_8-H_2 (major and minor rotamers)), 4.62 (2H, s, C_5-H_2 (major rotamer)), 4.57 (2H, s, C_5-H_2 (minor rotamer)), 4.03 (2H, d, *J*=5.0 Hz, C_6-H_2 (minor rotamer)), 3.90 (2H, bs, C_6-H_2 (major rotamer)), 2.28 (3H, s, C_{16}-H_3 (major rotamer)), 2.25 (3H, s, C_{16}-H_3 (minor rotamer)).

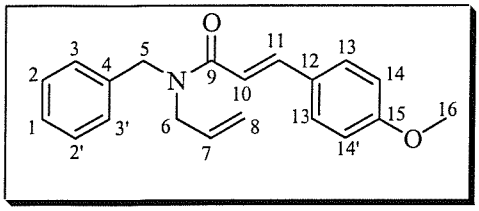
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 167.32 (C, C_9 (major rotamer)), 167.16 (C, C_9 (minor rotamer)), 143.64 (CH, C_{11} (minor rotamer)), 143.40 (CH, C_{11} (major rotamer)), 140.07 (C, C_{15} (major and minor rotamers)), 137.81 (C, C_4 (major rotamer)), 137.22 (C, C_4 (minor rotamer)), 133.17 (CH, C_7 (major and minor rotamers)), 132.72 (C, C_{12} (major rotamer)), 132.61 (C, C_{12} (minor rotamer)), 129.64 (CH, C_{14}, $C_{14'}$ (major and minor rotamers)), 129.06 (CH, C_1 (major rotamer)), 128.71 (CH, C_2, $C_{2'}$ (major rotamer)), 128.43 (CH, C_3, $C_{3'}$ (major rotamer)), 127.97 (CH, C_{13}, $C_{13'}$ (major and minor rotamers)), 127.76 (CH, C_1 (minor rotamer)), 127.49 (CH, C_2, $C_{2'}$ (minor rotamer)), 126.68 (CH, C_3, $C_{3'}$ (minor rotamer)), 117.76 (CH_2, C_8 (minor rotamer)), 117.12 (CH_2, C_8 (major rotamer)), 116.55 (CH, C_{10} (major rotamer)), 116.43 (CH, C_{10} (minor rotamer), 50.33 (CH_2, C_5 (minor rotamer)), 49.38 (CH_2, C_5 (major rotamer)), 49.21 (CH_2, C_6 (major rotamer)), 48.73 (CH_2, C_6 (minor rotamer)), 21.54 (CH_3, C_{16} (major and minor rotamers)).

IR (cm^{-1}): 1651 (s), 1608 (s), 1512 (w), 1464 (m), 1436 (m), 1415 (s), 1353 (w), 1321 (w), 1220 (m), 1206 (s), 1178 (m), 984 (s), 960 (m), 920 (m), 817 (s).

LRMS (EI): *m/z* 291 (M, 97 %), 276 (M-Me, 4 %), 250 (M-allyl, 43 %), 145 (M-benzyl-allyl-Me, 100 %).

HRMS (EI): $C_{20}H_{21}NO$ requires m/z 291.1623, found 291.1630

6.2.13. *(2E)-N-Allyl-N-benzyl-3-(4-methoxyphenyl)acrylamide*, **222c**



NaH (60% dispersion in mineral oil, 30 mmol, 1.2 g) was washed with petrol (30 mL) under argon and the petrol was removed *via* syringe. THF (20 mL) was added and the reaction flask was cooled to 0 °C. (E)-*N*-Allyl-3-(4-methoxy-phenyl)-acrylamide (20 mmol, 4.345 g) in THF (20 mL) were added and the reaction was stirred for 15 mins. Benzyl bromide (30 mmol, 5.13 g) in THF (10 mL) were then added slowly and the reaction was warmed to r.t. and stirred overnight. The reaction was cooled to 0 °C and the reaction was quenched with water (30 mL). Ether (50 mL) was added. The organic phase was washed with water (3 X 20 mL). The aqueous phase was washed with ether (3 X 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (SiO_2, 1:1 ether to petrol, R_f=0.3) to give the title compound as a yellow oil, 6.1 g, 100%.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.67 (2H, d, *J*=15.6 Hz, C_{11}-*H* (major and minor rotamers)), 7.43-7.12 (14H, m, Ar-*H* (major and minor rotamers)), 6.85-6.72 (4H, m, C_{14}-*H*, $C_{14'}$-*H* (major and minor rotamers)), 6.63 (2H, d, *J*=15.6 Hz, C_{10}-*H* (major and minor rotamers)), 5.84-5.66 (2H, m, C_7-*H* (major and minor rotamers)), 5.21-5.01 (4H, m, C_8-H_2 (major and minor rotamers)), 4.63 (2H, s, C_5-H_2 (major rotamer)), 4.58 (2H, s, C_5-H_2 (minor rotamer)), 4.03 (2H, d, *J*=4.8 Hz, C_6-H_2 (minor rotamer)), 3.90 (2H, bs, C_6-H_2 (major rotamer)), 3.74 (3H, s, C_{16}-H_3 (major rotamer)), 3.72 (3H, s, C_{16}-H_3 (minor rotamer)).

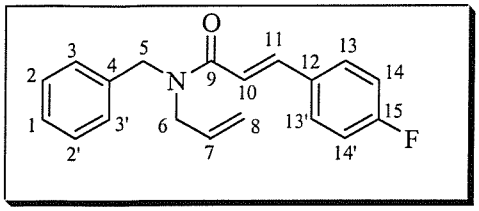
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 167.44 (C, C_9 (major rotamer)), 167.30 (C, C_9 (minor rotamer)), 161.05 (C, C_{15} (major and minor rotamers)), 143.34 (CH, C_{11} (minor rotamer)), 143.11 (CH, C_{11} (major rotamer)), 137.89 (C, C_4 (major rotamer)), 137.30 (C, C_4 (minor rotamer)), 133.24 (CH, C_7 (major and minor rotamers)), 129.57 (CH, C_{13}, $C_{13'}$ (major and minor rotamers)), 129.07 (CH, C_1 (major rotamer)), 128.72 (CH, C_2, $C_{2'}$ (major rotamer)), 128.43 (CH, C_3, $C_{3'}$ (major rotamer)), 128.22 (C, C_{12} (major rotamer)), 128.13 (C, C_{12} (minor rotamer)), 127.75 (CH, C_1 (minor rotamer)), 127.48 (CH, C_2, $C_{2'}$ (minor rotamer)), 126.68 (CH, C_3, $C_{3'}$ (minor rotamer)), 117.71 (CH_2, C_8 (minor rotamer)), 117.10 (CH_2, C_8 (major rotamer)), 115.16 (CH, C_{10} (major rotamer)), 115.04 (CH, C_{10} (minor rotamer)), 114.38 (CH, C_{14}, $C_{14'}$ (major and minor rotamers)), 55.49 (CH_3, C_{16} (major and minor rotamers)), 50.33 (CH_2, C_5 (minor rotamer)), 49.39 (CH_2, C_5 (major rotamer)), 49.22 (CH_2, C_6 (major rotamer)), 48.76 (CH_2, C_6 (minor rotamer)).

IR (cm^{-1}): 2359 (w), 2342 (w), 1645 (s), 1599 (s), 1574 (m), 1510 (s), 1495 (w), 1462 (m), 1439 (m), 1252 (s), 1172 (s), 1029 (m), 981 (w), 824 (s).

LRMS (EI): *m/z* 307 (M, 40 %), 292 (M-Me, 2 %), 266 (M-allyl, 12 %), 161 (M-benzyl-allyl-Me, 69 %).

HRMS (EI): $C_{20}H_{21}NO_2$ requires m/z 307.1572, found 307.1578

6.2.14. *(2E)-N-Allyl-N-benzyl-3-(4-fluorophenyl)acrylamide*, **222d**



NaH (60% dispersion in mineral oil, 30 mmol, 1.2 g) was washed with petrol (30 mL) under argon and the petrol was removed *via* syringe. THF (20 mL) was added and the reaction flask was cooled to 0 °C. (E)-*N*-Allyl-3-(4-fluoro-phenyl)-acrylamide (20 mmol, 4.105 g) in THF (20 mL) were added and the reaction was stirred for 15 mins. Benzyl bromide (30 mmol, 5.13 g) in THF (10 mL) were then added slowly and the reaction was warmed to r.t. and stirred overnight. The reaction was cooled to 0 °C and the reaction was quenched with water (30 mL). Ether (50 mL) was added. The organic phase was washed with water (3 X 20 mL). The aqueous phase was washed with ether (3 X 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (SiO_2, 1:1 ether to petrol, R_f=0.4) to give the title compound as a yellow oil, 3.1 g, 53 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.80 (2H, d, *J*=15.6 Hz, C_{11}-*H* (major and minor rotamers)), 7.60-7.25 (14H, m, Ar-*H* (major and minor rotamers)), 7.15-7.01 (4H, m, C_{14}-*H*, $C_{14'}$-*H* (major and minor rotamers)), 6.81 (2H, d, *J*=15.6 Hz, C_{10}-*H* (major and minor rotamers)), 6.00-5.81 (2H, m, C_7-*H* (major and minor rotamers)), 5.39-5.16 (4H, m, C_8-H_2 (major and minor rotamers)), 4.77 (2H, s, C_5-H_2 (major rotamer)), 4.71 (2H, s, C_5-H_2 (minor rotamer)), 4.17 (2H, d, *J*=5.3 Hz, C_6-H_2 (minor rotamer)), 4.04 (2H, bs, C_6-H_2 (major rotamer)).

^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 166.98 (C, C_9 (major rotamer)), 166.83 (C, C_9 (minor rotamer)), 163.65 (C, J_{CF}=250.3 Hz, C_{15} (major and minor rotamers)), 142.37 (CH, C_{11} (minor rotamer)), 142.15 (CH, C_{11} (major rotamer)), 137.67 (C, C_4 (major rotamer)), 137.09 (C, C_4 (minor rotamer)), 133.08 (CH, C_7 (major and minor rotamers)), 131.66 (C, C_{12} (major rotamer)), 131.58 (C, C_{12} (minor rotamer)), 129.80 (CH, J_{CF}=8.7 Hz, C_{13}, $C_{13'}$ (major and minor rotamers)), 129.10 (CH, C_1 (major rotamer)), 128.72 (CH, C_2, $C_{2'}$ (major rotamer)), 128.41 (CH, C_3, $C_{3'}$ (major rotamer)), 127.82 (CH, C_1 (minor rotamer)), 127.54 (CH, C_2, $C_{2'}$ (minor rotamer)), 126.60 (CH, C_3, $C_{3'}$ (minor rotamer)), 117.85 (CH_2, C_8 (minor rotamer)), 117.37 (CH, C_{10} (major rotamer)), 117.27 (CH, C_{10} (minor rotamer)), 117.14 (CH_2, C_8 (major rotamer)), 115.98 (CH, J_{CF}=21.9 Hz, C_{14}, $C_{14'}$ (major and minor rotamers)), 50.33 (CH_2, C_5 (minor rotamer)), 49.37 (CH_2, C_5 (major rotamer)), 49.26 (CH_2, C_6 (major rotamer)), 48.80 (CH_2, C_6 (minor rotamer)).

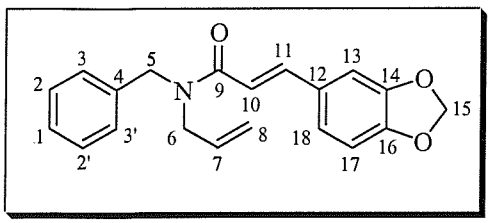
^{19}F NMR (100 MHz, $CDCl_3$): δ / ppm 51.09

IR (cm^{-1}): 1649 (s), 1600 (s), 1508 (s), 1467 (m), 1438 (m), 1409 (m), 1358 (w), 1312 (w), 1278 (w), 1206 (s).

LRMS (EI): *m/z* 295 (M, 49 %), 254 (M-allyl, 43 %), 149 (M-benzyl-allyl-F, 100 %).

HRMS (EI): $C_{19}H_{18}FNO$ requires m/z 295.1372, found 295.1377

6.2.15. *(2E)-N-Allyl-3-(1,3-benzodioxol-5-yl)-N-benzylacrylamide,* **222e**



NaH (60% dispersion in mineral oil, 15 mmol, 0.6 g) was washed with petrol (30 mL) under argon and the petrol was removed *via* syringe. THF (10 mL) was added and the reaction flask was cooled to 0 °C. (E)-*N*-Allyl-3-benzo[1,3]dioxyl-5-yl-acrylamide (10 mmol, 2.31 g) in THF (10 mL) were added and the reaction was stirred for 15 mins. Benzyl bromide (15 mmol, 2.57 g) in THF (5 mL) were then added slowly and the reaction was warmed to r.t. and stirred overnight. The reaction was cooled to 0 °C and the reaction was quenched with water (30 mL). Ether (50 mL) was added. The organic phase was washed with water (3 X 20 mL). The aqueous phase was washed with ether (3 X 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (SiO_2, 3:2 ether to petrol, R_f=0.4) to give the title compound as a yellow oil, 2.6 g, 82%.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.53 (2H, d, *J*=15.3 Hz, C_{11}-*H* (major and minor rotamers)), 7.25-7.02 (10H, m, C_1-*H*, C_2-*H*, $C_{2'}$-*H*, C_3-*H*, $C_{3'}$-*H* (major and minor rotamers)), 6.89-6.71 (4H, m, C_{13}-*H*, C_{18}-*H* (major and minor rotamers)), 6.67-6.56 (2H, m, C_{17}-*H* (major and minor rotamers)), 6.49 (2H, d, *J*=15.3 Hz, C_{10}-*H* (major and minor rotamers)), 5.82 (2H, s, C_{15}-H_2 (major rotamer)), 5.88 (2H, s, C_{15}-H_2 (minor rotamer)), 5.74-5.57 (2H, m, C_7-*H* (major and minor rotamers)), 5.14-4.92 (4H, m, C_8-H_2 (major and minor rotamers)), 4.53 (2H, s, C_5-H_2 (major rotamer)), 4.48 (2H, s, C_5-H_2 (minor rotamer)), 3.94 (2H, d, *J*=5.3 Hz, C_6-H_2 (minor rotamer)), 3.80 (2H, bs, C_6-H_2 (major rotamer)).

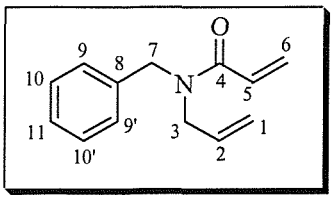
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 167.26 (C, C_9 (major rotamer)), 167.12 (C, C_9 (minor rotamer)), 149.21 (C, C_{14} (major and minor rotamers)), 148.36 (C, C_{16} (major and minor rotamers)), 143.40 (CH, C_{11} (minor rotamer)), 143.18 (CH, C_{11} (major rotamer)), 137.83 (C, C_4 (major rotamer)), 137.22 (C, C_4 (minor rotamer)), 133.19 (CH, C_7 (major and minor rotamers)), 129.90 (C, C_{12} (major rotamer)), 129.79 (C, C_{12} (minor rotamer)), 129.10 (CH, C_1 (major rotamer)), 128.73 (CH, C_2, $C_{2'}$ (major rotamer)), 128.44 (CH, C_3, $C_{3'}$ (major rotamer)), 127.79 (CH, C_1 (minor rotamer)), 127.51 (CH, C_2, $C_{2'}$ (minor rotamer)), 126.65 (CH, C_3, $C_{3'}$ (minor rotamer)), 124.07 (CH, C_{18} (major and minor rotamers)), 117.77 (CH_2, C_8 (minor rotamer)), 117.11 (CH_2, C_8 (major rotamer)), 115.63 (CH, C_{10} (major rotamer)), 115.50 (CH, C_{10} (minor rotamer)), 108.67 (CH, C_{17} (major and minor rotamers)), 106.57 (CH, C_{13} (major and minor rotamers)), 101.58 (CH_2, C_{15} (major and minor rotamers)), 50.34 (CH_2, C_5 (minor rotamer)), 49.39 (CH_2, C_5 (major rotamer), 49.26 (CH_2, C_6 (major rotamer)), 48.81 (CH_2, C_6 (minor rotamer)).

IR (cm^{-1}): 2363 (w), 1645 (s), 1599 (s), 1489 (s), 1465 (w), 1445 (s), 1413 (s), 1356 (m), 1238 (s), 1200 (s).

LRMS (EI): *m/z* 321 (M, 65 %), 230 (M-benzyl, 19 %), 187 (M-benzyl-allyl, 23 %),

HRMS (EI): $C_{20}H_{19}NO_3$ requires m/z 321.1365, found 321.1362

6.2.16. *N-Allyl-N-benzyl-acrylamide*, **223**



Allylamine (120 mmol, 10.0 mL) and K_2CO_3 (60 mmol, 8.3 g) in MeCN (50 mL) were cooled to 0 °C before benzyl bromide (4.1 g, 24 mmol) in MeCN (30 mL) were added slowly. Reaction was warmed to r.t. and stirred for 1 hour. The reaction was quenched with water (30 mL) and ether (30 mL) was added. Organic layer was washed with water (3 X 10 mL). The aqueous layer was washed with ether (3 X 10 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. 2M NaOH (40 mL) was added to the crude amine mixture and cooled to 0 °C. Acryloyl chloride (9.6 mL, 100 mmol) was added dropwise and the reaction was allowed to stir for a further 5 mins. Water (30 mL) and ether (30 mL) were added. The organic layer was washed successively with water (3 X 10 mL), 2M HCl (3 X 10 mL), then brine (3 X 10 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. The amide was purified by column chromatography (SiO_2, 1:1 ether to petrol, R_f=0.4) to give the title compound as a colourless oil, 2.5 g, 51 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.42-7.15 (10H, m, C_9-*H*, $C_{9'}$-*H*, C_{10}-*H*, $C_{10'}$-*H*, C_{11}-*H* (major and minor rotamers)), 6.63-6.39 (4H, m, C_5-*H*, C_6-*H* (*trans*), (major and minor rotamers)), 5.91-5.67 (4H, m, C_2-*H*, C_6-*H* (*cis*), (major and minor rotamers)), 5.29-5.10 (4H, m, C_1-H_2 (major and minor rotamers)), 4.67 (2H, s, C_7-H_2 (major rotamer)), 4.59 (2H. s, C_7-H_2 (minor rotamer)), 4.08 (2H, d, *J*=5.9 Hz, C_3-H_2 (minor rotamer)), 3.91 (2H, d, *J*=4.4 Hz, C_3-H_2 (major rotamer)).

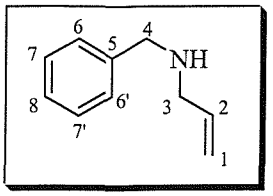
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 166.91 (C, C_4 (major rotamer)), 167.77 (C, C_4 (minor rotamer)), 137.47 (C, C_8 (major rotamer)), 136.84 (C, C_8 (minor rotamer)), 132.87 (CH, C_2 (minor rotamer)), 132.70 (CH, C_2 (major rotamer)), 128.98 (CH, *C*-H (rotamer)), 128.74 (CH_2, C_6 (major and minor rotamers)), 128.68 (CH, *C*-H (rotamer)), 128.38 (CH, *C*-H (rotamer)), 127.72 (CH, *C*-H (rotamer)), 127.51 (CH, *C*-H (rotamer)), 126.51 (CH, *C*-H (rotamer)), 117.89 (CH_2, C_1 (minor rotamer)), 117.09 (CH_2, C_1 (major rotamer)), 50.12 (CH_2, C_7 (minor rotamer)), 49.14 (CH_2, C_7 (major rotamer)), 48.83 (CH_2, C_3 (major rotamer)), 48.45 (CH_2, C_3 (minor rotamer)).

IR (cm^{-1}): 3029 (w), 2984 (w), 2920(w), 1649 (s), 1613 (s), 1495 (w), 1430 (s), 1359 (w), 1213 (s), 978 (m).

LRMS (EI): *m/z* 201 (M, 52 %), 160 (M-allyl, 48 %), 106 (M-allyl-acryloyl, 100 %), 91 ($PhCH_2$, 92 %).

In agreement with literature[209].

6.2.17. *N-Benzyl-N-allyl amine*, **224**



Allylamine (5 eq, 500 mmol, 28.55 g), anhydrous K_2CO_3 (1.5 eq, 150 mmol, 21.0 g) in acetonitrile (100 mL), cooled to 0 °C before benzyl bromide (1 eq, 100 mmol, 11.9 mL) in acetonitrile (100 mL) was added dropwise. The reaction was warmed to r.t. and stirred for 1.5 hours. Ether (100 mL) and water (100 mL) were added. The organic layer was washed with water (4 X 40 mL) and the aqueous layer was washed with ether (4 X 40 mL). The ether layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The secondary amine was purified by distillation (0.1 mmHg, 110 °C) to give the title compound as a colourless oil, 10.2 g, 69 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.39-7.23 (5H, m, Ar-*H*), 6.95 (1H, ddt, *J*=17.3 Hz, *J*=10.3 Hz, *J*=5.9 Hz, C_2-*H*), 5.22 (1H, dd, *J*=17.3 Hz, *J*=1.3 Hz, C_1-*H* (*trans*)), 5.13 (1H, dd, *J*=10.3 Hz, *J*=1.3 Hz, C_1-*H* (*cis*)), 3.83 (2H, s, C_4-H_2), 3.30 (2H, d, *J*=5.9 Hz, *J*=5.9 Hz, C_3-H_2), 1.55-1.40 (1H, bs, N-*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 140.41 (C, C_5), 136.93 (CH, C_2), 128.56 (CH, C_7, $C_{7'}$), 128.34 (CH, C_6, $C_{6'}$), 127.10 (CH, C_8), 116.18 (CH_2, C_1), 53.42 (CH_2, C_4), 51.93 (CH_2, C_3).

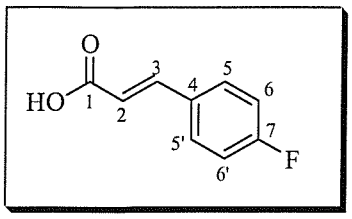
Lit. M.Pt: 40-41 °C[210]

IR (cm^{-1}): 3077 (w), 3027 (w), 2908 (w), 2810 (w), 1643 (w), 1604 (w), 1494 (w), 1453 (m).

LRMS (EI): *m/z* 147 (M, 50 %), 132 (M-CH_2, 53 %), 120 (M-$CHCH_2$, 32 %), 91 ($PhCH_2$, 100 %).

NMR data in agreement with literature[211].

6.2.18. *4-Fluoro cinnamic acid,* **225d**



Knoevenagel Condensation: Malonic acid (100 mmol, 10.41 g), 4-fluorobenzaldehyde (140 mmol, 17.38 g), pyridine (45.0 mL) and piperidine (5.0 mL) were stirred for 5 days at r.t.. The reaction was cooled to 0 °C before a solution of H_2SO_4 (100 mL) and water (100 mL) was added slowly. Ether (50 mL) was added. The organic layer was washed with water (3 X 30 mL). The organic layer was concentrated *in vacuo* to give a white solid. K_2CO_3 (40 g) in water (500 mL) was added, followed by ether (100 mL). Reaction stirred for 5 mins to ensure complete dissolution. The aqueous layer was washed with ether (3 X 30 mL), and the organic layer was discarded. The aqueous layer was acidified with 2M HCl and ether (500 mL) was added. The acidic aqueous layer was washed with ether (3 X 100 mL), and the organic layers were combined, dried ($MgSO_4$) and *concentrated in vacuo* to give a colourless solid, 14.1 g, 85 %. The 4-fluorocinnamic acid was used without any further purification.

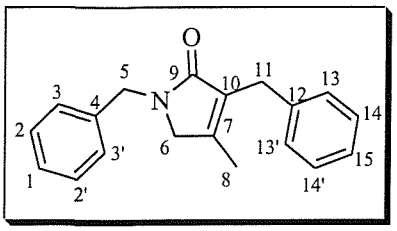
M.P.: 205-207 °C.

Lit. M.Pt: 203-204 °C

IR (cm^{-1}): 2834 (w), 2604 (w), 2539 (m), 2342 (m), 1680 (s), 1625 (s), 1595 (s), 1504 (s), 1425 (s), 1339 (m), 1222 (s), 980 (m), 824 (s).

In agreement with literature[212].

6.2.19. *1,3-Dibenzyl-4-methyl-1,5-dihydro-pyrrol-2-one,* **229**



N-Allyl-*N*-benzyl-acrylamide (1 mmol, 201 mg), $PdCl_2$ (5mol %, 9 mg), K_2CO_3 (2 mmol, 280 mg), LiCl (30 mmol, 1260 mg) and iodobenzene (2 mmol, 408 mg) were heated under an argon atmosphere at 120 °C for 12 hrs in DMF (10 mL) and water (3 mL). The reaction was allowed to cool, before being filtered through a pad of celite to remove the Pd catalyst. Ether (30 mL) and water (30 mL) were added. The organic phase was washed with water (3 X 20 mL). The aqueous phase was washed with ether (3 X 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The cyclic lactam was purified using radial chromatography (SiO_2, 1:1 petrol to ether, R_f=0.3) to give the title compound as a yellow oil, 152 mg, 55 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.29-7.10 (10H, m, Ar-*H*), 4.54 (2H, s, C_5-*H*$_2$), 3.61-3.57 (4H, bs, C_6-*H*$_2$, C_{11}-*H*$_2$), 1.86 (3H, s, C_8-*H*$_3$).

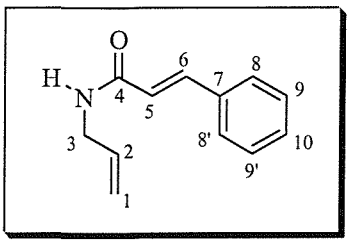
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 172.22 (C, C_9), 147.43 (C, C_7), 139.62 (C, C_{12}), 137.75 (C, C_4), 132.15 (C, C_{10}), 128.85 (CH, C_{13}, $C_{13'}$), 128.80 (CH, C_{14}, $C_{14'}$), 128.61 (CH, C_2, $C_{2'}$), 128.25 (CH, C_3, $C_{3'}$), 127.61 (CH, C_1), 126.21 (CH, C_{15}), 53.96 (CH_2, C_5), 46.34 (CH_2, C_6), 30.00 (CH_2, C_{11}), 13.40 (CH_3, C_8).

IR (cm^{-1}): 3028 (w), 2912 (w), 1669 (s), 1600 (w), 1449 (m), 1359 (w), 1146 (m), 758 (m).

LRMS (EI): *m/z* 277 (M, 47 %), 200 (M-Ph, 12 %), 186 (M-CH_2-Ph, 24 %), 91 (Ph-CH_2, 100 %).

Microanalysis: Found: C 81.93, H 6.94, N 5.05. Requires: C 82.28, H 6.90, N 5.05.

6.2.20. *(2E)-N-Allyl-3-phenylacrylamide*, **231a**



Cinnamic acid (100 mmol, 14.82 g) in dry DCM (150 mL) were cooled to 0 °C before oxalyl chloride (150 mmol, 13.0 mL) was added, followed by DMF (10 drops). The reaction was warmed to r.t. and stirred overnight. The resulting solution had DCM and other volatile material removed *via* low pressure evaporation to give a yellow solid. DCM (30 mL) was added, and the reaction was cooled to 0 °C. NaOH (200 mmol, 8.0 g) in water (100 mL) were cooled to 0 °C and added to the acid chloride solution. Allylamine (30 mL) was cooled to 0 °C and added dropwise to the reaction mixture. The reaction was warmed to r.t. and stirred for a further 20 mins. DCM (100 mL) was added. The organic layer was washed with water (3 X 20 mL). The aqueous layer was washed with DCM (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a light brown solid. The amide was recrystallised from a minimum volume of hot ethanol to give the title compound as a pale yellow powder, 9.3 g, 50 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.65 (1H, d, *J*=15.4 Hz, C_6-*H*), 7.52-7.44 (2H, m, Ar-*H*), 7.36-7.29 (3H, m, Ar-*H*), 6.55 (1H, d, *J*=15.4 Hz, C_5-*H*), 6.53-6.46 (1H, bs, N-*H*), 5.90 (1H, ddt, *J*=17.3 Hz, *J*=10.3 Hz, *J*=5.9 Hz, C_2-*H*), 5.24 (1H, dd, *J*=17.3 Hz, *J*=1.5 Hz, C_1-*H* (*trans*)), 5.15 (1H, dd, *J*=10.3 Hz, *J*=1.5 Hz, C_1-*H* (*cis*)), 4.02 (2H, dd, *J*=5.9 Hz, *J*=5.9 Hz, C_3-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 166.13 (C, C_4), 141.14 (CH, C_6), 134.91 (C, C_7), 134.21 (CH, C_2), 129.75 (CH, C_{10}), 128.90 (CH, C_9, $C_{9'}$), 127.90 (CH, C_8, $C_{8'}$), 120.81 (CH, C_5), 116.58 (CH_2, C_1), 42.28 (CH_2, C_3).

IR (cm^{-1}): 3281 (m), 3104 (w), 3065 (w), 3034 (w), 3009 (w), 1670 (m), 1653 (m), 1615 (s), 1577 (w), 1543 (m), 1493 (m), 1446 (m), 1434 (m), 1217 (s), 990 (m), 972 (s), 912 (m), 863 (m).

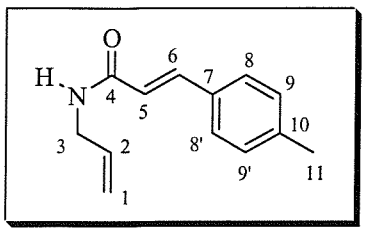
LRMS (EI): *m/z* 187 (M, 14%), 131 (M-O-allyl, 100%).

M.P.: 89-91 °C

Lit. M.P.: 88-89 °C.

In agreement with literature[213].

6.2.21. *(2E)-N-Allyl-3-(4-methylphenyl)acrylamide*, **231b**



3-(4-methyl-phenyl)-acrylic acid (100 mmol, 16.22 g) in dry DCM (150 mL) were cooled to 0 °C before oxalyl chloride (150 mmol, 13.0 mL) was added, followed by DMF (10 drops). The reaction was warmed to r.t. and stirred overnight. The resulting solution had DCM and other volatile material removed *via* low pressure evaporation to give a white powder. DCM (30 mL) was added, and the reaction was cooled to 0 °C. NaOH (200 mmol, 8.0 g) in water (100 mL) was cooled to 0 °C and added to the acid chloride solution. Allylamine (30 mL) were cooled to 0 °C and added dropwise to the reaction mixture. The reaction was warmed to r.t. and stirred for a further 20 mins. DCM (100 mL) was added. The organic layer was washed with water (3 X 20 mL). The aqueous layer was washed with DCM (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow/orange powder. The amide was recrystallised from a minimum volume of hot ethanol to give the title compound as a white crystalline powder, 11.8 g, 59 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.63 (1H, d, *J*=15.6 Hz, C_6-*H*), 7.40 (2H, d, *J*=8.1 Hz, C_8-*H*, $C_{8'}$-*H*), 7.16 (2H, d, *J*=8.1 Hz, C_9-*H*, $C_{9'}$-*H*), 6.42 (1H, d, *J*=15.6 Hz, C_5-*H*), 6.01 (1H, bs, N-*H*), 5.90 (1H, ddt, *J*=17.3 Hz, *J*=10.3 Hz, *J*=5.9 Hz, C_2-*H*), 5.25 (1H, dd, *J*=17.3 Hz, *J*=1.5Hz, C_1-*H* (*trans*)), 5.18 (1H, dd, *J*=10.3 Hz, *J*=1.1 Hz, C_1-*H* (*cis*)), 4.02 (2H, dd, *J*=5.9 Hz, *J*=5.9 Hz, C_3-H_2), 2.38 (3H, s, C_{11}-H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 166.16 (C, C_4), 141.33 (CH, C_6), 140.13 (C, C_{10}), 134.33 (CH, C_2), 132.17 (C, C_7), 129.69 (CH, C_9, $C_{9'}$), 127.93 (CH, C_8, $C_{8'}$), 119.58 (CH, C_5), 116.69 (CH_2, C_1), 42.30 (CH_2, C_3), 21.58 (CH_3, C_{11}).

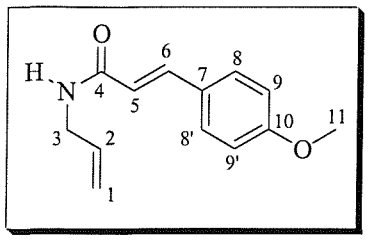
IR (cm^{-1}): 3264 (m), 3082 (w), 3068 (w), 3024 (w), 3009 (w), 1675 (m), 1656 (m), 1615 (s), 1553 (s), 1511 (m), 1455 (w), 1423 (m), 1225 (s), 989 (m), 975 (s), 911 (s), 805 (s).

LRMS (EI): *m/z* 201 (M, 53 %), 145 (M-O-allyl, 100 %).

M.P.: 108-110 °C

Microanalysis: Found: C 77.54, H 7.56, N 6.95. Requires: C 77.58, H 7.51, N 6.96.

6.2.22. *(2E)-N-Allyl-3-(4-methoxyphenyl)acrylamide*, **231c**



3-(4-methoxy-phenyl)-acrylic acid (100 mmol, 17.82 g) in dry DCM (150 mL) were cooled to 0 °C before oxalyl chloride (150 mmol, 13.0 mL) was added, followed by DMF (10 drops). The reaction was warmed to r.t. and stirred for 4 hours. The resulting solution had DCM and other volatile material removed *via* low pressure evaporation to give a yellow solid. DCM (30 mL) was added, and the reaction was cooled to 0 °C. NaOH (200 mmol, 8.0 g) in water (100 mL) were cooled to 0 °C and added to the acid chloride solution. Allylamine (30 mL) was cooled to 0 °C and added dropwise to the reaction mixture. The reaction was warmed to r.t. and stirred for a further 20 mins. DCM (100 mL) was added. The organic layer was washed with water (3 X 20 mL). The aqueous layer was washed with DCM (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid. The amide was recrystallised from a minimum volume of hot ethanol to give the title compound as white crystals, 18.9 g, 87 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.60 (1H, d, *J*=15.6 Hz, C_6-*H*), 7.45 (2H, d, *J*=8.8 Hz, C_8-*H*, C_8'-*H*), 6.86 (2H, d, *J*=8.8 Hz, C_9-*H*, $C_{9'}$-*H*), 6.34 (1H, d, *J*=15.6 Hz, C_5-*H*), 6.00 (1H, bs, N-*H*), 5.90 (1H, ddt, *J*=17.1 Hz, *J*=10.3 Hz, *J*=5.9 Hz, C_2-*H*), 5.23 (1H, dd, *J*=17.1 Hz, *J*=1.1 Hz, C_1-*H* (*trans*)), 5.16 (1H, dd, *J*=10.3 Hz, *J*=1.1 Hz, C_1-*H* (*cis*)), 4.02 (2H, dd, *J*=5.9 Hz, *J*=5.9 Hz, C_3-H_2), 3.82 (3H, s, C_{11}-H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 166.30 (C, C_4), 160.97 (C, C_{10}), 140.93 (CH, C_6), 134.37 (CH, C_2), 129.48 (CH, C_8 , $C_{8'}$), 127.63 (C, C_7), 118.24 (CH, C_5), 116.60 (CH_2, C_1), 114.34 (CH, C_9 , $C_{9'}$), 55.48 (CH_3, C_{11}), 42.27 (CH_2, C_3).

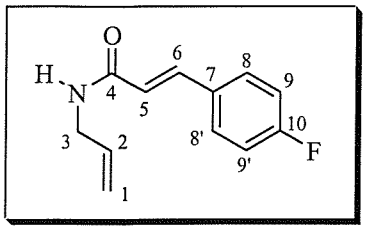
IR (cm^{-1}): 3262 (m), 3071 (w), 3053 (w), 3009 (w), 1666 (m), 1651 (m), 1603 (s), 1544 (s), 1510 (s), 1467 (w), 1421 (m), 1219 (s), 987 (m), 913 (s), 823 (s).

LRMS (EI): *m/z* 217 (M, 14 %), 161 (M-O-allyl, 100 %).

M.P.: 123-125 °C

Microanalysis: Found: C 71.81, H 6.99, N 6.48. Requires: C 71.87, H 6.96, N 6.44.

6.2.23. *(2E)-N-Allyl-3-(4-fluorophenyl)acrylamide,* **231d**



3-(4-fluoro-phenyl)-acrylic acid (50 mmol, 8.31 g) in dry DCM (80 mL) were cooled to 0 °C before oxalyl chloride (75 mmol, 6.5 mL) was added, followed by DMF (5 drops). The reaction was warmed to r.t. and stirred overnight. The resulting solution had DCM and other volatile material removed *via* low pressure evaporation to give a white powder. DCM (30 mL) was added, and the reaction was cooled to 0 °C. NaOH (100 mmol, 4.0 g) in water (100 mL) were cooled to 0 °C and added to the acid chloride solution. Allylamine (15 mL) was cooled to 0 °C and added dropwise to the reaction mixture. The reaction was warmed to r.t. and stirred for a further 20 mins. DCM (100 mL) was added. The organic layer was washed with water (3 X 20 mL). The aqueous layer was washed with DCM (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give an off-white solid. The amide was recrystallised from a minimum volume of hot ethanol to give the title compound as white/beige crystals, 9.1 g, 89 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.61 (1H, d, *J*=15.6 Hz, C_6-*H*), 7.47 (2H, dd, *J*=8.8 Hz, *J*=5.5 Hz, C_8-*H*, $C_{8'}$-*H*), 7.04 (2H, dd, *J*=8.8 Hz, *J*=8.8 Hz, C_9-*H*, $C_{9'}$-*H*), 6.40 (1H, d, *J*=15.6 Hz, C_5-*H*), 6.11 (1H, bs, N-*H*), 5.90 (1H, ddt, *J*=17.3 Hz, *J*=10.0 Hz, *J*=5.9 Hz, C_2-*H*), 5.24 (1H, dd, *J*=17.3 Hz, *J*=1.1 Hz, C_1-*H* (*trans*)), 5.16 (1H, dd, *J*=10.0 Hz, *J*=1.1 Hz, C_1-*H* (*cis*)), 4.03 (2H, dd, *J*=5.9 Hz, *J*=5.9 Hz, C_3-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 165.84 (C, C_4), 163.64 (C, J_{CF}=250.4 Hz, C_{10}), 140.10 (CH, C_6), 134.18 (CH, C_2), 131.14 (C, J_{CF}=3.4 Hz, C_7), 129.71 (CH, J_{CF}=8.5 Hz, C_8, $C_{8'}$), 120.40 (CH, J_{CF}=2.3 Hz, C_5), 116.75 (CH_2, C_1), 116.05 (CH, J_{CF}=22.0 Hz, C_9, $C_{9'}$), 42.21 (CH_2, C_3).

^{19}F NMR (100 MHz, $CDCl_3$): δ / ppm 51.16

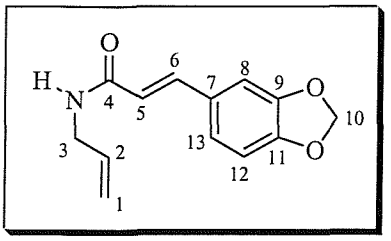
IR (cm^{-1}): 3251 (m), 3184 (w), 3070 (m), 1660 (m), 1613 (s), 1596 (s), 1506 (s), 1425 (m), 1343 (m), 1218 (s), 1157 (m), 979 (m), 920 (m), 826 (s).

LRMS (EI): *m/z* 205 (M, 35 %), 149 (M-O-allyl, 100 %).

M.P.: 117-119 °C

Microanalysis: Found: C 70.05, H 5.91, N 6.83. Requires: C 70.23, H 5.89, N 6.82.

6.2.24. *(2E)-N-Allyl-3-(1,3-benzodioxol-5-yl)acrylamide*, **231e**



3-Benzo[1,3]dioxol-5-yl-acrylic acid (70 mmol, 13.45 g) in dry DCM (150 mL) were cooled to 0 °C before oxalyl chloride (100 mmol, 9.0 mL) was added, followed by DMF (5 drops). The reaction was warmed to r.t. and stirred overnight. The resulting solution had DCM and other volatile material removed *via* low pressure evaporation to give an orange powder. DCM (30 mL) was added, and the reaction was cooled to 0 °C. NaOH (150 mmol, 6.0 g) in water (100 mL) was cooled to 0 °C and added to the acid chloride solution. Allylamine (20 mL) were cooled to 0 °C and added dropwise to the reaction mixture. The reaction was warmed to r.t. and stirred for a further 20 mins. DCM (100 mL) was added. The organic layer was washed with water (3 X 20 mL). The aqueous layer was washed with DCM (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a brown powder. The amide was recrystallised from a minimum volume of hot ethanol to give the title compound as a light brown crystalline solid, 9.6 g, 59 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.56 (1H, d, *J*=15.6 Hz, C_6-*H*), 7.00 (1H, s, C_8-*H*), 6.98 (1H, d, *J*=7.7 Hz, C_{13}-*H*), 6.79 (1H, d, *J*=7.7 Hz, C_{12}-*H*), 6.27 (1H, d, *J*=15.6 Hz, C_5-*H*), 6.00 (2H, s, C_{10}-H_2), 5.99-5.79 (2H, m, N-*H*, C_2-*H*), 5.24 (1H, dd, *J*=16.9 Hz, *J*=1.1 Hz, C_1-*H* (*trans*)), 5.17 (1H, dd, *J*=10.3 Hz, *J*=1.1 Hz, C_1-*H* (*cis*)), 4.02 (2H, dd, *J*=5.9 Hz, *J*=5.9 Hz, C_3-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 166.07 (C, C_4), 149.22 (C, C_9), 148.38 (C, C_{11}), 141.12 (CH, C_6), 134.35 (CH, C_2), 129.36 (C, C_7), 124.01 (CH, C_5), 118.68 (CH, C_{13}), 116.70 (CH_2, C_1), 108.67 (CH, C_{12}), 106.49 (CH, C_8), 101.58 (CH_2, C_{10}), 42.30 (CH_2, C_3).

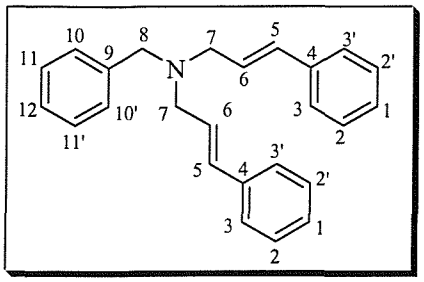
IR (cm^{-1}): 3257 (m), 3168 (w), 3070 (w), 3013 (w), 2898 (w), 1654 (w), 1601 (s), 1554 (s), 1493 (s), 1447 (s), 1426 (m), 1249 (s), 1221 (m), 1036 (s), 1002 (m), 980 (s), 922 (s).

LRMS (EI): *m/z* 231 (M, 45 %), 175 (M-O-allyl, 100 %).

M.P.: 153-155 °C

Microanalysis: Found: C 67.40, H 5.66, N 6.07. Requires: C 67.52, H 5.67, N 6.05.

6.2.25. *N-Benzyl-dicinnamyl-amine*, **233**



Benzylamine (10 mmol, 1.1 g), K_2CO_3 (20 mmol, 2.8 g) in MeCN (10 mL) was cooled to 0 °C before cinnamyl amine (20 mmol, 3.94 g) in MeCN (10 mL) was added slowly. The reaction was warmed to r.t. and stirred overnight. Ether (30 mL) and water (50 mL) were added. The organic layer was washed with water (3 X 50 mL). The aqueous layer was washed with ether (3 X 50 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The amine was recrystallised from hot pentane to give the title compound as a light brown solid, 2.9 g, 85 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.33-7.11 (15H, m, Ar-*H*), 6.47 (2H, d, *J*=15.8 Hz, C_5-*H*), 6.24 (2H, dt, *J*=15.8 Hz, *J*=6.5 Hz, C_6-*H*), 3.60 (2H, s, C_8-H_2), 3.22 (4H, d, *J*=6.5 Hz, C_7-H_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 139.48 (C, C_9), 137.31 (C, C_4), 132.80 (CH, C_6), 129.16 (CH, C_{10}, $C_{10'}$), 128.71 (CH, C_2, $C_{2'}$), 128.43 (CH, C_{11}, $C_{11'}$), 127.76 (CH, C_5), 127.52 (CH, C_1), 127.08 (CH, C_{12}), 126.44 (CH, C_3, $C_{3'}$), 58.13 (CH_2, C_8), 56.18 (CH_2, C_7).

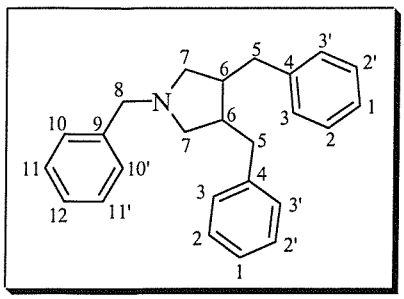
IR (cm^{-1}): 3025 (w), 2911 (w), 2786 (w), 1599 (w), 1492 (m), 1365 (m), 968 (s).

LRMS (EI): *m/z* 339 (M, 7 %), 248 (M-CH_2-Ph, 9 %), 132 (M-CH_2-Ph-cinnamyl, 5 %), 91 ($PhCH_2$, 100 %).

M.P.: 61-63 °C

Microanalysis: Found: C 88.31, H 7.34, N 4.15. Requires: C 88.45, H 7.42, 4.12.

6.2.26. *1,3,4-tribenzyl-pyrrolidine*, **234**



Cp_2ZrCl_2 (1.7 mmol, mg) in THF (10 mL) was cooled to -78 °C before BuLi (3.4 mmol, mL) was added slowly. The reaction was stirred for 20 mins at -78 °C before diene (1 mmol, 339 mg) in THF (5 mL) was added. The reaction was warmed to r.t. and stirred for 24 hours. MeOH (5 mL) and $NaHCO_3$ solution (5 mL) were added to the dark red zirconacycle solution and stirred overnight. Ether (30 mL) and water (30 mL) were added. The organic layer was washed with water (3 X 10 mL). The aqueous layer was washed with ether (3 X 10 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The pyrrolidine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 2 % Et_3N, 98 % petrol, R_f=0.3). This gave a 11:1 inseparable mixture of *trans* to *cis* diastereoisomers as a colourless oil, 270 mg, 79%.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.23-6.98 (30H, m, Ar-*H* (*cis* and *trans*)), 3.56-3.49 (3H, m, C_8-*H*$_2$ (*cis*), C_8-*H* (*trans*)), 3.40 (1H, d, *J*=13.3 Hz, C_8-*H* (*trans*)), 2.84 (4H, d, *J*=9.3 Hz, 2 X C_5-*H*$_2$ (*cis*)), 2.68 (2H, dd, *J*=3.0 Hz, *J*=9.0 Hz, 2 X C_7-*H* (*cis*)), 2.60-2.47 (8H, m, 2 X C_7-*H* (*trans*), 2 X C_5-*H*$_2$ (*trans*), 2 X C_6-*H* (*cis*)), 2.26 (2H, dd, *J*=3.3 Hz, *J*=9.0 Hz, 2 X C_7-*H* (*trans*)), 2.22 (2H, dd, *J*=3.0 Hz, *J*=9.0 Hz, 2 X C_7-*H* (*cis*)), 2.07 (2H, m, 2 X C_6-*H* (*trans*)).

^{13}C NMR (75 MHz, $CDCl_3$): *Trans* Isomer: δ / ppm 141.37 (C, C_4), 139.48 (C, C_9), 129.01 (CH, C_2, $C_{2'}$), 128.78 (CH, C_{10}, $C_{10'}$), 128.45 (CH, C_3, $C_{3'}$), 128.33 (CH, C_{11}, $C_{11'}$), 126.94 (CH, C_{12}), 126.03 (CH, C_1), 60.60 (CH_2, C_8), 60.19 (CH_2, C_7), 46.05 (CH, C_6), 41.48 (CH_2, C_5).

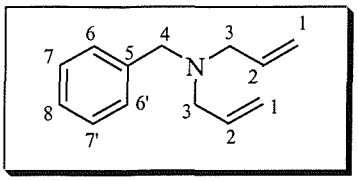
^{13}C NMR (75 MHz, $CDCl_3$): *Cis* Isomer: δ / ppm 141.52 (C, C_4), 139.70 (C, C_9), 128.88 (CH, C_2, $C_{2'}$), 128.74 (CH, C_{10}, $C_{10'}$), 128.51 (CH, C_3, $C_{3'}$), 128.32 (CH, C_{11}, $C_{11'}$), 126.94 (CH, C_{12}), 126.03 (CH, C_1), 60.91 (CH_2, C_8), 59.69 (CH_2, C_7), 41.94 (CH, C_6), 35.98 (CH_2, C_5).

IR (cm^{-1}): 3083 (w), 3025 (w), 2912 (w), 2783 (w), 1603 (w), 1494 (m), 1476 (w), 1453 (m).

LRMS (EI): *m/z* 341 (M, 64 %), 264 (M-Ph, 28 %), 250 (M-CH_2Ph, 19 %), 172 (M-Ph-CH_2Ph, 68 %), 91 ($PhCH_2$, 100 %).

HRMS (EI): $C_{25}H_{27}N$ requires m/z 341.2144, found 341.2134

6.2.27. *N-Diallyl-benzyl-amine*, **245**



N,N-Diallylamine (50 mmol, 4.86 g), K_2CO_3 (70 mmol, 9.80 g) in MeCN (50 mL) had benzyl bromide (70 mmol, 12.97 g) in MeCN (50 mL) added to it. The reaction was stirred overnight. Water (100 mL) and ether (100 mL) were added. The organic layer was washed with water (3 X 30 mL). The aqueous layer was washed with ether (3 X 30 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The amine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 1 % Et_3N, 99 % petrol, R_f=0.4). The amine was distilled at 0.1 mm Hg, 130 °C to give the title compound as a colourless oil, 3.81 g, 41 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.43-7.21 (5H, m, Ar-H), 5.90 (2H, ddt, *J*=17.6 Hz, *J*=9.9 Hz, *J*=6.6 Hz, C_2-H), 5.22 (2H, dd, *J*=17.6 Hz, *J*=1.5 Hz, C_1-H (*trans*)), 5.08 (2H, d, *J*=9.9 Hz, C_1-H (*cis*)), 3.59 (2H, s, C_4-H_2), 3.09 (4H, d, *J*=6.6 Hz, C_3-H_2).

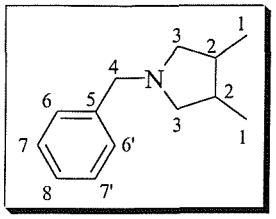
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 139.58 (C, C_5), 136.06 (CH, C_2), 129.09 (CH, C_6, $C_{6'}$), 128.35 (CH, C_7, $C_{7'}$), 126.98 (CH, C_8), 117.60 (CH_2, C_1), 57.68 (CH_2, C_4), 56.59 (CH_2, C_3).

IR (cm^{-1}): 3078 (w), 3066 (w), 3027 (w), 3006 (w), 2978 (w), 2923 (w), 2793 (w), 1643 (w), 1494 (w), 1453 (w), 1256 (w), 1118 (m), 994 (m), 916 (s), 736 (s).

LRMS (EI): *m/z* 187 (M, 62 %), 146 (M-allyl, 57 %), 91 ($PhCH_2$, 100 %).

In agreement with literature[214].

6.2.28. *1-benzyl-3,4-dimethyl-pyrrolidine*, **246**



Method A: Cp_2ZrCl_2 (3.6 mmol, 1051 mg) in THF (15 mL) was cooled to -78 °C before BuLi (7.2 mmol, 2.9 mL) was added slowly. The reaction was stirred for 20 mins before *N*-diallyl-benzyl-amine (3 mmol, 561 mg) in THF (15 mL) was added. The reaction was warmed to r.t. and stirred for 36 hours. MeOH (5 mL) and $NaHCO_3$ solution (5 mL) were added to the zirconacycle solution and stirred overnight. Ether (40 mL) and water (40 mL) were added. The organic layer was washed with water (3 X 30 mL) and the aqueous layer was washed with ether (3 X 30 mL). The organic layers were combined and the pyrrolidine was extracted with 2M HCl (3 X 40 mL). The acidic layer was basified with NaOH pellets and the pyrrolidine was extracted with ether (3 X 40 mL). The organic washings were dried ($MgSO_4$) and concentrated *in vacuo*. The pyrrolidine was purified by Kügelrohr distillation (130 °C, 0.1 mm Hg). This gave a 2:1 inseparable mixture of *trans* to *cis* diastereoisomers as a colourless oil, 488 mg, 86 %.

Method B: $Ti(O^iPr)_4$ (1.26 mmol, 0.37 mL) and *N*-diallyl-benzyl-amine (1 mmol, 187 mg) in DEE (10 mL) were cooled to -78 °C before ^{i}PrMgCl (2.75 mmol, 1.38 mL) was added. The resulting yellow solution was stirred for 30 mins at -78 °C before being warmed to –50 °C and stirred for a further 2 hours. The resulting red solution was quenched with 3M HCl (10 mL), warmed to r.t. and left to stir overnight. Ether (40 mL) and 3M HCl (30 mL) were added. The organic layer was washed with 3M HCl (3 X 30 mL). The aqueous layer was basified with NaOH pellets and the pyrrolidine was extracted with ether (3 X 40 mL). The organic washings were dried ($MgSO_4$) and concentrated *in vacuo*. The pyrrolidine was purified by Kügelrohr distillation (130 °C, 0.1 mm Hg) to give a 1:9 inseparable mixture of *trans* to *cis* isomers as a colourless oil, 130 mg, 69 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.41-7.24 (10H, m, Ar-H (*cis* and *trans*)), 3.70 (1H, d, *J*=13.1 Hz, C_4-H (*trans*)), 3.65-3.57 (3H, m, 2 X C_4-H (*cis*), C_4-H (*trans*)), 3.05 (2H, dd, *J*=2.0 Hz, *J*=8.8 Hz, 2 X C_3-H (*cis*)), 2.82 (2H, dd, *J*=1.5 Hz, *J*=7.4 Hz, 2 X C_3-H (*trans*)), 2.39-2.31 (2H, m, 2 X C_2-H (*cis*)), 2.30 (2H, dd, *J*=2.0 Hz, *J*=8.8 Hz, 2 X C_3-H (*trans*)), 2.02 (2H, dd, *J*=2.0 Hz, *J*=8.8 Hz, 2 X C_3-H (*cis*)), 1.77 (2H, m, 2 X C_2-H (*trans*)), 1.06 (6H, d, *J*=6.3 Hz, 2 X C_1-H_3 (*trans*)), 0.95 (6H, d, *J*=6.5 Hz, 2 X C_1-H_3 (*cis*)).

^{13}C NMR (75 MHz, $CDCl_3$): *Trans* Isomer: δ / ppm 139.79 (C, C_5), 128.96 (CH, C_6, $C_{6'}$), 128.31 (CH, C_7, $C_{7'}$), 126.90 (CH, C_8), 62.41 (CH_2, C_4), 61.16 (CH_2, C_3), 40.97 (CH, C_2), 18.63 (CH_3, C_1).

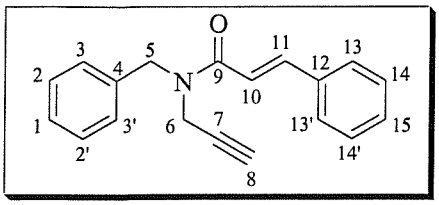
^{13}C NMR (75 MHz, $CDCl_3$): *Cis* Isomer: δ / ppm 139.79 (C, C_5), 128.99 (CH, C_6, $C_{6'}$), 128.33 (CH, C_7, $C_{7'}$), 126.94 (CH, C_8), 62.47 (CH_2, C_4), 61.25 (CH_2, C_3), 34.64 (CH, C_2), 14.61 (CH_3, C_1).

IR (cm^{-1}): 3064 (w), 2953 (s), 2783 (m), 1495 (m), 1207 (w), 1128 (s).

LRMS (EI): *m/z* 189 (M, 58 %), 172 (M-Me, 3 %), 112 (M-Me-Ph, 67 %), 91 ($PhCH_2$, 100 %).

In agreement with literature[215].

6.2.29. *(2E)-N-Propargyl-N-benzyl-3-phenylacrylamide,* **252**



Cinnamic acid (30 mmol, 4.45 g) in dry DCM (50 mL) was cooled to 0 °C before oxalyl chloride (45 mmol, 4.0 mL) was added, followed by DMF (5 drops). The reaction was warmed to r.t. and stirred overnight. The resulting solution had DCM and other volatile material removed *via* low pressure evaporation to give a yellow solid. DCM (20 mL) was added, and the reaction was cooled to 0 °C. 2M NaOH (100 mL) was cooled to 0 °C and added to the acid chloride solution, followed by addition of *N*-benzyl-*N*-propargyl amine (1.5 eq, 45 mmol, 6.34 g) in DCM (10 mL). The reaction was warmed to r.t. and stirred for a further 2 hours. DCM (50 mL) was added. The organic layer was washed with water (3 X 30 mL). The aqueous layer was washed with DCM (3 X 30 mL). The organic layers were combined and washed with 2M HCl (3 X 30 mL). The organic layers was dried ($MgSO_4$) and concentrated *in vacuo* to give a light orange oil. The amide was purified by column chromatography (SiO_2, 1:1 ether to petrol, R_f=0.5) to give the title compound as a yellow oil, 6.9 g, 84 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.71 (2H, d, *J*=15.6 Hz, C_{11}-*H* (major and minor rotamers)), 7.53-7.05 (20H, m, Ar-*H* (major and minor rotamers)), 6.88 (1H, d, *J*=14.3 Hz, C_{10}-*H* (minor rotamer)), 6.76 (1H, d, *J*=15.1 Hz, C_{10}-*H* (major rotamer)), 4.73 (4H, s, C_5-H_2 (major and minor rotamers)), 4.24 (2H, s, C_6-H_2 (major rotamer)), 4.00 (2H, s, C_6-H_2 (minor rotamer)), 2.24 (1H, s, C_8-*H* (minor rotamer)), 2.15 (1H, s, C_8-*H* (major rotamer)).

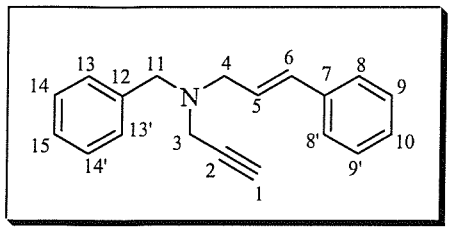
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 166.88 (C, C_9 (major and minor rotamers)), 144.27 (CH, C_{11} (major rotamer)), 143.97 (CH, C_{11} (minor rotamer)), 136.97 (C, C_4 (minor rotamer)), 136.61 (C, C_4 (major rotamer)), 135.27 (C, C_{12} (major and minor rotamers)), 129.99 (CH, *C*-H, (rotamer)), 129.13 (CH, *C*-H, (rotamer)), 128.98 (CH, *C*-H, (rotamer)), 128.59 (CH, *C*-H, (rotamer)), 128.10 (CH, *C*-H, (rotamer)), 127.88 (CH, *C*-H, (rotamer)), 126.94 (CH, *C*-H, (rotamer)), 117.15 (CH, C_{10} (major and minor rotamers), 79.04 (C, C_7 (major rotamer)), 78.74 (C, C_7 (minor rotamer)), 73.18 (CH, C_8 (minor rotamer)), 72.21 (CH, C_8 (major rotamer)), 50.49 (CH_2, C_5 (major rotamer)), 49.19 (CH_2, C_5 (minor rotamer)), 36.78 (CH_2, C_6 (minor rotamer)), 35.05 (CH_2, C_6 (major rotamer)).

IR (cm^{-1}): 3289 (w), 3029 (w), 2923 (w), 2363 (w), 1649 (s), 1605 (s), 1578 (w), 1495 (m), 1451 (m), 1414 (s), 1200 (s), 976 (m).

LRMS (EI): *m/z* 275 (M, 21 %), 274 (M-H, 20 %), 182 (M-H-CH_2Ph, 48 %), 91 ($PhCH_2$, 100 %).

HRMS (EI): $C_{19}H_{17}NO$ requires m/z 275.1310, found 275.1308

6.2.30. *Benzyl-(3-phenyl-allyl)-prop-2-ynyl-amine,* **253**



AlH_3 in THF (0.68 M, 1.3 eq, 2.6 mmol, 3.8 mL) in THF (10 mL) was cooled to 0 °C before (2E)-*N*-Propargyl-*N*-benzyl-3-phenylacrylamide (2 mmol, 550 mg) in THF (10 mL) were added slowly. The reaction was stirred for 30 mins at 0 °C. The reaction was quenched by addition of water (5 mL) at 0 °C. 2M NaOH (30 mL) and ether (30 mL) were added and the organic layer was washed with water (3 X 30 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The amine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 2 % Et_3N, 98 % petrol, R_f=0.2). The amine was purified by distillation (0.1 mmHg, 200 °C) to give the title compound as a pale yellow oil, 311 mg, 60 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.34-7.12 (10H, m, Ar-*H*), 6.53 (1H, d, *J*=15.8 Hz, C_6-*H*), 6.19 (1H, dt, *J*=15.8 Hz, *J*=6.6 Hz, C_5-*H*), 3.62 (2H, s, C_{11}-H_2), 3.29 (2H, d, *J*=2.3 Hz, C_3-H_2), 3.25 (2H, d, *J*=6.6 Hz, C_4-H_2), 2.20 (1H, t, *J*=2.3 Hz, C_1-*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 138.77 (C, C_{12}), 137.24 (C, C_7), 133.19 (CH, C_5), 129.34 (CH, C_{13}, $C_{13'}$), 128.73 (CH, C_9, $C_{9'}$), 128.52 (CH, C_{14}, $C_{14'}$), 127.65 (CH, C_6), 127.37 (CH, C_{10}), 127.33 (CH, C_{15}), 126.55 (CH, C_8, $C_{8'}$), 78.78 (C, C_2), 73.51 (CH, C_1), 57.62 (CH_2, C_{11}), 56.09 (CH_2, C_4), 41.57 (CH_2, C_3).

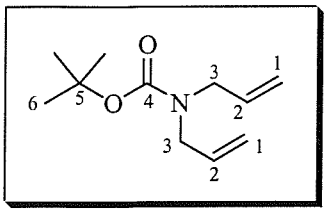
IR (cm^{-1}): 3197 (m), 3026 (w), 2822 (m), 2759 (w), 1600 (w), 1495 (m), 1420 (m), 1389 (w).

LRMS (EI): *m/z* 260 (M-H, 50 %), 170 (M-CH_2Ph, 71 %), 130 (M-CH_2Ph-CH_2CCH, 37 %), 91 ($PhCH_2$, 100 %).

HRMS (ES+): $C_{19}H_{20}N^+$ requires m/z 262.1590, found 262.1591.

6.3. Experimental For Chapter 3

6.3.1. *N*-BOC-*N*,*N*-diallylamine, **303**



BOC-anhydride (21.6 mmol, 4.7 g) in cyclohexane (4 mL) was cooled to 10 °C before *N*,*N*-diallylamine (21.3 mmol, 2.1 g) in cyclohexane (10 mL) was added dropwise. The reaction was stirred at r.t. overnight. The organic reaction mixture was washed with 0.01 M HCl (10 mL), followed by brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. This gave the title compound as a colourless oil, 4.2 g, 100 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 5.85-5.68 (2H, bm, C_2-*H*), 5.17-5.04 (4H, bm, C_1-*H*$_2$), 3.90-3.69 (4H, bs, C_3-*H*$_2$), 1.45 (9H, s, C_6-*H*$_2$).

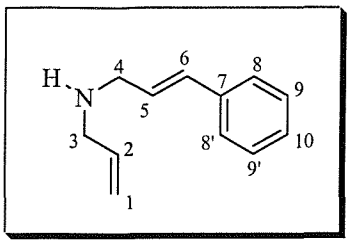
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 155.58 (C, C_4), 134.13 (CH, C_2), 116.68 (CH_2, C_1), 79.75 (C, C_5), 48.83 (CH_2, C_3), 28.53 (CH_3, C_6).

IR (cm^{-1}): 3082 (w), 2978 (w), 1811 (w), 1691 (s), 1643 (w), 1454 (m).

LRMS (EI): *m/z* 141 (M-^{t}Bu, 63 %), 126 (M-^{t}Bu-O, 45 %), 96 (M-101, 35 %).

In agreement with literature[216].

6.3.2. *N-Allyl-3-phenyl allylamine*



Allylamine (5 eq, 100 mmol, 7.5 mL), anhydrous K_2CO_3 (3 eq, 60 mmol, 8.4 g) in acetonitrile (30 mL), cooled to 0 °C before cinnamyl bromide (1 eq, 20 mmol, 3.94 g) in acetonitrile (20 mL) was added dropwise. The reaction was warmed to r.t. and refluxed at 60 °C overnight. Ether (40 mL) and water (40 mL) were added. The organic layer was washed with water (3 X 30 mL) and the aqueous layer was washed with ether (3 X 30 mL). The ether layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, 5% NEt_3 in petrol), followed by Kügelrohr distillation (0.1 mmHg, 140 °C) gave the title compound as a colourless oil, 3.2 g, 90 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.43 (2H, d, *J*=7.3 Hz, C_8-*H*, $C_{8'}$-*H*), 7.37 (2H, t, *J*=7.3 Hz, C_9-*H*, $C_{9'}$-*H*), 7.28 (2H, t, *J*=7.3 Hz, C_{10}-*H*), 6.59 (1H, d, *J*=15.8 Hz, C_6-*H*), 6.31 (1H, dt, *J*=15.8 Hz, *J*=6.3 Hz, C_5-*H*), 5.99 (1H, ddt, *J*=17.1 Hz, *J*=11.0 Hz, *J*=5.8 Hz, C_2-*H*), 5.26 (1H, dd, *J*=17.1 Hz, *J*=1.3 Hz, C_1-*H* (trans)), 5.17 (1H, dd, *J*=11.0 Hz, *J*=1.3 Hz, C_1-*H* (cis)), 3.48 (2H, dd, *J*=6.3 Hz, *J*=1.0 Hz, C_4-H_2), 3.36 (2H, d, *J*=5.8 Hz, C_3-H_2), 1.53-1.41 (1H, bs, N-*H*).

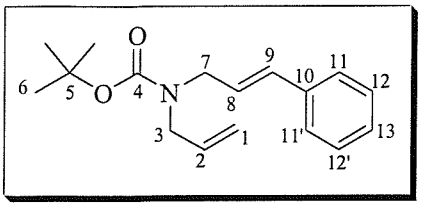
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 137.29 (C, C_7), 136.89 (CH, C_2), 131.52 (CH, C_5), 128.68 (CH, C_9, $C_{9'}$), 128.53 (CH, C_6), 127.49 (CH, C_{10}), 126.41 (CH, C_8, $C_{8'}$), 116.15 (CH_2, C_1), 51.96 (CH_2, C_3) 51.35 (CH_2, C_4).

IR (cm^{-1}): 3025 (w), 2811 (w), 1643 (w), 1448 (m), 1114 (m), 965 (s).

LRMS (EI): *m/z* 173 (M, 45 %), 158 (M-H-CH_2, 28 %), 130 (M-H-allyl, 70 %).

HRMS (ES+): $C_{12}H_{16}N^+$ requires m/z 174.1283, found 174.1270.

6.3.3. *N-BOC-allyl-(3-phenyl-allyl)-amine,* **305**



BOC-anhydride (20.3 mmol, 4.43 g) in cyclohexane (4 mL) cooled to 10 °C before *N*-allyl-(3-phenyl-allyl)-amine (20 mmol, 3.46 g) in cyclohexane (10 mL) was added dropwise. The reaction was stirred at r.t. overnight. The resulting yellow solution was washed with 0.01M HCl (10 mL), followed by brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The carbamate was purified by column chromatography (SiO_2, 95% petrol / 5% EtOAc) to give the title compounds as a pale yellow oil, 4.0 g, 72 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.42-7.21 (5H, m, Ar-*H*), 6.46 (1H, d, *J*=15.8 Hz, C_9-*H*), 6.24-6.08 (1H, m, C_8-*H*), 5.89-5.72 (1H, m, C_2-*H*), 5.26-5.06 (2H, m, C_1-H_2), 4.11-3.75 (4H, m, C_3-H_2, C_7-H_2), 1.49 (9H, s, 3 X C_6-H_3).

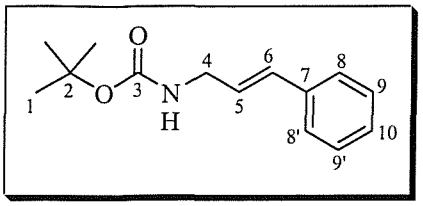
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 155.61 (C, C_4), 136.94 (C, C_{10}), 134.17 (CH, C_2), 132.28 (CH, C_9 (rotamer)), 131.90 (CH, C_9 (rotamer)), 128.73 (d), 127.71 (d), 126.50 (d), 125.74 (CH, C_8), 116.62 (CH_2, C_1 (rotamer)), 116.39 (CH_2, C_1 (rotamer)), 79.90 (C, C_5), 48.87 (CH_2, C_3), 48.39 (CH_2, C_7), 28.59 (CH_3, C_6).

IR (cm^{-1}): 3029 (w), 2976 (w), 2930 (w), 1690 (s), 1495 (w), 1453 (m), 1405 (m).

LRMS (EI): *m/z* 217 (M+H-^{t}Bu, 8 %), 172 (M-BOC, 9 %), 115 (M-158, 58 %).

HRMS (ES+): $C_{17}H_{23}NNaO_2^+$ requires m/z 296.1626, found 296.1618.

6.3.4. *N-BOC-(3-benzyl-allyl)-amine,* **308**



Cp_2ZrCl_2 (1 mmol, 292 mg) in THF (5 mL) was cooled to -78 °C before BuLi (2 mmol, 0.8 mL) was added slowly. The reaction was stirred for 20 mins at -78 °C before *N*-BOC-allyl-(3-benzyl-allyl)-amine (1 mmol, 273 mg) in THF (5 mL) was added slowly. The reaction was warmed to r.t. and stirred for 24 hours. MeOH (5 mL) and $NaHCO_3$ solution (5 mL) were added and stirred overnight. Ether (50 mL) and water (50 mL) were added. The organic layer was washed with water (3 X 30 mL). The aqueous layer was washed with ether (3 X 30 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The carbamate was recrystallised from hot hexane to give the title compound as yellow crystals, 70 mg, 30 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.30-7.11 (5H, m, Ar-*H*), 6.42 (1H, d, *J*=15.8 Hz, C_6-*H*), 6.10 (1H, dt, *J*=15.8 Hz, *J*=6.0 Hz, C_5-*H*), 4.73-4.52 (1H, bs, N-*H*), 3.88-3.73 (2H, bs, C_4-H_3), 1.40-1.37 (9H, bs, 3 X C_1-H_3).

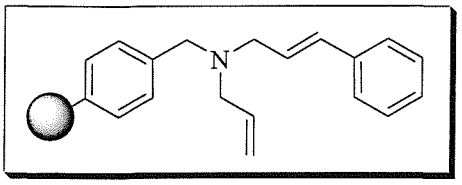
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 155.93 (C, C_3), 136.86 (C, C_7), 131.57 (CH, C_6), 128.70 (CH, C_9, $C_{9'}$), 127.73 (CH, C_{10}), 126.54 (CH, C_5), 126.51 (CH, C_8, $C_{8'}$), 79.61 (C, C_2 (rotamer)), 79.50 (C, C_2 (rotamer)), 42.90 (CH_2, C_4), 28.57 (CH_3, C_1).

IR (cm^{-1}): 3365 (w), 2979 (w), 2356 (w), 1699 (s), 1600 (w), 1482 (m).

LRMS (EI): *m/z* 177 (M-^{t}Bu, 24 %), 159 (M-^{t}Bu-O, 49 %), 130 (M-^{t}Bu-CO_2, 47 %), 116 (M-^{t}Bu-NCO_2, 40 %).

In agreement with literature[217].

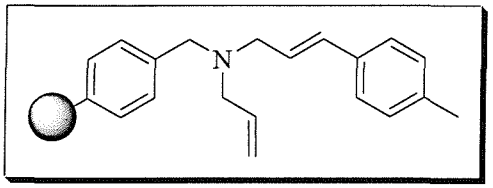
6.3.5. *Resin-bound N-Allyl-N-benzyl-N-[(2E)-3-phenylprop-2-enyl] amine*, **313a**



In a dry peptide tube, resin-bound (2E)-*N*-Allyl-*N*-benzyl-3-phenylacrylamide (0.5 mmol, 329 mg) was suspended in THF (40 mL). AlH_3 (0.55 M solution in THF, 1.3 eq, 0.65 mmol, 1.2 mL) was added under an argon atmosphere. The reaction was shaken overnight, filtered and washed under argon with dry THF and ether. The resin was dried under vacuum for 2 hours.

IR (cm^{-1}): 3025 (w), 2922 (w), 1645 (w), 1601 (w), 1493 (m), 1452 (m), 1067 (m).

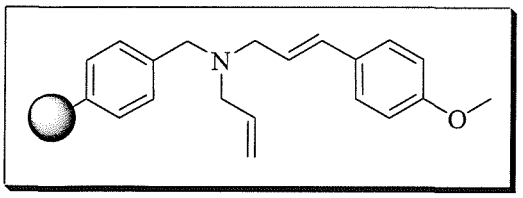
6.3.6. *Resin-bound N-Allyl-N-benzyl-N-[(2E)-3-(4-methylphenyl) prop-2-enyl]amine*, **313b**



In a dry peptide tube, resin-bound (2E)-*N*-Allyl-*N*-benzyl-3-(4-methylphenyl)acryl amide (0.5 mmol, 338 mg) was suspended in THF (40 mL). AlH_3 (0.55 M solution in THF, 1.3 eq, 0.65 mmol, 1.2 mL) was added under an argon atmosphere. The reaction was shaken overnight, filtered and washed under argon with dry THF and ether. The resin was dried under vacuum for 2 hours.

IR (cm^{-1}): 3025 (w), 2921 (w), 1644 (w), 1602 (w), 1493 (m), 1452 (m), 1067 (m).

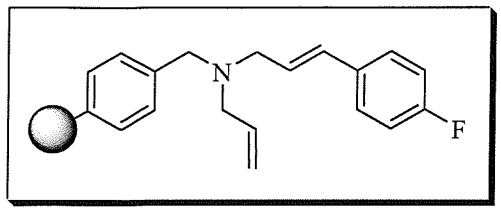
6.3.7. *Resin-bound N-Allyl-N-benzyl-N-[(2E)-3-(4-methoxyphenyl) prop-2-enyl]amine*, **313c**



In a dry peptide tube, resin-bound (2E)-*N*-Allyl-*N*-benzyl-3-(4-methoxyphenyl)acryl amide (0.5 mmol, 338 mg) was suspended in THF (40 mL). AlH_3 (0.55 M solution in THF, 1.3 eq, 0.65 mmol, 1.2 mL) was added under an argon atmosphere. The reaction was shaken overnight, filtered and washed under argon with dry THF and ether. The resin was dried under vacuum for 2 hours.

IR (cm^{-1}): 3026 (w), 2923 (w), 1643 (w), 1607 (w), 1510 (s), 1452 (m), 1247 (s).

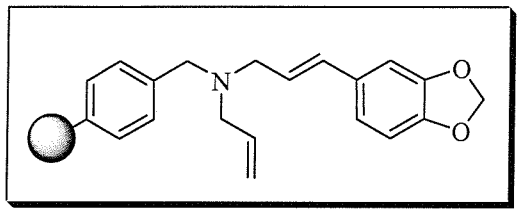
6.3.8. *Resin-bound N-Allyl-N-benzyl-N-[(2E)-3-(4-fluorophenyl) prop-2-enyl]amine*, **313d**



In a dry peptide tube, resin-bound (2E)-*N*-Allyl-*N*-benzyl-3-(4-fluorophenyl)acryl amide (0.5 mmol, 323 mg) was suspended in THF (40 mL). AlH_3 (0.55 M solution in THF, 1.3 eq, 0.65 mmol, 1.2 mL) was added under an argon atmosphere. The reaction was shaken overnight, filtered and washed under argon with dry THF and ether. The resin was dried under vacuum for 2 hours.

IR (cm^{-1}): 3025 (w), 2926 (w), 1649 (w), 1601 (w), 1508 (m), 1493 (m), 1452 (m), 1067 (m).

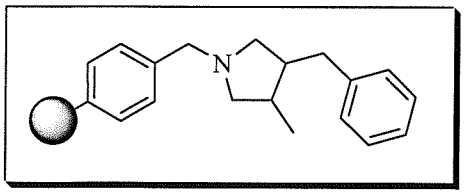
6.3.9. *Resin-bound N-Allyl-N-[(2E)-3-(1,3-benzodioxol-5-yl)prop-2-enyl]-N-benzylamine*, **313e**



In a peptide tube, resin-bound (2E)-*N*-Allyl-3-(1,3-benzodioxol-5-yl)-*N*-benzylacrylamide (0.5 mmol, 331 mg) was suspended in THF (40 mL), before AlH_3 (0.55 M solution in THF, 1.3 eq, 0.65 mmol, 1.2 mL) was added. The resin was shaken overnight, filtered and washed with dry THF and ether. The resin was dried under vacuum for 2 hours.

IR (cm^{-1}): 3025 (w), 2924 (w), 1645 (w), 1602 (w), 1490 (m), 1446 (m), 1248 (m), 1039 (s).

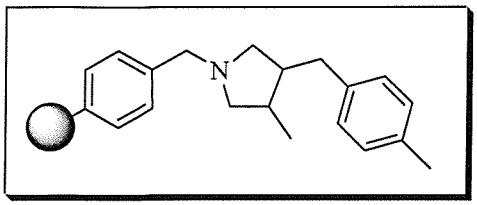
6.3.10. *Resin-bound 1,3-Dibenzyl-4-methylpyrrolidine*, **314a**



Resin-bound *N*-Allyl-*N*-benzyl-*N*-[(2E)-3-phenylprop-2-enyl] amine (0.5 mmol) was suspended in THF (40 mL). In a separate flask, Cp_2ZrCl_2 (3 eq, 1.5 mmol, 438 mg) in THF (10 mL) was cooled to -78 °C before BuLi (3 mmol, 1.2 mL) was added. The reaction was stirred for 30 mins at -78 °C before being added *via* cannular to the resin. The reaction was warmed to r.t. and shaken for 20 hours. The resulting burgundy coloured resin mixture was quenched with MeOH (5 mL) and sat. $NaHCO_3$ (5 mL). The resin was shaken overnight, filtered and washed with hot water, MeOH, DCM and ether. The resin was dried under vacuum for 2 hours.

IR (cm^{-1}): 2923 (w), 1573 (m), 1493 (w), 1452 (w), 1360 (m), 1029 (w).

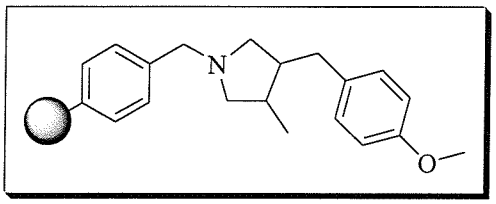
6.3.11. *Resin-bound 1-Benzyl-3-methyl-4-(4-methylbenzyl) pyrrolidine,* **314b**



Resin-bound *N*-Allyl-*N*-benzyl-*N*-[(2E)-3-(4-methylphenyl)prop-2-enyl]amine (0.5 mmol) was suspended in THF (40 mL). In a separate flask, Cp_2ZrCl_2 (3 eq, 1.5 mmol, 438 mg) in THF (10 mL) was cooled to -78 °C before BuLi (3 mmol, 1.2 mL) was added. The reaction was stirred for 30 mins at -78 °C before being added *via* cannular to the resin. The reaction was warmed to r.t. and shaken for 20 hours. The resulting burgundy coloured resin mixture was quenched with MeOH (5 mL) and sat. $NaHCO_3$ (5 mL). The resin was shaken overnight, filtered and washed with hot water, MeOH, DCM and ether. The resin was dried under vacuum for 2 hours.

IR (cm^{-1}): 2923 (w), 1567 (m), 1493 (w), 1451 (w), 1367 (m), 1020 (w).

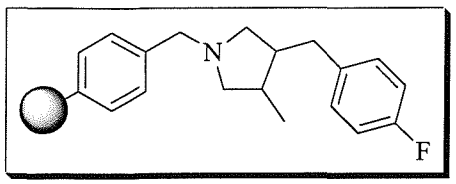
6.3.12. *Resin-bound 1-Benzyl-3-(4-methoxybenzyl)-4-methyl pyrrolidine,* **314c**



Resin-bound *N*-Allyl-*N*-benzyl-*N*-[(2E)-3-(4-methoxyphenyl) prop-2-enyl]amine (0.5 mmol) was suspended in THF (40 mL). In a separate flask, Cp_2ZrCl_2 (3 eq, 1.5 mmol, 438 mg) in THF (10 mL) was cooled to -78 °C before BuLi (3 mmol, 1.2 mL) was added. The reaction was stirred for 30 mins at -78 °C before being added *via* cannular to the resin. The reaction was warmed to r.t. and shaken for 20 hours. The resulting burgundy coloured resin mixture was quenched with MeOH (5 mL) and sat. $NaHCO_3$ (5 mL). The resin was shaken overnight, filtered and washed with hot water, MeOH, DCM and ether. The resin was dried under vacuum for 2 hours.

IR (cm^{-1}): 2921 (w), 1569 (m), 1511 (m), 1493 (w), 1452 (w), 1361 (m), 1034 (w).

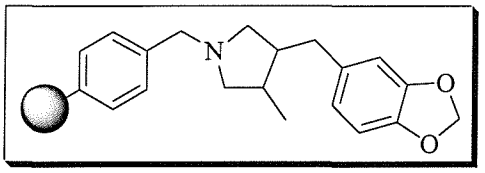
6.3.13. *Resin-bound 1-Benzyl-3-(4-fluorobenzyl)-4-methylpyrrolidine,* **314d**



Resin-bound *N*-Allyl-*N*-benzyl-*N*-[(2E)-3-(4-fluorophenyl)prop-2-enyl]amine (0.5 mmol) was suspended in THF (40 mL). In a separate flask, Cp_2ZrCl_2 (3 eq, 1.5 mmol, 438 mg) in THF (10 mL) was cooled to -78 °C before BuLi (3 mmol, 1.2 mL) was added. The reaction was stirred for 30 mins at -78 °C before being added *via* cannular to the resin. The reaction was warmed to r.t. and shaken for 20 hours. The resulting burgundy coloured resin mixture was quenched with MeOH (5 mL) and sat. $NaHCO_3$ (5 mL). The resin was shaken overnight, filtered and washed with hot water, MeOH, DCM and ether. The resin was dried under vacuum for 2 hours.

IR (cm^{-1}): 2923 (w), 1566 (m), 1509 (m), 1493 (w), 1452 (w), 1359 (m), 1028 (m).

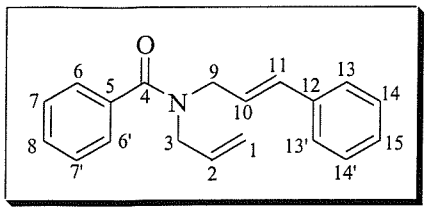
6.3.14. *Resin-bound 3-(1,3-benzodioxol-5-ylmethyl)-1-benzyl-4-methylpyrrolidine,* **314e**



Resin-bound *N*-Allyl-*N*-[(2E)-3-(1,3-benzodioxol-5-yl)prop-2-enyl]-*N*-benzylamine (0.5 mmol) was suspended in THF (40 mL). In a separate flask, Cp_2ZrCl_2 (3 eq, 1.5 mmol, 438 mg) in THF (10 mL) was cooled to -78 °C before BuLi (3 mmol, 1.2 mL) was added. The reaction was stirred for 30 mins at -78 °C before being added *via* cannular to the resin. The reaction was warmed to r.t. and shaken for 20 hours. The resulting burgundy coloured resin mixture was quenched with MeOH (5 mL) and sat. $NaHCO_3$ (5 mL). The resin was shaken overnight, filtered and washed with hot water, MeOH, DCM and ether. The resin was dried under vacuum for 2 hours.

IR (cm^{-1}): 2921 (w), 1563 (m), 1555 (m), 1490 (w), 1443 (w), 1360 (m), 1039 (m).

6.3.15. *N-Allyl-N-(3-phenyl-allyl)-benzamide*, **315**



N-Allyl-(3-phenyl-allyl)-amine (35 mmol, 6.09 g), benzoyl chloride (35 mmol, 4.8 mL) in 2M NaOH (50 mL) was stirred overnight at r.t.. The reaction was quenched with water (30 mL) and ether (30 mL) was added. The ether layer was washed with water (3 X 20 mL). The aqueous layer was washed with ether (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was dissolved in ether (20 mL) and washed with 2M HCl (4 X 20 mL) to remove unreacted amine. The organic layer was collected, dried ($MgSO_4$) and concentrated *in vacuo*. The amide was purified by column chromatography (SiO_2, 1:3 ether to petrol, R_f=0.2) to give the title compound as a yellow solid, 7.7 g, 79 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.34-7.08 (20H, m, Ar-*H* (rotamer signals)), 6.53-6.23 (2H, m, C_{11}-*H* (rotamer signals)), 6.22-6.05 (1H, bs, C_{10}-*H* (rotamer signal)), 6.04-5.85 (1H, bs, C_{10}-*H* (rotamer signal)), 5.85-5.69 (1H, bs, C_2-*H* (rotamer signal)), 5.68-5.53 (1H, bs, C_2-*H* (rotamer signal)), 5.15-5.03 (4H, m, C_1-H_2 (rotamer signals)), 4.22-4.11 (2H, bs, C_3-H_2 (rotamer signal)), 4.10-3.98 (2H, bs, C_3-H_2 (rotamer signal)), 3.95-3.80 (2H, bs, C_9-H_2 (rotamer signal)), 3.79-3.68 (2H, bs, C_9-H_2 (rotamer signal)),

^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 171.93 (C, C_4), 136.47 (C, C_{12}), 133.45 (C, C_5), 133.10 (CH, C_2), 129.81 (CH, C_8), 128.80 (CH, C_{14}, $C_{14'}$), 128.57 (CH, C_7, $C_{7'}$), 128.00 (CH, C_{11}, C_{15}), 126.84 (CH, C_6, $C_{6'}$), 126.60 (CH, C_{13}, $C_{13'}$), 124.60 (d. C_{10}), 117.85 (CH_2, C_1), 50.92 (CH_2, C_3 (rotamer signal)), 50.65 (CH_2, C_3 (rotamer signal)), 47.25 (CH_2, C_9 (rotamer signal)), 46.79 (CH_2, C_9 (rotamer signal)).

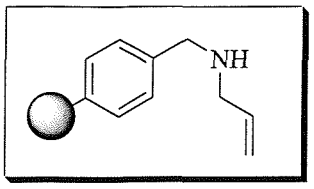
IR (cm^{-1}): 3078 (w), 3033 (w), 2923 (w), 1625 (s), 1598 (m), 1575 (m). 1493 (w).

LRMS (EI): *m/z* 277 (M, 39 %), 236 (M-allyl, 70 %), 172 (M-PhCO, 47 %), 105 (PhCO, 100 %).

M.P.: 56-58 °C

Microanalysis: Found: C 82.00, H 6.82, N 4.89. Requires: C 82.28, H 6.90, N 5.05.

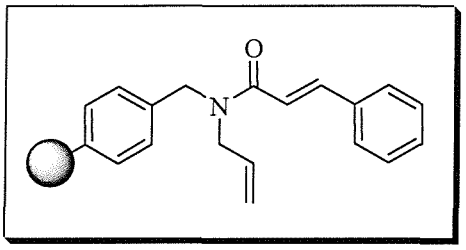
6.3.16. *Resin-bound N-Allyl-N-benzyl-amine*, **316**



Merrifield resin (Ex-Aldrich, 1.6 mmol g^{-1}, 1 % Coss-Linking, 30 mmol, 18.75 g) and allylamine (600 mmol, 45 mL) in THF (120 mL) were heated at 75 °C overnight. The resin was filtered and washed with dry distilled THF (10 X 60 mL) only. The resin was dried in a vacuum oven at 40 °C for 5 days to give a colourless resin.

IR (cm^{-1}): 3082 (w), 3025 (w), 2919 (m), 2848 (w), 1601 (w), 1510 (m), 1493 (m), 1452 (s).

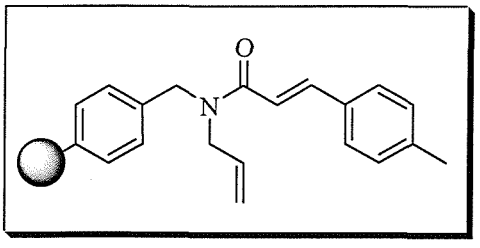
6.3.17. *Resin-bound (2E)-N-Allyl-N-benzyl-3-phenylacrylamide*, **317a**



Cinnamic acid (20 mmol, 2.96 g) and HOBt (20 mmol, 2.70 g) were stirred for 15 mins in DMF (30 mL). The reaction flask was cooled to 0 °C before DIC (20 mmol, 3.1 mL) was added. The flask was warmed to RT before stirring for a further 15 mins. The reaction mixture was then poured into a plastic filter vessel containing resin-bound *N*-Allyl-*N*-benzylamine, suspended in DMF (30 mL). The reaction was agitated for 1 week, filtered and washed with hot DMF, MeOH, DCM and ether. The resin was dried using a vacuum oven for 2 days to give a pale yellow resin.

IR (cm^{-1}): 3024 (w), 2925 (m), 1650 (s), 1605 (s), 1510 (m), 1451 (s), 1412 (s), 1202 (s).

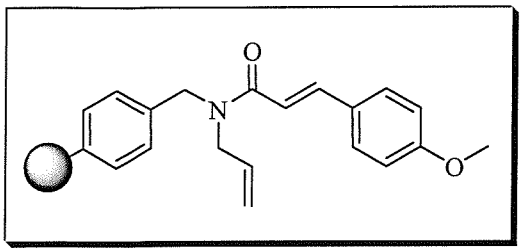
6.3.18. *Resin-bound (2E)-N-Allyl-N-benzyl-3-(4-methylphenyl)acryl amide*, **317b**



4-Methylcinnamic acid (20 mmol, 3.24 g) and HOBt (20 mmol, 2.70 g) were stirred for 15 mins in DMF (30 mL). The reaction flask was cooled to 0 °C before DIC (20 mmol, 3.1 mL) was added. The flask was warmed to RT before stirring for a further 15 mins. The reaction mixture was then poured into a plastic filter vessel containing resin-bound *N*-Allyl-*N*-benzylamine, suspended in DMF (30 mL). The reaction was agitated for 1 week, filtered and washed with hot DMF, MeOH, DCM and ether. The resin was dried using a vacuum oven for 2 days to give a pale yellow resin.

IR (cm^{-1}): 3024 (w), 2924 (m), 1650 (s), 1605 (s), 1512 (m), 1452 (s), 1411 (s), 1200 (s).

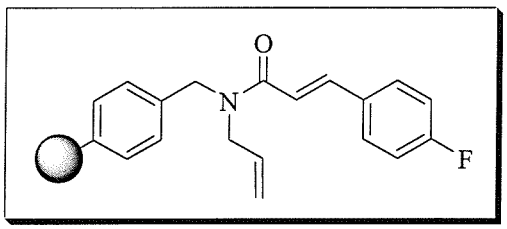
6.3.19. *Resin-bound (2E)-N-Allyl-N-benzyl-3-(4-methoxyphenyl) acrylamide,* **317c**



4-Methoxycinnamic acid (20 mmol, 3.56 g) and HOBt (20 mmol, 2.70 g) were stirred for 15 mins in DMF (30 mL). The reaction flask was cooled to 0 °C before DIC (20 mmol, 3.1 mL) was added. The flask was warmed to RT before stirring for a further 15 mins. The reaction mixture was then poured into a plastic filter vessel containing resin-bound *N*-Allyl-*N*-benzylamine, suspended in DMF (30 mL). The reaction was agitated for 1 week, filtered and washed with hot DMF, MeOH, DCM and ether. The resin was dried using a vacuum oven for 2 days to give a pale yellow resin.

IR (cm^{-1}): 3025 (w), 2922 (m), 1650 (s), 1601 (s), 1511 (s), 1452 (s), 1411 (m), 1253 (s), 1203 (s).

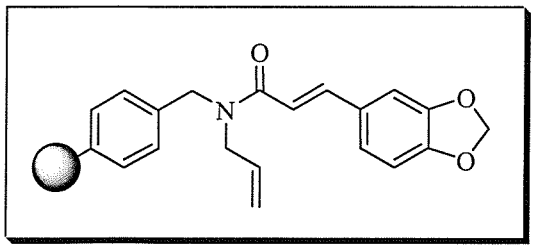
6.3.20. *Resin-bound (2E)-N-Allyl-N-benzyl-3-(4-fluorophenyl)acryl amide,* **317d**



4-Fluorocinnamic acid (20 mmol, 3.32 g) and HOBt (20 mmol, 2.70 g) were stirred for 15 mins in DMF (30 mL). The reaction flask was cooled to 0 °C before DIC (20 mmol, 3.1 mL) was added. The flask was warmed to RT before stirring for a further 15 mins. The reaction mixture was then poured into a plastic filter vessel containing resin-bound *N*-Allyl-*N*-benzylamine, suspended in DMF (30 mL). The reaction was agitated for 1 week, filtered and washed with hot DMF, MeOH, DCM and ether. The resin was dried using a vacuum oven for 2 days to give a pale orange resin.

IR (cm^{-1}): 3026 (w), 2923 (m), 1650 (s), 1601 (s), 1509 (m), 1452 (s), 1416 (s), 1203 (s).

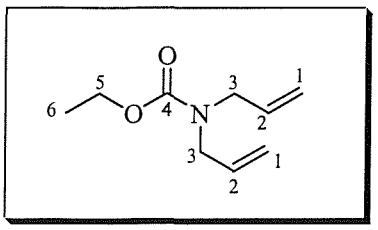
6.3.21. *Resin-bound (2E)-N-Allyl-3-(1,3-benzodioxol-5-yl)-N-benzyl acrylamide,* **317e**



3-Benzo[1,3]dioxol-5-yl-acrylic acid (20 mmol, 3.84 g) and HOBt (20 mmol, 2.70 g) were stirred for 15 mins in DMF (30 mL). The reaction flask was cooled to 0 °C before DIC (20 mmol, 3.1 mL) was added. The flask was warmed to RT before stirring for a further 15 mins. The reaction mixture was then poured into a plastic filter vessel containing resin-bound *N*-Allyl-*N*-benzylamine, suspended in DMF (30 mL). The reaction was agitated for 1 week, filtered and washed with hot DMF, MeOH, DCM and ether. The resin was dried using a vacuum oven for 2 days to give a pale yellow resin.

IR (cm^{-1}): 3025 (w), 2922 (m), 1650 (s), 1601 (s), 1490 (s), 1446 (s), 1412 (s), 1240 (s).

6.3.22. *Diallyl-carbamic acid ethyl ester*, **318**



N-benzyl-diallyl amine (1 eq, 1 mmol, 187 mg) and ethyl chloroformate (3 eq, 3 mmol, 0.29 mL) in DCM (5 mL) were refluxed for 2 hours under an argon atmosphere. The contents of the flask were transferred to a round bottom flask, and the DCM was removed *in vacuo*. The benzyl chloride by-product (Rf=31/35) was separated from the carbamate product (Rf=11/35) using column chromatography (SiO_2, 1:9 ether to petrol), before being purified by Kügelrohr distillation (125 °C, 0.1 mm Hg) to give the title compound as a colourless oil, 110 mg, 65 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 5.76-5.63 (2H, m, 2 X C_2-*H*), 5.11-5.00 (4H, m, C_1-*H*$_2$), 4.08 (2H, q, *J*=7.0 Hz, C_5-*H*$_2$), 3.86-3.70 (4H, bs, 2 X C_3-*H*$_2$), 1.18 (3H, t, *J*=7.0 Hz, C_6-*H*$_3$).

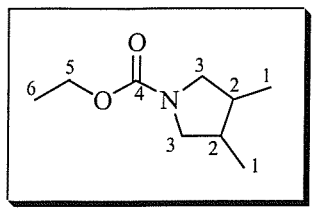
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 156.45 (C, C_4), 133.87 (CH, C_2), 117.03 (CH_2, C_1, rotamer signal), 116.80 (CH_2, C_1, rotamer signal), 61.53 (CH_2, C_5), 49.03 (CH_2, C_3, rotamer signal), 48.68 (CH_2, C_3, rotamer signal), 14.85 (CH_3, C_6).

IR (cm^{-1}): 3082 (w), 2982 (w), 2934 (w), 1695 (s), 1644 (w), 1412 (m), 1298 (w), 1238 (s), 1156 (m), 1024 (w), 921 (m).

LRMS (EI): *m/z* 169 (M, 21 %), 154 (M-Me, 59 %), 140 (M-Et, 40 %), 124 (M-Et-O, 22 %), 110 (M-Et-O-CH_2, 17 %), 96 (M-Et-O-CH_2-CH_2, 44 %).

In agreement with literature[218].

6.3.23. *N-Ethyl 3,4-dimethylpyrrolidine-1-carboxylate*, **320**



Resin-bound *N*-benzyl-diallylamine (0.5 mmol) was suspended in THF (5 mL) and cooled to - 78 °C. In a separate 25 mL Schlenk flask, Cp_2ZrCl_2 (2 eq, 1 mmol, 292 mg) in THF (5 mL) was cooled to - 78 °C before BuLi (2 mmol, 0.8 mL) was added slowly. The reaction was stirred for 30 mins, transferred *via* cannular to the suspended resin and then warmed to r.t. The taps on the Schlenk flask were then sealed, and the reaction mixture was shaken for 36 hours, before being quenched under an argon atmosphere *via* addition of MeOH (5 mL) and saturated $NaHCO_3$ solution (5 mL). The reaction was shaken overnight to ensure complete zirconacycle quench. The resin was filtered and washed thoroughly with hot water, MeOH, DCM and ether. The resin was transferred to a Schlenk flask and dried under vacuum as before. Dry DCM (10 mL) and ethyl chloroformate (3 eq, 1.5 mmol, 0.15 mL) were added to the resin, before being refluxed for 2 hours. The resin was filtered, washed with DCM (3 X 50 mL) and the washings were concentrated *in vacuo*. This gave the title compound as a colourless oil, 74 mg, 86 % as a 2:1 mixture of *trans* to *cis* diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 4.05 (4H, q, *J*=7.0 Hz, C_5-$\underline{H}_2$ (*cis* and *trans* rotamers)), 3.63-3.49 (2H, m, 2 X C_3-$\underline{H}$ (*trans* rotamer)), 3.45-3.33 (2H, m, 2 X C_3-$\underline{H}$ (*cis* rotamer)), 3.04 (1H, dd, *J*=10.5 Hz, *J*=5.5 Hz, C_3-$\underline{H}$ (*cis* rotamer)), 2.96 (1H, dd, *J*=10.5 Hz, *J*=5.5 Hz, C_3-$\underline{H}$ (*cis* rotamer)), 2.88-2.76 (2H, m, 2 X C_3-$\underline{H}$ (*trans* rotamer)), 2.22-2.08 (2H, m, 2 X C_2-$\underline{H}$ (*cis* rotamers)), 1.72-1.56 (2H, m, 2 X C_2-$\underline{H}$ (*trans* rotamers)), 1.18 (6H, t, *J*=7.0 Hz, 2 X C_6-$\underline{H}_3$ (*cis* and *trans* rotamers)), 0.98-0.91 (6H, bs, 2 X C_1-$\underline{H}_3$ (*trans* rotamers)), 0.86 (6H, d, *J*=6.8 Hz, 2 X C_1-$\underline{H}_3$ (*cis* rotamers)).

^{13}C NMR (100 MHz, $CDCl_3$): ***Trans*** **Isomer** δ / ppm 155.23 (C, C_4), 60.94 (CH_2, C_5), 53.66 (CH_2, C_3 (rotamer), 53.41 (CH_2, C_3 (rotamer), 40.81 (CH, C_2 (rotamer), 40.04 (CH, C_2 (rotamer), 15.81 (CH_3, C_1), 15.03 (CH_3, C_6).

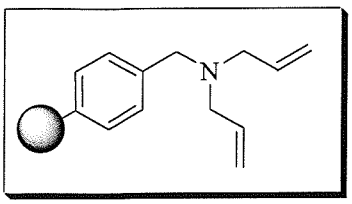
^{13}C NMR (100 MHz, $CDCl_3$): ***Cis*** **Isomer** δ / ppm 155.23 (C, C_4), 60.94 (CH_2, C_5), 52.51 (CH_2, C_3 (rotamer), 52.14 (CH_2, C_3 (rotamer), 36.36 (CH, C_2 (rotamer), 35.57 (CH, C_2 (rotamer), 15.03 (CH_3, C_6), 13.27 (CH_3, C_1 (rotamer), 13.24 (CH_3, C_1 (rotamer).

IR (cm^{-1}): 2962 (m), 2876 (w), 2357 (w), 1791 (w), 1698 (s), 1418 (s).

LRMS (EI): *m/z* 171 (M, 40 %), 142 (M-ethyl, 75 %), 126 (M-ethyl-O, 46 %).

HRMS (EI): $C_9H_{17}NO_2$ requires m/z 171.1259, found 171.1261

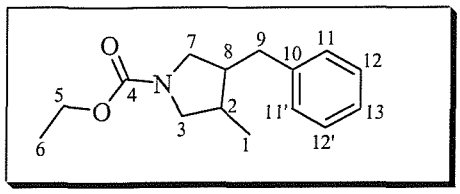
6.3.24. *Resin-bound N-Diallyl-N-benzyl-amine*, **322**



Merrifield resin (1 mmol, 625 mg) and *N*-diallyl amine (4 mmol, 389 mg) in NMP (10 mL) were heated at 120 °C overnight. The resin was filtered and washed with dry distilled THF (3 X 10 mL) only. The resin was dried at 0.1 mm Hg for 2 hours to give a pale yellow resin.

IR (cm^{-1}): 2922 (w), 1509 (w), 1492 (w), 1450 (w), 1276 (w).

6.3.25. *N-Ethyl 3-benzyl-4-methylpyrrolidine-1-carboxylate*, **324a**



N-1,3-dibenzyl-4-methylpyrrolidine (1 mmol, 265 mg) and ethyl chloroformate (3 mmol, 0.29 mL) in DCM (10 mL) were heated at 65 °C for 3 hours. The DCM was removed *in vacuo* and the resulting brown oil was purified by column chromatography (SiO_2, 1:1 ether to petrol, R_f=0.6). The carbamate was distilled by Kügelrohr distillation (0.1 mm Hg, 210 °C) to give the title compound as a colourless oil, 155 mg, 63 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.26-7.04 (10H, m, Ar-*H* (*cis* and *trans* rotamers)), 4.08-3.97 (4H, m, C_5-*H*$_2$ (*cis* and *trans* rotamers)), 3.66-3.50 (1H, m, C_3-*H* (*trans* rotamer)), 3.48-3.21 (2H, m, C_3-*H* (*trans* rotamer), C_3-*H* (*cis* rotamer)), 3.19-2.77 (5H, m, C_3-*H* (*cis* rotamer), C_7-*H* (*cis* rotamer), C_7-*H* (*cis* rotamer), C_7-*H* (*trans* rotamer), C_7-*H* (*trans* rotamer)), 2.71-2.62 (2H, m, C_9-*H*$_2$ (*cis* rotamers)), 2.48-2.31 (2H, m, C_9-*H*$_2$ (*trans* rotamers)), 2.28-2.17 (2H, m, C_2-*H*, C_8-*H* (*cis* rotamers)), 1.99-1.76 (2H, m, C_2-*H*, C_8-*H* (*trans* rotamers)), 1.21-1.10 (6H, m, C_6-*H*$_3$ (*cis* and *trans* rotamers)), 1.01-0.96 (3H, m, C_1-*H*$_3$ (*trans* rotamers)), 0.95 (3H, d, *J*=7.0 Hz, C_1-*H*$_3$ (*cis* rotamers)).

^{13}C NMR (100 MHz, $CDCl_3$): *Trans* Isomer: δ / ppm 155.21 (C, C_4), 140.25 (C, C_{10}, (*trans* rotamer)), 140.11 (C, C_{10}, (*trans* rotamer)), 128.82 (CH, C_{11}, $C_{11'}$), 128.61 (CH, C_{12}, $C_{12'}$), 126.33 (CH, C_{13}), 60.97 (CH_2, C_5), 53.42 (CH_2, C_3, (*trans* rotamer)), 53.19 (CH_2, C_3, (*trans* rotamer)), 51.73 (CH_2, C_7, (*trans* rotamer)), 51.35 (CH_2, C_7, (*trans* rotamer)), 47.64 (CH, C_8, (*trans* rotamer)), 46.94 (CH, C_8, (*trans* rotamer)), 38.73 (CH, C_2, (*trans* rotamer)), 38.18 (CH_2, C_9, (*trans* rotamer)), 38.09 (CH_2, C_9, (*trans* rotamer)), 38.02 (CH, C_2, (*trans* rotamer)), 16.44 (CH_3, C_1), 15.00 (CH_3, C_6).

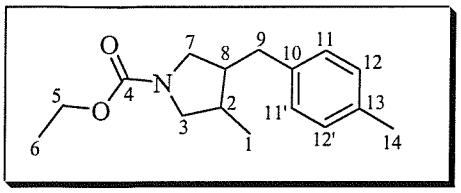
^{13}C NMR (100 MHz, $CDCl_3$): *Cis* Isomer: δ / ppm 155.57 (C, C_4), 140.62 (C, C_{10}, (*cis* rotamer)), 140.56 (C, C_{10}, (*cis* rotamer)), 128.77 (CH, C_{11}, $C_{11'}$), 128.65 (CH, C_{12}, $C_{12'}$), 126.25 (CH, C_{13}), 60.99 (CH_2, C_5), 53.33 (CH_2, C_3), 49.41 (CH_2, C_7, (*cis* rotamer)), 49.07 (CH_2, C_7, (*cis* rotamer)), 43.82 (CH, C_8, (*cis* rotamer)), 43.16 (CH, C_8, (*cis* rotamer)), 35.48 (CH, C_2, (*cis* rotamer)), 34.75 (CH, C_2, (*cis* rotamer)), 34.33 (CH_2, C_9), 15.00 (CH_3, C_6), 13.70 (CH_3, C_1, (*cis* rotamer)), 13.63 (CH_3, C_1, (*cis* rotamer)).

IR (cm^{-1}): 2932 (w), 2872 (w), 1693 (s), 1420 (s), 1349 (m).

LRMS (EI): *m/z* 247 (M, 42 %), 202 (M-Et-O, 10 %), 156 (M-CH_2Ar, 64 %), 91 (CH_2Ph, 100 %).

HRMS (ES+): $C_{15}H_{21}NO_2Na^+$ requires m/z 270.1464, found 270.1464

6.3.26. *N-Ethyl 3-(4-methylbenzyl)-4-methylpyrrolidine-1-carboxylate*, **324b**



N-Benzyl-3-methyl-4-(4-methylbenzyl)pyrrolidine (0.5 mmol, 140 mg) and ethyl chloroformate (1.5 mmol, 0.15 mL) in DCM (10 mL) were heated at 65 °C for 3 hours. The DCM was removed *in vacuo* and the resulting brown oil was purified by column chromatography (SiO_2, 1:1 ether to petrol, R_f=0.5). The carbamate was distilled using Kügelrohr distillation (0.1 mm Hg, 220 °C) to give the title compound as a colourless oil, 94 mg, 72 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.18-7.06 (8H, m, Ar-*H* (*cis* and *trans* rotamers)), 4.21-4.10 (4H, m, C_5-*H*$_2$ (*cis* and *trans* rotamers)), 3.77-3.62 (1H, m, C_3-*H* (*trans* rotamer)), 3.62-3.34 (2H, m, C_3-*H* (*trans* rotamer), C_3-*H* (*cis* rotamer)), 3.31-2.86 (5H, m, C_3-*H* (*cis* rotamer), C_7-*H* (*cis* rotamer), C_7-*H* (*cis* rotamer), C_7-*H* (*trans* rotamer), C_7-*H* (*trans* rotamer)), 2.81-2.71 (2H, m, C_9-*H*$_2$ (*cis* rotamers)), 2.58-2.41 (2H, m, C_9-*H*$_2$ (*trans* rotamers)), 2.38 (3H, s, C_{14}-*H*$_3$ (*cis* and *trans* rotamers)), 2.36 (3H, s, C_{14}-*H*$_3$ (*cis* and *trans* rotamers)), 2.36-2.29 (2H, m, C_2-*H*, C_8-*H* (*cis* rotamers)), 2.10-1.88 (2H, m, C_2-*H*, C_8-*H* (*trans* rotamers)), 1.33-1.23 (6H, m, C_6-*H*$_3$ (*cis* and *trans* rotamers)), 1.14-1.08 (3H, m, C_1-*H*$_3$ (*trans* rotamers)), 1.07 (3H, d, *J*=7.0 Hz, C_1-*H*$_3$ (*cis* rotamers)).

^{13}C NMR (100 MHz, $CDCl_3$): *Trans* Isomer: δ / ppm 155.23 (C, C_4), 137.13 (C, C_{10}, (*trans* rotamer)), 136.99 (C, C_{10}, (*trans* rotamer)), 135.80 (C, C_{13}), 129.29 (CH, C_{12}, $C_{12'}$), 128.74 (CH, C_{11}, $C_{11'}$ (*trans* rotamer)), 128.71 (CH, C_{11}, $C_{11'}$ (*trans* rotamer)), 60.95 (CH_2, C_5), 53.45 (CH_2, C_3, (*trans* rotamer)), 53.21 (CH_2, C_3, (*trans* rotamer)), 51.73 (CH_2, C_7, (*trans* rotamer)), 51.35 (CH_2, C_7, (*trans* rotamer)), 47.70 (CH, C_8, (*trans* rotamer)), 46.99 (CH, C_8, (*trans* rotamer)), 38.66 (CH, C_2, (*trans* rotamer)), 37.98 (CH_2, C_9, (*trans* rotamer)), 37.71 (CH_2, C_9, (*trans* rotamer)), 37.61 (CH, C_2, (*trans* rotamer)), 21.13 (CH_3, C_{14}), 16.46 (CH_3, C_1), 15.02 (CH_3, C_6).

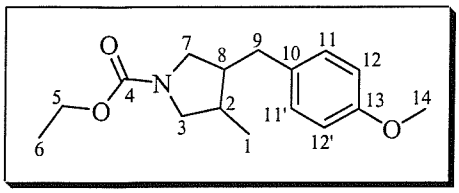
^{13}C NMR (100 MHz, $CDCl_3$): *Cis* Isomer: δ / ppm 155.58 (C, C_4), 137.52 (C, C_{10}, (*cis* rotamer)), 137.47 (C, C_{10}, (*cis* rotamer)), 135.72 (C, C_{13}, (*cis* rotamer)), 135.69 (C, C_{13}, (*cis* rotamer)), 129.33 (CH, C_{12}, $C_{12'}$), 128.65 (CH, C_{11}, $C_{11'}$), 60.98 (CH_2, C_5), 53.35 (CH_2, C_3), 49.44 (CH_2, C_7, (*cis* rotamer)), 49.09 (CH_2, C_7, (*cis* rotamer)), 43.89 (CH, C_8, (*cis* rotamer)), 43.24 (CH, C_8, (*cis* rotamer)), 35.45 (CH, C_2, (*cis* rotamer)), 34.74 (CH, C_2, (*cis* rotamer)), 33.88 (CH_2, C_9, (*cis* rotamer)), 33.84 (CH_2, C_9, (*cis* rotamer)), 21.13 (CH_3, C_{14}), 15.02 (CH_3, C_6), 13.71 (CH_3, C_1, (*cis* rotamer)), 13.64 (CH_3, C_1, (*cis* rotamer)).

IR (cm^{-1}): 2931 (w), 2870 (w), 1695 (s), 1515 (w), 1420 (s), 1349 (m).

LRMS (EI): *m/z* 261 (M, 33 %), 216 (M-Et-O, 8 %), 156 (M-CH_2Ar, 79 %), 105 (CH_2Ar, 100 %).

Microanalysis: Found: C 73.29, H 8.78, N 5.40. Requires: C 73.53, H 8.87, N 5.36.

6.3.27. *N-Ethyl 3-(4-methoxybenzyl)-4-methylpyrrolidine-1-carboxylate*, **324c**



N -Benzyl-3-(4-methoxy-benzyl)-4-methyl-pyrrolidine (1 mmol, 295 mg) and ethyl chloroformate (3 mmol, 0.29 mL) in DCM (10 mL) were heated at 65 °C for 3 hours. The DCM was removed *in vacuo* and the resulting brown oil was purified by column chromatography (SiO_2, 1:1 ether to petrol, R_f=0.5). The carbamate was distilled using Kügelrohr distillation (0.1 mm Hg, 220 °C) to give the title compound as a colourless oil, 158 mg, 57 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.15-7.07 (4H, m, C_{11}-*H*, $C_{11'}$-*H* (*cis* and *trans* rotamers)), 6.91-6.82 (4H, m, C_{12}-*H*, $C_{12'}$-*H* (*cis* and *trans* rotamers)), 4.20-4.09 (4H, m, C_5-H_2 (*cis* and *trans* rotamers)), 3.87-3.80 (6H, bs, C_{14}-H_3 (*cis* and *trans* rotamers)), 3.76-3.62 (1H, m, C_3-*H* (*trans* rotamer)), 3.59-3.33 (2H, m, C_3-*H* (*trans* rotamer), C_3-*H* (*cis* rotamer)), 3.30-2.83 (5H, m, C_3-*H* (*cis* rotamer), C_7-*H* (*cis* rotamer), C_7-*H* (*cis* rotamer), C_7-*H* (*trans* rotamer), C_7-*H* (*trans* rotamer)), 2.77-2.69 (2H, m, C_9-H_2 (*cis* rotamers)), 2.55-2.39 (2H, m, C_9-H_2 (*trans* rotamers)), 2.37-2.28 (2H, m, C_2-*H*, C_8-*H* (*cis* rotamers)), 2.06-1.87 (2H, m, C_2-*H*, C_8-*H* (*trans* rotamers)), 1.33-1.23 (6H, m, C_6-H_3 (*cis* and *trans* rotamers)), 1.13-1.07 (3H, m, C_1-H_3 (*trans* rotamers)), 1.06 (3H, d, *J*=7.0 Hz, C_1-H_3 (*cis* rotamers)).

^{13}C NMR (100 MHz, $CDCl_3$): Trans isomer: δ / ppm 158.22 (C, C_{13}), 155.23 (C, C_4), 132.27 (C, C_{10}, (*trans* rotamer)), 132.17 (C, C_{10}, (*trans* rotamer)), 129.74 (CH, C_{11}), 114.04 (CH, C_{12}), 60.95 (CH_2, C_5), 55.41 (CH_3, C_{14}), 53.46 (CH_2, C_3, (*trans* rotamer)), 53.23 (CH_2, C_3, (*trans* rotamer)), 51.71 (CH_2, C_7, (*trans* rotamer)), 51.34 (CH_2, C_7, (*trans* rotamer)), 47.83 (CH, C_8, (*trans* rotamer)), 47.11 (CH, C_8, (*trans* rotamer)), 38.61 (CH, C_2, (*trans* rotamer)), 37.92 (CH, C_2, (*trans* rotamer)), 37.23 (CH_2, C_9, (*trans* rotamer)), 37.15 (CH_2, C_9, (*trans* rotamer)), 16.47 (CH_3, C_1), 15.01 (CH_3, C_6).

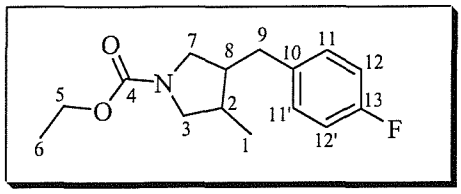
^{13}C NMR (100 MHz, $CDCl_3$): Cis isomer: δ / ppm 158.14 (C, C_{13}), 155.59 (C, C_4), 132.62 (C, C_{10}), 129.66 (CH, C_{11}), 114.09 (CH, C_{12}), 60.98 (CH_2, C_5), 55.41 (CH_3, C_{14}), 53.37 (CH_2, C_3), 49.42 (CH_2, C_7, (*cis* rotamer)), 49.07 (CH_2, C_7, (*cis* rotamer)), 44.02 (CH, C_8, (*cis* rotamer)), 43.35 (CH, C_8, (*cis* rotamer)), 35.44 (CH, C_2, (*cis* rotamer)), 34.70 (CH, C_2, (*cis* rotamer)), 33.39 (CH_2, C_9), 15.01 (CH_3, C_6), 13.69 (CH_3, C_1, (*cis* rotamer)), 13.62 (CH_3, C_1, (*cis* rotamer)).

IR (cm^{-1}): 2934 (w), 2873 (w), 1693 (s), 1612 (w), 1464 (m), 1420 (s), 1174 (m).

LRMS (EI): *m/z* 277 (M, 13 %), 188 (M-Me-$C_3H_5O_2$, 29 %), 173 (M-Me-Me-$C_3H_5O_2$, 10 %), 121 (CH_2Ar, 100 %).

HRMS (ES+): $C_{16}H_{23}NO_3Na^+$ requires m/z 300.1570, found 300.1575

6.3.28. *N-Ethyl 3-(4-fluorobenzyl)-4-methylpyrrolidine-1-carboxylate*, **324d**



N-Benzyl-3-(4-fluoro-benzyl)-4-methyl-pyrrolidine (1 mmol, 283 mg) and ethyl chloroformate (3 mmol, 0.29 mL) in DCM (10 mL) were heated at 65 °C for 3 hours. The DCM was removed *in vacuo* and the resulting brown oil was purified by column chromatography (SiO_2, 1:1 ether to petrol, R_f=0.4). The carbamate was distilled using Kügelrohr distillation (0.1 mm Hg, 210 °C) to give the title compound as a colourless oil, 197 mg, 74 %.

^{1}H NMR (100 MHz, $CDCl_3$): δ / ppm 7.20-7.11 (4H, m, C_{11}-*H*, $C_{11'}$-*H* (*cis* and *trans* rotamers)), 7.06-6.96 (4H, m, C_{12}-*H*, $C_{12'}$-*H* (*cis* and *trans* rotamers)), 4.20-4.10 (4H, m, C_5-H_2 (*cis* and *trans* rotamers)), 3.77-3.62 (1H, m, C_3-*H* (*trans* rotamer)), 3.58-3.31 (2H, m, C_3-*H* (*trans* rotamer), C_3-*H* (*cis* rotamer)), 3.30-2.86 (5H, m, C_3-*H* (*cis* rotamer), C_7-*H* (*cis* rotamer), C_7-*H* (*cis* rotamer), C_7-*H* (*trans* rotamer), C_7-*H* (*trans* rotamer)), 2.80-2.71 (2H, m, C_9-H_2 (*cis* rotamers)), 2.57-2.40 (2H, m, C_9-H_2 (*trans* rotamers)), 2.38-2.28 (2H, m, C_2-*H*, C_8-*H* (*cis* rotamers)), 2.07-1.87 (2H, m, C_2-*H*, C_8-*H* (*trans* rotamers)), 1.33-1.23 (6H, m, C_6-H_3 (*cis* and *trans* rotamers)), 1.13-1.07 (3H, m, C_1-H_3 (*trans* rotamers)), 1.06 (3H, d, *J*=7.0 Hz, C_1-H_3 (*cis* rotamers)).

^{13}C NMR (400 MHz, $CDCl_3$): *Trans* Isomer: δ / ppm 161.65 (C, J_{CF}=242.5 Hz, C_{13}), 155.21 (C, C_4), 136.20 (C, C_{10}, (*trans* rotamer)), 135.83 (C, J_{CF}=8.2 Hz, C_{10}, (*trans* rotamer)), 130.20 (CH, J_{CF}=3.4 Hz, C_{11}, $C_{11'}$), 115.43 (CH, J_{CF}=20.8 Hz, C_{12}, $C_{12'}$), 61.02 (CH_2, C_5), 53.43 (CH_2, C_3, (*trans* rotamer)), 53.19 (CH_2, C_3, (*trans* rotamer)), 51.65 (CH_2, C_7, (*trans* rotamer)), 51.26 (CH_2, C_7, (*trans* rotamer)), 47.74 (CH, C_8, (*trans* rotamer)), 47.02 (CH, C_8, (*trans* rotamer)), 38.72 (CH, C_2, (*trans* rotamer)), 38.00 (CH, C_2, (*trans* rotamer)), 37.37 (CH_2, C_9, (*trans* rotamer)), 37.29 (CH_2, C_9, (*trans* rotamer)), 16.44 (CH_3, C_1), 15.00 (CH_3, C_6).

^{13}C NMR (400 MHz, $CDCl_3$): *Cis* Isomer: δ / ppm 161.58 (C, J_{CF}=242.5 Hz, C_{13}), 155.57 (C, C_4), 136.20 (C, J_{CF}=6.8 Hz, C_{10}, (*cis* rotamer)), 135.86 (C, J_{CF}=6.8 Hz, C_{10}, (*cis* rotamer)), 130.07 (CH, J_{CF}=2.4 Hz, C_{11}, $C_{11'}$), 115.40 (CH, J_{CF}=21.3 Hz, C_{12}, $C_{12'}$), 61.04 (CH_2, C_5), 53.30 (CH_2, C_3, (*cis* rotamer)), 53.13 (CH_2, C_3, (*cis* rotamer)), 49.34 (CH_2, C_7, (*cis* rotamer)), 48.99 (CH_2, C_7, (*cis* rotamer)), 43.92 (CH, C_8, (*cis* rotamer)), 43.24 (CH, C_8, (*cis* rotamer)), 35.47 (CH, C_2, (*cis* rotamer)), 34.71 (CH, C_2, (*cis* rotamer)), 33.53 (CH_2, C_9), 15.00 (CH_3, C_6), 13.69 (CH_3, C_1, (*cis* rotamer)), 13.61 (CH_3, C_1, (*cis* rotamer)).

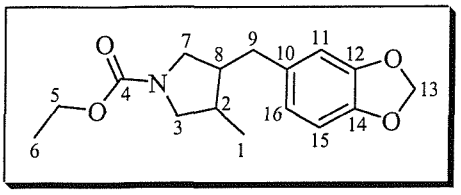
^{19}F NMR (100 MHz, $CDCl_3$): δ / ppm 44.67 (major *trans* rotamer), 44.76 (minor *trans* rotamer), 44.55 (*cis*).

IR (cm^{-1}): 2934 (w), 2873 (w), 1692 (s), 1602 (w), 1509 (m), 1015 (w).

LRMS (EI): *m/z* 265 (M, 42 %), 236 (M-Et, 8 %), 220 (M-Et-O, 12 %), 109 (CH_2Ar, 100 %).

Microanalysis: Found: C 67.51, H 7.71, N 5.10. Requires: C 67.90, H 7.60, N 5.28.

6.3.29. *N-Ethyl 3-(1,3-benzodioxol-5-ylmethyl)-4-methylpyrrolidine-1-carboxylate,* **324e**



N-3-Benzo[1,3]dioxol-5-ylmethyl-1-benzyl-4-methyl-pyrrolidine (1 mmol, 309 mg) and ethyl chloroformate (3 mmol, 0.29 mL) in DCM (10 mL) were heated at 65 °C for 3 hours. The DCM was removed *in vacuo* and the resulting brown oil was purified by column chromatography (SiO_2, 1:1 ether to petrol, R_f=0.4). The carbamate was distilled using Kügelrohr distillation (0.1 mm Hg, 250 °C) to give the title compound as a colourless oil, 127 mg, 44 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 6.68-6.61 (2H, m, C_{15}-*H* (*cis* and *trans* rotamers)), 6.59-6.49 (4H, m, C_{11}-*H*, C_{16}-*H* (*cis* and *trans* rotamers)), 5.88-5.82 (4H, bs, C_{13}-H_2 (*cis* and *trans* rotamers)), 4.08-3.99 (4H, m, C_5-H_2 (*cis* and *trans* rotamers)), 3.64-3.49 (1H, m, C_3-*H* (*trans* rotamer)), 3.48-3.19 (2H, m, C_3-*H* (*trans* rotamer), C_3-*H* (*cis* rotamer)), 3.17-2.69 (5H, m, C_3-*H* (*cis* rotamer), C_7-*H* (*cis* rotamer), C_7-*H* (*cis* rotamer), C_7-*H* (*trans* rotamer), C_7-*H* (*trans* rotamer)), 2.63-2.55 (2H, m, C_9-H_2 (*cis* rotamers)), 2.40-2.16 (4H, m, C_9-H_2 (*trans* rotamers), C_2-*H*, C_8-*H* (*cis* rotamers)), 1.92-1.75 (2H, m, C_2-*H*, C_8-*H* (*trans* rotamers)), 1.20-1.12 (6H, m, C_6-H_3 (*cis* and *trans* rotamers)), 1.00-0.95 (3H, m, C_1-H_3 (*trans* rotamers)), 0.93 (3H, d, *J*=7.0 Hz, C_1-H_3 (*cis* rotamers)).

^{13}C NMR (100 MHz, $CDCl_3$): Trans isomer: δ / ppm 155.23 (C, C_4), 147.83 (C, C_{12}), 146.09 (C, C_{14}), 134.03 (C, C_{10}, (*trans* rotamer)), 133.91 (C, C_{10}, (*trans* rotamer)), 121.66 (CH, C_{16}, (*trans* rotamer)), 121.63 (CH, C_{16}, (*trans* rotamer)), 109.21 (CH, C_{11}, (*trans* rotamer)), 109.15 (CH, C_{11}, (*trans* rotamer)), 108.37 (CH, C_{15}), 101.00 (CH_2, C_{13}), 60.99 (CH_2, C_5), 53.44 (CH_2, C_3, (*trans* rotamer)), 53.21 (CH_2, C_3, (*trans* rotamer)), 51.67 (CH_2, C_7, (*trans* rotamer)), 51.29 (CH_2, C_7, (*trans* rotamer)), 47.85 (CH, C_8, (*trans* rotamer)), 47.13 (CH, C_8, (*trans* rotamer)), 38.63 (CH, C_2), 37.91 (CH_2, C_9, (*trans* rotamer)), 37.82 (CH_2, C_9, (*trans* rotamer)), 16.47 (CH_3, C_1), 15.02 (CH_3, C_6).

^{13}C NMR (100 MHz, $CDCl_3$): Cis isomer: δ / ppm 155.58 (C, C_4), 147.83 (C, C_{12}), 146.02 (C, C_{14}), 134.39 (C, C_{10}, (*cis* rotamer)), 134.33 (C, C_{10}, (*cis* rotamer)), 121.60 (CH, C_{16}, (*cis* rotamer)), 121.57 (CH, C_{16}, (*cis* rotamer)), 109.10 (CH, C_{11}, (*cis* rotamer)), 109.09 (CH, C_{11}, (*cis* rotamer)), 108.42 (CH, C_{15}), 101.00 (CH_2, C_{13}), 60.99 (CH_2, C_5), 53.34 (CH_2, C_3 (*cis* rotamer)), 53.27 (CH_2, C_3 (*cis* rotamer)), 49.35 (CH_2, C_7, (*cis* rotamer)), 49.01 (CH_2, C_7, (*cis* rotamer)), 44.02 (CH, C_8, (*cis* rotamer)), 43.34 (CH, C_8, (*cis* rotamer)), 35.42 (CH, C_2, (*cis* rotamer)), 34.71 (CH, C_2, (*cis* rotamer)), 34.07 (CH_2, C_9 (*cis* rotamer)), 34.05 (CH_2, C_9 (*cis* rotamer)), 15.00 (CH_3, C_6), 13.70 (CH_3, C_1, (*cis* rotamer)), 13.62 (CH_3, C_1, (*cis* rotamer)).

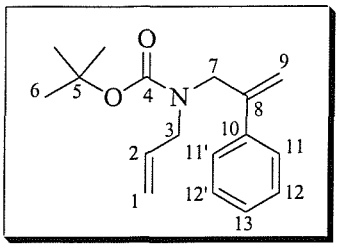
IR (cm^{-1}): 2931 (w), 2876 (w), 1691 (s), 1608 (w), 1488 (m), 1307 (w).

LRMS (EI): *m/z* 291 (M, 82 %), 262 (M-Et, 2 %), 246 (M-Et-O, 8 %), 135 (CH_2Ar, 100 %).

HRMS (ES+): $C_{16}H_{21}NO_4Na^+$ requires m/z 314.1363, found 314.1364

6.4. Experimental For Chapter 4

6.4.1. *N-BOC-allyl-(2-phenyl-allyl)-amine,* **415**



BOC-anhydride (20.3 mmol, 4.43 g) in cyclohexane (4 mL) cooled to 10 °C before *N*-allyl-(2-phenyl-allyl)-amine (20 mmol, 3.46 g) in cyclohexane (10 mL) was added dropwise. The reaction was stirred at r.t. overnight. Resulting yellow solution was washed with 0.01 M HCl (10 mL), followed by brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The carbamate was purified by column chromatography (SiO_2, 9:1 petrol to ether) to give the title compound as a colourless oil, 4.8 g, 88 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.45-7.14 (5H, m, Ar-$\underline{H}$), 5.77-5.55 (1H, bs, C_2-$\underline{H}$), 5.42-5.23 (1H, 2 X bs, C_9-$\underline{H}$ (*cis* to phenyl (rotamers)), 5.10-4.94 (3H, bs, C_9-$\underline{H}$ (*trans* to phenyl), C_1-$\underline{H_2}$), 4.32-4.08 (2H, 2 X bs, C_7-$\underline{H_2}$ (rotamers)), 3.83-3.55 (2H, 2 X bs, C_3-$\underline{H_2}$ (rotamers)), 1.37 (9H, s, 3 X C_6-$\underline{H_3}$).

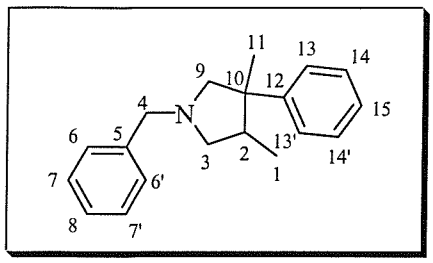
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 155.72 (C, C_4 (rotamer)), 155.51 (C, C_4 (rotamer)), 144.93 (C, C_8), 144.37 (C, C_{10}), 133.88 (CH, C_2), 128.44 (CH, C_{12}, $C_{12'}$), 127.95 (CH, C_{13}), 126.57 (CH, C_{11}, $C_{11'}$), 116.94 (CH_2, C_1 (rotamer)), 116.45 (CH_2, C_1 (rotamer)), 113.94 (CH_2, C_9 (rotamer)), 113.36 (CH_2, C_9 (rotamer)), 79.90 (C, C_5), 49.81 (CH_2, C_7 (rotamer)), 49.23 (CH_2, C_7 (rotamer)), 48.33 (CH_2, C_3), 28.52 (CH_3, C_6).

IR (cm^{-1}): 1808 (w), 1757 (w), 1690 (s), 1630 (w), 1576 (w), 1495 (w).

LRMS (EI): *m/z* 217 (M-^{t}Bu, 81 %), 189 (M-^{t}Bu -C_2H_3, 96 %), 174 (M-$CO_2{}^t$Bu, 82 %).

HRMS (ES+): $C_{17}H_{23}NNaO_2^+$ requires m/z 296.1626, found 296.1615.

6.4.2. *1-Benzyl-3,4-dimethyl-3-phenyl-pyrrolidine*, **420**



Cp_2ZrCl_2 (1.2 mmol, 350 mg) in THF (5 mL) was cooled to -78 °C before BuLi (2.4 mmol, 0.96 mL) was added slowly. The reaction was stirred for 20 mins at -78 °C before *N*-Benzyl-allyl-(2-phenyl-allyl)-amine (1 mmol, 263 mg) in THF (5 mL) was added slowly. The reaction was warmed to r.t. and stirred for 4 hours. MeOH (5 mL) and $NaHCO_3$ solution (5 mL) were added to the zirconacycle solution and stirred overnight. Ether (30 mL) and water (30 mL) were added. The organic layer was washed with water (3 X 20 mL). The aqueous layer was washed with ether (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The pyrrolidine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 2 % Et_3N, 98 % petrol, R_f=0.5). This gave the title compound as a colourless oil, 141 mg, 53 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.35-7.05 (10H, m, Ar-*H*), 3.64 (1H, d, *J*=13.3 Hz, C_4-*H*), 3.55 (1H, d, *J*=13.3 Hz, C_4-*H*), 3.02 (1H, d, *J*=9.3 Hz, C_9-*H*), 2.90 (1H, t, *J*=8.5 Hz, C_3-*H*), 2.53 (1H, d, *J*=9.3 Hz, C_9-*H*), 2.51-2.40 (1H, m, C_2-*H*), 2.33 (1H, t, *J*=8.5 Hz, C_3-*H*), 1.23 (3H, s, C_{11}-H_3), 0.89 (3H, d, *J*=6.8 Hz, C_1-H_3).

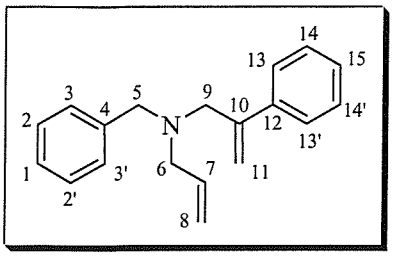
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 150.31 (C, C_{12}), 139.95 (C, C_5), 128.73 (CH, C_6, $C_{6'}$), 128.36 (CH, C_7, $C_{7'}$), 128.27 (CH, C_{14}, $C_{14'}$), 126.93 (CH, C_8), 126.04 (CH, C_{13}, $C_{13'}$), 125.74 (CH, C_{15}), 69.82 (CH_2, C_9), 61.75 (CH_2, C_3), 60.94 (CH_2, C_4), 47.04 (C, C_{10}), 43.69 (CH, C_2), 22.67 (CH_3, C_{11}), 13.78 (CH_3, C_1).

IR (cm^{-1}): 3026 (w), 2963 (m), 2787 (m), 2361 (w), 1704 (w), 1601 (m), 1495 (s), 1452 (s), 1029 (s).

LRMS (EI): *m/z* 265 (M, 52 %), 174 (M-phenyl-CH_3, 10 %), 133 (M-phenyl-CH_2-N-CH_2-CH_2, 76 %).

HRMS (ES+): $C_{19}H_{22}N^+$ requires m/z 266.1903, found 266.1902.

6.4.3. *N-Benzyl-allyl-(2-phenyl-allyl)-amine*, **421**



N-Allyl-(2-phenyl-allyl)-amine (1 eq, 20 mmol, 3.46 g), K_2CO_3 (2 eq, 40 mmol, 6.2 g) in acetonitrile (30 mL) was cooled to 0 °C before benzyl bromide (2 eq, 40 mmol, 4.7 mL) in acetonitrile (10 mL) was added. The reaction was warmed to r.t. and stirred overnight. Ether (50 mL) and water (50 mL) were added. The organic layer was washed with water (3 X 30 mL), and the aqueous layer was washed with ether (3 X 30 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give an orange / brown oil. Column chromatography (SiO_2, 95% petrol / 5% NEt_3), followed by Kügelrohr distillation (0.1 mmHg, 170 °C) gave the title compound as a colourless oil, 3.62 g, 69 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.36-7.09 (10H, m, Ar-*H*), 5.78 (1H, ddt, *J*=17.3 Hz, *J*=10.3 Hz, *J*=6.3 Hz, C_7-*H*), 5.37 (1H, s, C_{11}-*H* (*cis* to phenyl)), 5.26 (1H, d, *J*=1.2 Hz, C_{11}-*H* (*trans* to phenyl)), 5.09 (1H, d, *J*=17.3 Hz, C_8-*H*), 5.05 (1H, d, *J*=10.3 Hz, C_8-*H*), 3.49 (2H, s, C_5-H_2), 3.36 (2H, s, C_9-H_2), 2.98 (2H, d, *J*=6.3 Hz, C_6-H_2).

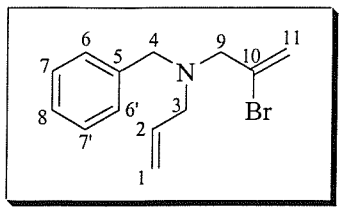
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 146.09 (C, C_{10}), 140.53 (C, C_4), 139.81 (C, C_{12}), 135.98 (CH, C_7), 129.08 (CH, C_3, $C_{3'}$), 128.25 (CH, C_{14}, $C_{14'}$), 128.15 (CH, C_2, $C_{2'}$), 127.55 (CH, C_{15}), 126.93 (CH, C_1), 126.78 (CH, C_{13}, $C_{13'}$), 117.61 (CH_2, C_8), 115.15 (CH_2, C_{11}), 58.20 (CH_2, C_9), 57.90 (CH_2, C_5), 56.56 (CH_2, C_6).

IR (cm^{-1}): 3089 (w), 3026 (w), 2792 (m), 1628 (w), 1493 (m), 1444 (w).

LRMS (EI): *m/z* 263 (M, 46 %), 160 (M-Bn-CH_2, 94 %), 144 (M-119, 24 %), 115 (M-148, 62 %), 91 (M-172, 100 %).

HRMS (ES+): $C_{19}H_{22}N^+$ requires m/z 264.1752, found 264.1750.

6.4.4. *N-Benzyl-allyl-(2-bromo-allyl)-amine,* **422**



N-Allyl-*N*-benzyl-amine (10 mmol, 1.47 g), K_2CO_3 (30 mmol, 4.2 g) in acetonitrile (15 mL) was cooled to 0 °C before 2,3-dibromopropene (15 mmol, 3.6 g) in acetonitrile (10 mL) was added. The reaction was warmed to r.t. and stirred overnight. Ether (50 mL) and water (50 mL) were added. The organic layer was washed with water (3 X 30 mL), and the aqueous layer was washed with ether (3 X 30 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The bromide was purified by column chromatography (SiO_2, 95% petrol / 5% NEt_3), and Kügelrohr distillation (0.1 mmHg, 140 °C) to give the title compound as a yellow oil, 1.73 g, 65 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.45-7.22 (5H, m, Ar-H), 5.96 (1H, d, *J*=1.1 Hz, C_{11}-H (trans to bromide)), 5.90 (1H, ddt, *J*=17.3 Hz, *J*=10.3 Hz, *J*=6.3 Hz, C_2-H), 5.62 (1H, s, C_{11}-H (cis to bromide)), 5.24 (1H, dd, *J*=17.3 Hz, *J*=1.5 Hz, C_1-H (trans)), 5.18 (1H, d, *J*=10.3 Hz, C_1-H (cis)), 3.66 (2H, s, C_4-H_2), 3.29 (2H, s, C_9-H_2), 3.14 (2H, d, *J*=6.3 Hz, C_3-H_2).

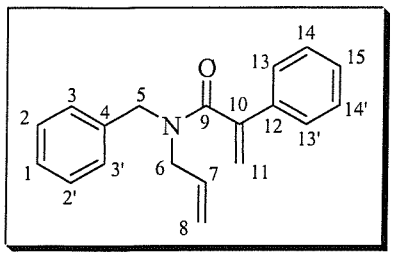
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 139.15 (C, C_5), 135.45 (CH, C_2), 132.32 (C, C_{10}), 128.89 (CH, C_6, $C_{6'}$), 128.44 (CH, C_7, $C_{7'}$), 127.16 (CH, C_8), 118.30 (CH_2, C_1), 117.93 (CH_2, C_{11}), 61.56 (CH_2, C_9), 57.48 (CH_2, C_4), 56.15 (CH_2, C_3).

IR (cm^{-1}): 3080 (w), 2920 (w), 2800 (w), 1629 (w), 1444 (w), 1453 (w), 893 (s).

LRMS (EI): *m/z* 265 (M, 20 %), 240 (M-$CHCH_2$, 8 %), 186 (M-Br, 32 %),160 (M-Br-$CHCH_2$, 65 %), 91 ($PhCH_2$, 100 %).

HRMS (EI): $C_{13}H_{17}NBr$ requires m/z 266.0539, found 266.0538

6.4.5. *N-Allyl-N-benzyl-2-phenyl-acrylamide*, **432**



Atropic acid (2 mmol, 296 mg) in DCM (5 mL) was cooled to 0 °C before oxalyl chloride (3 mmol, 0.26 mL) was added slowly, followed by DMF (2 drops). The reaction was warmed to r.t. and stirred overnight under argon. The DCM solvent was removed *via* vacuum transfer to give the acid chloride as a brown oil. 2M NaOH (10 mL) was cooled to 0 °C and added to the acid chloride. The reaction was cooled to 0 °C before *N*-allyl-benzyl-amine (3 mmol, 442 mg) in DCM (5 mL) was added dropwise. The reaction was warmed to r.t. and stirred overnight. The reaction was quenched with water (30 mL) and ether (50 mL) was added. The organic phase was washed with water (3 X 20 mL), followed by 2M HCl (3 X 20 mL) to remove the excess amine. The aqueous phase was washed with ether (3 X 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting orange / red oil was purified by column chromatography (SiO_2, 1:1 ether to petrol, R_f=0.5) to give the title compound as an orange oil, 289 mg, 52 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.43-6.95 (20H, m, Ar-*H* (major and minor rotamers)), 5.82-5.70 (1H, m, C_7-*H* (minor rotamer)), 5.63 (2H, d, *J*=4.5 Hz, C_{11}-H_2 (major rotamer)), 5.51-5.40 (1H, m, C_7-*H* (major rotamer)), 5.33 (2H, d, *J*=10.0 Hz, C_{11}-H_2 (minor rotamer)), 5.16-4.96 (4H, m, C_8-H_2 (major and minor rotamers)), 4.64 (2H, s, C_5-H_2 (major rotamer)), 4.33 (2H, s, C_5-H_2 (minor rotamer)), 3.97 (2H, d, *J*=6.0 Hz, C_6-H_2 (minor rotamer)), 3.66 (2H, d, *J*=5.8 Hz, C_6-H_2 (major rotamer)).

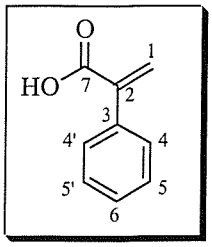
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 171.16 (C, C_9 (major rotamer)), 171.05 (C, C_9 (minor rotamer)), 145.17 (C, C_{10} (minor rotamer)), 145.12 (C, C_{10} (major rotamer)), 137.30 (C, C_4 (major rotamer)), 136.55 (C, C_4 (minor rotamer)), 135.87 (C, C_{12} (major and minor rotamers)), 132.94 (CH, C_7 (major rotamer)), 132.51 (CH, C_7 (minor rotamer)), 129.05 (CH, C_{14}, $C_{14'}$ (minor rotamer)), 128.97 (CH, C_{14}, $C_{14'}$ (major rotamer)), 128.85 (CH, C_2, $C_{2'}$ (minor rotamer)), 128.80 (CH, C_3,$C_{3'}$ (major and minor rotamers)), 128.63 (CH, C_2, $C_{2'}$ (major rotamer)), 127.77 (CH, C_{15} (minor rotamer)), 127.64 (CH, C_{15} (major rotamer)), 127.35 (CH, C_1 (major and minor rotamers)), 125.92 (CH, C_{13},$C_{13'}$ (major and minor rotamers)), 118.43 (CH_2, C_{11} (major rotamer)), 118.33 (CH_2, C_{11} (minor rotamer)), 114.40 (CH_2, C_8 (minor rotamer)), 114.04 (CH_2, C_8 (major rotamer)), 51.22 (CH_2, C_5 (minor rotamer)), 50.19 (CH_2, C_5 (major rotamer)), 46.59 (CH_2, C_6 (major rotamer)), 46.15 (CH_2, C_6 (minor rotamer)).

IR (cm^{-1}): 3062 (w), 2924 (w), 2360 (m), 2342 (m), 1635 (s), 1495 (m), 1416 (s), 1283 (m), 1212 (s), 912 (s).

LRMS (EI): *m/z* 277 (M, 71 %), 220 (M-O-allyl, 8 %), 186 (M-O-phenyl, 8%), 146 (M-O-phenyl-allyl, 24%).

HRMS (EI): $C_{19}H_{19}NO$ requires m/z 277.1467, found 277.1469

6.4.6. *2-Phenyl acrylic acid*, **433**



$Pd(OAc)_2$ (0.0125 mmol, 3 mg), 2-pyridyl phosphine (0.5 mmol, 20 mol%, 132 mg), phenyl acetylene (25 mmol, 2.55 g), H_2O (1 g, 55 mmol) and methane sulfonic acid (2 mmol, 192 mg) in THF (30 mL) were heated at 50 °C for 24 hours in a CO atmosphere. The reaction had water (50 mL) and ether (50 mL) added. The 2-phenyl acrylic acid was extracted into 2M NaOH (30 mL) and ether (40 mL) was added. The organic layer was washed with 2M NaOH (3 X 30 mL). The basic washings were acidified with 2M HCl (150 mL). Ether (80 mL) was added and the acidic layer was washed with ether (3 X 30 mL). The organic layer was washed with water (3 X 30 mL), before being dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow solid was recrystallised from a minimum volume of hot hexane to give the title compound as an orange / yellow solid, 355 mg, 10 %.

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 172.20 (C, C_7), 140.75 (C, C_2), 136.25 (C, C_3), 129.62 (CH, C_6), 128.62 (CH, C_5, $C_{5'}$), 128.53 (CH_2, C_1), 128.31 (CH, C_4, $C_{4'}$).

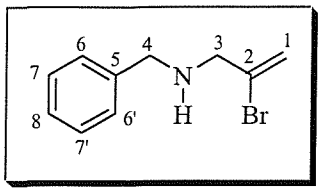
IR (cm^{-1}): 3005 (m), 2630 (m), 2360 (w), 1682 (s), 1613 (m), 1495 (m), 1430 (s), 1219 (s), 1073 (m).

M.P.: 103-105 °C

Lit. M.P.: 108-109 °C

In agreement with literature[219].

6.4.7. *Benzyl-(2-bromo-allyl)-amine*, **435**



Benzyl amine (200 mmol, 20.42 g), K_2CO_3 (240 mmol, 33.0 g) in MeCN (100 mL) were cooled to 0 °C before 2,3-dibromopropene (60 mmol, 12.0 g) in MeCN (50 mL) was added slowly. The reaction was warmed to r.t. and stirred overnight. The reaction was quenched with water (50 mL) and ether (50 mL) was added. The organic layer was washed with water (3 X 20 mL) and the aqueous layer was washed with ether (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting red/brown oil was purified by column chromatography (SiO_2, 1:4 ether:petrol, R_f=0.3) to give the title compound as a yellow oil, 8.25 g, 61 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.42-7.24 (5H, m, C_6-*H*, $C_{6'}$-*H*, C_7-*H*, $C_{7'}$-*H*, C_8-*H*), 5.82 (1H, d, *J*=1.1 Hz, C_1-*H* (*trans* to bromide)), 5.63 (1H, d, *J*=1.1 Hz, C_1-*H* (*cis* to bromide)), 3.76 (2H, s, C_4-H_2), 3.48 (2H, s, C_3-H_2), 1.83-1.77 (1H, bs, N-*H*).

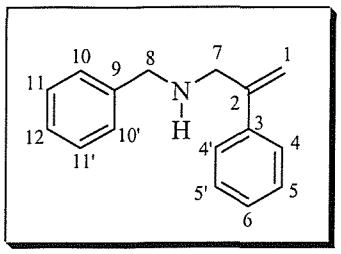
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 139.83 (C, C_5), 133.66 (C, C_2), 128.62 (CH, C_7, $C_{7'}$), 128.49 (CH, C_6, $C_{6'}$), 127.28 (CH, C_8), 118.15 (CH_2, C_1), 56.77 (CH_2, C_3), 51.66 (CH_2, C_4).

IR (cm^{-1}): 3026 (w), 2835 (w), 2359 (w), 2338 (w), 1626 (m), 1495 (m), 1453 (m).

LRMS (EI): *m/z* 226 (M, 53 %), 146 (M-Br, 63 %), 91 ($PhCH_2$, 100 %).

In agreement with literature[220].

6.4.8. *Benzyl-(2-phenyl-allyl)-amine*, **436**



Method A: *N*-bromosuccinimide (30 g, 170 mmol) and α-methyl styrene (31 g, 270 mmol) in CCl_4 were heated in a 1 L flask in an argon atmosphere at 150 °C for 2 hours. The reaction was cooled to r.t., filtered and concentrated *in vacuo* to give an orange oil. K_2CO_3 (150 mmol, 21.0 g) and benzyl amine (300 mmol, 30.14 g) in MeCN (40 mL) were prepared in a separate flask, cooled to 0 °C before the crude bromide (30.68 g) in MeCN (50 mL) was added slowly to the flask containing the benzyl amine. The reaction was allowed to warm to r.t. and stirred for 2 hours. Ether (80 mL) and water (80 mL) were added. The organic layer was washed with water (3 X 20 mL) and the aqueous layer was washed with ether (3 X 20 mL). The organic layers were combined and the amine was extracted into 2M HCl (3 X 100 mL). The aqueous extracts were basified with NaOH pellets and ether (80 mL) was added. The acidic aqueous layer was washed with ether (3 X 100 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The benzylamine was removed *via* distillation (1 mm Hg, 120 °C). The secondary amine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 2 % Et_3N, 98 % petrol, R_f=0.3). This gave the title compound as a pale yellow oil, 15.72 g, 41 %.

Method B: *N*-Benzyl-(2-bromo)-allyl amine (1 mmol, 225 mg), 1M KOH solution (3 mmol, 3 mL), phenyl boronic acid (2 mmol, 245 mg) and $Pd(PPh_3)_4$ (5 mol%, 22 mg) in THF (12 mL) were heated at 80 °C overnight. The reaction was quenched with water (50 mL) and ether (50 mL) was added. The organic layer was washed with water (3 X 20 mL) and the aqueous layer was washed with ether (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 2 % Et_3N, 98 % petrol, R_f=0.3). This gave the title compound as a yellow oil, 93 mg, 42 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.52-7.24 (10H, m, C_4-*H*, $C_{4'}$-*H*, C_5-*H*, $C_{5'}$-*H*, C_6-*H*, C_{10}-*H*, $C_{10'}$-*H*, C_{11}-*H*, $C_{11'}$-*H*, C_{12}-*H*), 5.47 (1H, d, *J*=1.1 Hz, C_1-*H* (*cis* to phenyl)), 5.31 (1H, d, *J*=1.1 Hz, C_1-*H* (*trans* to phenyl)), 3.86 (2H, s, C_8-H_2), 3.71 (2H, s, C_7-H_2), 1.65-1.50 (1H, bs, N-*H*).

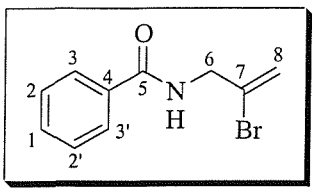
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 146.44 (C, C_2), 140.38 (C, C_9), 139.98 (C, C_3), 128.60 (CH, C_5, $C_{5'}$), 128.52 (CH, C_{11}, $C_{11'}$), 128.38 (CH, C_{10}, $C_{10'}$), 127.83 (CH, C_6), 127.09 (CH, C_{12}), 126.37 (CH, C_4, $C_{4'}$), 113.68 (CH_2, C_1), 53.13 (CH_2, C_7), 52.86 (CH_2, C_8).

IR (cm^{-1}): 3059 (w), 2828 (w), 1628 (w), 1574 (w), 1494 (m), 1453 (m), 1360 (w), 1027 (m), 902 (s), 778 (s).

LRMS (EI): *m/z* 223 (M, 24 %), 120 ($PhCH_2NHCH_2$, 85 %), 91 ($PhCH_2$, 100 %).

In agreement with literature[221].

6.4.9. *N-(2-bromo-allyl)-benzamide*, **437**



Benzamide (10 mmol, 1.21 g), KOH solution (15 mmol, 842 mg) and tetrabutylammonium bromide (0.3 mmol, 97 mg) were stirred for 15 mins at r.t., before 2,3-dibromopropene (12.5 mmol, 1.3 mL) was added *via* syringe and heated in an oil bath for 15 mins at 80 °C. The reaction was quenched with water (40 mL) and DCM (40 mL) was added. The organic layer was washed with brine (3 X 20 mL) and the aqueous layer was washed with DCM (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting brown solid was purified by column chromatography (SiO_2, 1:1 ether:petrol, R_f=0.3), followed by Kügelrohr distillation (190 °C, 0.5 mm Hg) to give the title compound as a colourless solid, 313 mg, 8 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.73 (2H, d, *J*=7.3 Hz, C_3-*H*, $C_{3'}$-*H*), 7.48-7.32 (3H, m, Ar-*H*), 6.66-6.45 (1H, bs, N-*H*), 5.81 (1H, s, C_8-*H*), 5.51 (1H, s, C_8-*H*), 4.24 (2H, d, *J*=6.0 Hz, C_6-H_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 167.41 (C, C_5), 134.17 (C, C_4), 131.99 (CH, C_1), 129.59 (C, C_7), 128.85 (CH, C_2, $C_{2'}$), 127.20 (CH, C_3, $C_{3'}$), 118.39 (CH_2, C_8), 43.03 (CH_2, C_6).

IR (cm^{-1}): 3293 (m), 3062 (w), 2931 (w), 1635 (s), 1602 (m), 1578 (m), 1538 (s).1488 (m).

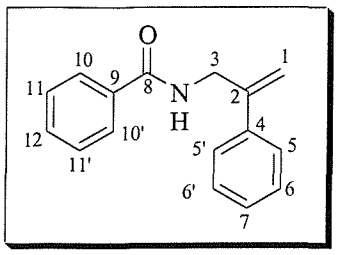
LRMS (EI): *m/z* 240 (M, 1 %), 160 (M-Br, 100 %), 105 (M-Br-allyl-O, 50 %), 91 ($PhCH_2$, 1 %), 77 (Ph, 85 %).

M.P.: 96-98 °C.

Lit. M.P.: 97-98 °C.

In agreement with literature[222].

6.4.10. *N-(2-phenyl-allyl)-benzamide*, **438**



N-(2-bromo-allyl)-benzamide (0.25 mmol, 61 mg), Cs_2CO_3 (0.75 mmol, 245 mg), phenyl boronic acid (0.5 mmol, 61 mg) and $Pd(PPh_3)_4$ (5 mol%, 3 mg) in DME (5 mL) were heated at 90 °C overnight. The reaction was quenched with water (50 mL) and ether (50 mL) was added. The organic layer was washed with water (3 X 20 mL) and the aqueous layer was washed with ether (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting brown oil was purified by column chromatography (SiO_2, 1:1 ether:petrol, R_f=0.4) to give the title compound as a colourless solid, 26 mg, 44 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.48-7.13 (10H, m, Ar-*H*), 6.33-6.15 (1H, bs, N-*H*), 5.43 (1H, s, C_1-*H* (*cis* to phenyl)), 5.24 (1H, s, C_1-*H* (*trans* to phenyl)), 4.45 (2H, d, *J*=5.5 Hz, C_3-H_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 167.54 (C, C_8), 144.43 (C, C_2), 138.52 (C, C_4), 131.63 (C, C_9), 131.63 (CH, C_{12}), 128.74 (CH, C_{11}, $C_{11'}$), 128.71 (CH, C_6, $C_{6'}$), 128.27 (CH, C_7), 127.06 (CH, C_{10}, $C_{10'}$), 126.25 (CH, C_5, $C_{5'}$), 114.16 (CH_2, C_1), 43.88 (CH_2, C_3).

IR (cm^{-1}): 3316 (m), 3061 (w), 1725 (w), 1643 (s), 1633 (s), 1602 (m), 1578 (m).

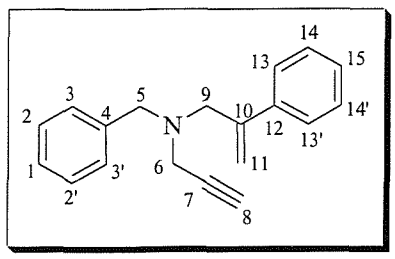
LRMS (EI): *m/z* 237 (M, 46 %), 105 (M-Ph-allyl-O, 79 %), 91 ($PhCH_2$, 4 %), 77 (Ph, 100 %)

M.P.: 120-122 °C.

Lit. M.P.: 122-123 °C.

In agreement with literature[223].

6.4.11. *N-Benzyl-(2-phenyl-allyl)-prop-2-ynyl-amine*, **440**



N-Benzyl-2-phenyl-allyl amine (50 mmol, 11.17 g) and K_2CO_3 (70 mmol, 9.8 g) in MeCN (30 mL) had propargyl bromide (60 mmol, 4.5 mL) added slowly. Reaction stirred for 2 hours. Ether (50 mL) and water (50 mL) were added. The organic layer was washed with water (3 X 50 mL) and the aqueous layer was washed with ether (3 X 50 mL). The organic layers were combined and the amine was extracted into 2M HCl (3 X 50 mL). The aqueous extracts were basified with NaOH pellets and ether (80 mL) was added. The acidic aqueous layer was washed with ether (3 X 100 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. NaOH (20 mmol, 800 mg) and water (20 mL) were added to the crude amine mixture and the reaction was cooled to 0 °C. Acryloyl chloride (20 mmol, 1.6 mL) was added slowly, to the reaction to remove unreacted secondary amine. The reaction was warmed to r.t. and stirred for 1 hour. Ether (50 mL) and water (50 mL) were added. The organic layer was washed with water (3 X 50 mL) and the aqueous layer was washed with ether (3 X 50 mL). The organic layers were combined and the amine was extracted into 2M HCl (3 X 50 mL). The aqueous extracts were basified with NaOH pellets and ether (80 mL) was added. The acidic aqueous layer was washed with ether (3 X 100 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting colourless oil was purified by Kügelrohr distillation, 240 °C, 0.1 mm Hg to give the title compound as a colourless oil, 8.48 g, 65 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.58-7.52 (2H, m, Ar-*H*), 7.43-7.28 (8H, m, Ar-*H*), 5.59 (1H, s, C_{11}-*H* (cis to phenyl)), 5.45 (1H, s, C_{11}-*H* (trans to phenyl)), 3.75 (2H, s, C_5-H_2), 3.65 (2H, s, C_9-H_2), 3.39 (2H, d, *J*=2.3 Hz, C_6-H_2), 2.34 (1H, t, *J*=2.3 Hz, C_8-*H*).

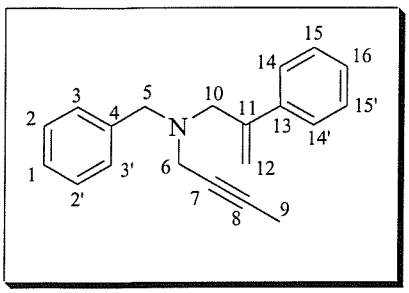
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 144.95 (C, C_{10}), 140.00 (C, C_4), 138.90 (C, C_{12}), 129.31 (CH, C_3, $C_{3'}$), 128.39 (CH, C_{14}, $C_{14'}$), 128.25 (CH, C_2, $C_{2'}$), 127.70 (CH, C_{15}), 127.29 (CH, C_1), 126.70 (CH, C_{13}, $C_{13'}$), 115.85 (CH_2, C_{11}), 78.70 (C, C_7), 73.52 (CH, C_8), 57.79 (CH_2, C_9), 57.50 (CH_2, C_5), 41.21 (CH_2, C_6).

IR (cm^{-1}): 3294 (m), 3057 (w), 3029 (w), 2832 (m), 2361 (m), 2342 (m), 1494 (m), 1368 (w), 1124 (m), 905 (s), 854 (w), 697 (s).

LRMS (EI): *m/z* 261 (M, 16 %), 246 (M-CH_2, 10 %), 144 (M-CH_2CCH_2Ph, 11 %), 91 ($PhCH_2$, 100 %).

HRMS (EI): $C_{19}H_{19}N$ requires m/z 261.1518, found 261.1520.

6.4.12. *N-Benzyl-but-2-ynyl-(2-phenyl-allyl)-amine*, **441**



N-Benzyl-(2-phenyl-allyl)-prop-2-ynyl-amine (6 mmol, 1.57 g) in THF (15 mL) was cooled to -78 °C before BuLi (8 mmol, 3.2 mL) was added dropwise. The reaction was stirred for 20 mins to give an orange solution before HMPA (8 mmol, 1.36 g) was added. The resulting burgundy solution was warmed to -20 °C before MeI (9 mmol, 0.56 mL) was added. The reaction was warmed to r.t. and stirred for 2 hours. Ether (30 mL) and water (30 mL) was added. The organic layer was washed with water (3 X 20 mL) and the aqueous layer was washed with ether (3 X 20 mL). The organic layers were combined, and the enyne was extracted into 2M HCl (3 X 30 mL). The aqueous extracts were basified with NaOH pellets and ether (50 mL) was added. The acidic aqueous layer was washed with ether (3 X 20 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The enyne was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 1 % Et_3N, 99 % petrol, R_f=0.2). The enyne was distilled at 200 °C, 0.1 mm Hg to give the title compound as a yellow oil, 738 mg, 45 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.42-7.36 (2H, m, Ar-*H*), 7.26-7.11 (8H, m, Ar-*H*), 5.41 (1H, s, C_{12}-*H* (cis to phenyl)), 5.29 (1H, s, C_{12}-*H* (trans to phenyl)), 3.56 (2H, s, C_5-H_2), 3.46 (2H, s, C_{10}-H_2), 3.18 (2H, d, *J*=2.3 Hz, C_6-H_2), 1.82 (3H, t, *J*=2.3 Hz, C_9-H_3).

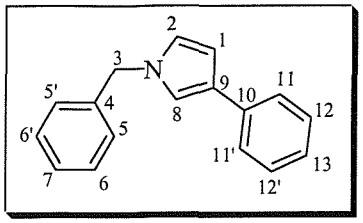
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 145.27 (C, C_{11}), 140.23 (C, C_4), 139.29 (C, C_{13}), 129.31 (CH, C_3, $C_{3'}$), 128.31 (CH, C_{15}, $C_{15'}$), 128.22 (CH, C_2, $C_{2'}$), 127.62 (CH, C_{16}), 127.13 (CH, C_1), 126.72 (CH, C_{14}, $C_{14'}$), 115.58 (CH_2, C_{12}), 81.06 (C, C_7), 73.95 (C, C_8), 57.86 (CH_2, C_{10}), 57.55 (CH_2, C_5), 41.84 (CH_2, C_6), 3.70 (CH_3, C_9).

IR (cm^{-1}): 3082 (w), 3028 (w), 3029 (w), 2918 (w), 1628 (w), 1494 (m), 1453 (m), 1246 (w), 1128 (m), 905 (s), 855 (w), 697 (s).

LRMS (EI): *m/z* 275 (M, 5 %), 172 (M-Me-benzyl, 52 %), 144 (M-CC-Me-benzyl, 10 %), 91 ($PhCH_2$, 100 %).

HRMS (ES+): $C_{20}H_{22}N^+$ requires m/z 276.1747, found 276.1745.

6.4.13. *1-benzyl-3-phenyl-pyrrol*, **444**



N-Benzyl-allyl-(2-phenyl-allyl)-amine (0.5 mmol, 132 mg) and Grubbs' catalyst (6 mol%, 27 mg) in toluene (30 mL) was heated at 80 °C for 24 hours under an argon atmosphere. Ether (50 mL) and water (50 mL) were added. The organic layer was washed with water (3 X 20 mL). The aqueous layer was washed with ether (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The pyrrole was purified by Kügelrohr distillation (0.1 mm Hg, 180 °C), followed by column chromatography (SiO_2, 1:9 ether to petrol, R_f=0.5). This gave the title compound as a yellow oil, 46 mg, 39 %.

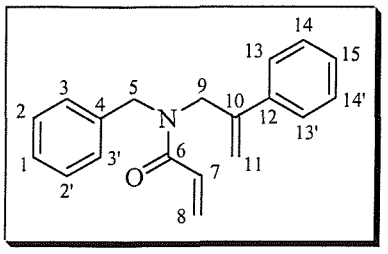
^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.40 (2H, d, *J*=7.3 Hz, C_{11}-*H*, $C_{11'}$-*H*), 7.26-7.15 (5H, m, Ar-*H*), 7.08-7.02 (3H, m, Ar-*H*), 6.88 (1H, t, *J*=1.8 Hz, C_8-*H*), 6.60 (1H, t, *J*=2.4 Hz, C_2-*H*), 6.41 (1H, t, *J*=2.4 Hz, C_1-*H*), 4.95 (2H, bs, C_3-H_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 137.98 (C, C_4), 136.00 (C, C_{10}), 128.93 (CH, C_5, $C_{5'}$), 128.73 (CH, C_{12}, $C_{12'}$), 127.91 (CH, C_{13}), 127.25 (CH, C_6, $C_{6'}$), 125.49 (CH, C_7), 125.36 (C, C_9), 125.12 (CH, C_{11}, $C_{11'}$), 122.41 (CH, C_2), 118.13 (CH, C_8), 106.78 (CH, C_1), 53.72 (CH_2, C_3).

LRMS (EI): *m/z* 233 (M, 91 %), 156 (M-Ph, 15 %), 142 (M-CH_2Ph, 18 %), 91 (CH_2Ph, 100 %).

In agreement with literature[224].

6.4.14. *N-Benzyl-N-(2-phenyl-allyl)-acrylamide*, **445**



N-Benzyl-(2-phenyl-allyl)-amine (10 mmol, 2.23 g) and NaOH (20 mmol, 800 mg) in water (20 mL) were cooled to 0 °C. Acryloyl chloride (20 mmol, 1.6 mL) was added slowly. The reaction was warmed to r.t. and stirred for 1 hour. Water (30 mL) and ether (30 mL) were added. The organic phase was washed with water (3 X 20 mL), followed by 2M HCl (3 X 20 mL) to remove any unreacted amine. The aqueous phase was washed with ether (3 X 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (SiO_2, 2:3 ether to petrol, R_f=0.5) to give the title compound as a pale yellow oil, 1.07 g, 39 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.31-7.25 (2H, m, Ar-*H* (major and minor rotamers)), 7.20-7.06 (16H, m, Ar-*H* (major and minor rotamers)), 6.99-6.93 (2H, m, Ar-*H* (major and minor rotamers)), 6.41-6.17 (4H, m, C_7-*H*, C_8-*H* (*cis*), (major and minor rotamers)), 5.54 (1H, d, *J*=9.5 Hz, C_8-*H* (*trans*), (major rotamer)), 5.49 (1H, d, *J*=10.3 Hz, C_8-*H* (*trans*), (minor rotamer)), 5.35 (1H, s, C_{11}-*H* (*cis* to phenyl), (major rotamer)), 5.32 (1H, s, C_{11}-*H* (*cis* to phenyl), (minor rotamer)), 4.98 (1H, s, C_{11}-*H* (*trans* to phenyl), (major rotamer)), 4.92 (1H, s, C_{11}-*H* (*trans* to phenyl), (minor rotamer)), 4.54 (2H, s, C_5-H_2 (major rotamer)), 4.41 (2H, s, C_5-H_2 (minor rotamer)), 4.34 (2H, s, C_9-H_2 (minor rotamer)), 4.08 (2H, s, C_9-H_2 (major rotamer)).

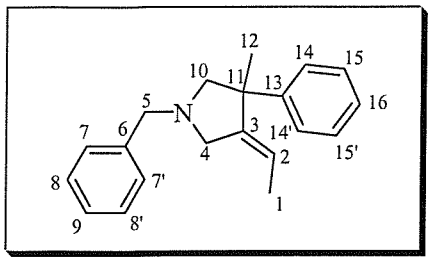
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 167.39 (C, C_6 (major rotamer)), 167.06 (C, C_6 (minor rotamer)), 143.40 (C, C_{10} (minor rotamer)), 142.75 (C, C_{10} (major rotamer)), 138.87 (C, C_4 (major rotamer)), 138.60 (C, C_4 (minor rotamer)), 137.53 (C, C_{12} (major rotamer)), 136.76 (C, C_{12} (minor rotamer)), 129.01 (CH, C_7 (major and minor rotamers)), 128.95 (CH_2, C_8 (major and minor rotamers)), 128.80 (CH), 128.76 (CH), 128.57 (CH), 128.49 (CH), 128.44 (CH), 128.16 (CH), 127.79 (CH), 127.65 (CH), 126.64 (CH), 126.45 (CH), 126.05 (CH), 114.94 (CH_2, C_{11} (minor rotamer)), 113.20 (CH_2, C_{11} (major rotamer)), 50.21 (CH_2, C_9 (major rotamer)), 49.71 (CH_2, C_9 (minor rotamer)), 49.24 (CH_2, C_5 (major rotamer)), 48.43 (CH_2, C_5 (minor rotamer)).

IR (cm^{-1}): 3083 (w), 3028 (w), 2359 (w), 1649 (s), 1615 (m), 1495 (m), 1429 (s).

LRMS (EI): *m/z* 277 (M, 35 %), 262 (M-O, 21 %), 262 (M-O-CH_2, 4 %), 186 (M-Ph, 18 %).

HRMS (EI): $C_{19}H_{19}NO$ requires m/z 277.1467, found 277.1466.

6.4.15. *1-Benzyl-4-ethylidene-3-methyl-3-phenyl-pyrrolidine,* **447**



Cp_2ZrCl_2 (1 mmol, 292 mg) in THF (5 mL) was cooled to -78 °C before BuLi (2 mmol, 0.8 mL) was added slowly. The reaction was stirred for 20 mins at -78 °C before diene (1 mmol, 275 mg) in THF (5 mL) was added slowly. The reaction was warmed to r.t. and stirred for 3 hours. MeOH (5 mL) and $NaHCO_3$ solution (5 mL) were added to the zirconacycle solution and stirred overnight. Ether (30 mL) and water (30 mL) were added. The organic layer was washed with water (3 X 20 mL). The aqueous layer was washed with ether (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The pyrrolidine was purified by column chromatography (column pre-treated with 2 % Et_3N, 98 % petrol, followed by 2 % Et_3N, 98 % petrol, R_f=0.6), followed by Kügelrohr distillation at 220 °C, 0.1 mm Hg. This gave the title compound as a colourless oil, 143 mg, 52 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.34 (2H, d, *J*=7.5 Hz, C_{14}-*H*, $C_{14'}$-*H*), 7.25-7.06 (8H, m, Ar-*H*), 5.06 (1H, qdd, *J*=6.8 Hz, *J*=2.5 Hz, *J*=2.5 Hz, C_2-*H*), 3.59 (2H, d, *J*=2.3 Hz, C_5-H_2), 3.33-3.28 (2H, bs, C_4-H_2), 2.88 (1H, d, *J*=8.9 Hz, C_{10}-*H*), 2.57 (1H, d, *J*=8.9 Hz, C_{10}-*H*), 1.51 (3H, d, *J*=6.8 Hz, C_1-H_3), 1.41 (3H, s, C_{12}-H_3),

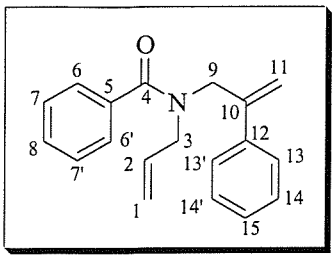
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 148.63 (C, C_{13}), 148.43 (C, C_3), 139.46 (C, C_6), 128.71 (CH, C_7, $C_{7'}$), 128.38 (CH, C_{15}, $C_{15'}$), 128.02 (CH, C_8, $C_{8'}$), 127.00 (CH, C_9), 126.91 (CH, C_{14}, $C_{14'}$), 125.84 (CH, C_{16}), 116.34 (CH, C_2), 69.73 (CH_2, C_{10}), 60.52 (C, C_{11}), 57.21 (CH_2, C_5), 49.78 (CH_2, C_4), 27.14 (CH_3, C_1), 14.85 (CH_3, C_{12}).

IR (cm^{-1}): 3059 (w), 2965 (m), 2784 (m), 1600 (w), 1494 (s), 1453 (s), 1444 (s), 1264 (w).

LRMS (EI): *m/z* 277 (M, 17 %), 262 (M-CH_3, 28 %), 200 (M-Ph, 6 %), 91 ($PhCH_2$, 100 %).

HRMS (ES+): $C_{20}H_{24}N^+$ requires m/z 278.1903, found 278.1904.

6.4.16. *N-Allyl-N-(2-phenyl-allyl)-benzamide*, **451**



N-Allyl-(2-phenyl-allyl)-amine (30 mmol, 5.22 g), benzoyl chloride (30 mmol, 4.1 mL) in 2M NaOH (50 mL) were stirred overnight at r.t.. The reaction was quenched with water (30 mL) and ether (30 mL) was added. The ether layer was washed with water (3 X 20 mL). The aqueous layer was washed with ether (3 X 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was dissolved in ether (20 mL) and washed with 2M HCl (4 X 20 mL) to remove unreacted amine. The organic layer was collected, dried ($MgSO_4$) and concentrated *in vacuo*. The amide was purified by column chromatography (SiO_2, 3:1 petrol to ether, R_f=0.2) to give the title amide as a yellow solid, 6.20 g, 78 %.

^{1}H NMR (400 MHz, CDCl3): δ / ppm 7.45-6.95 (20H, m, Ar-H), 5.90-5.67 (1H, bs, C_2-H (rotamer)), 5.64-5.43 (1H, bs, C_2-H (rotamer)), 5.38 (2H, s, C_{11}-H (*cis* to phenyl)), 5.23-4.91 (6H, m, C_1-H_2, C_{11}-H (*trans* to phenyl)), 4.66-4.42 (2H, bs, C_9-H (rotamer)), 4.22-3.95 (4H, m, C_9-H (rotamer), C_3-H (rotamer)), 3.65-3.48 (2H, bs, C_3-H (rotamer)).

^{13}C NMR (100 MHz, CDCl3): δ / ppm 172.06 (C, C_4), 143.82 (C, C_{10}), 138.98 (C, C_{12} (rotamer)), 138.76 (C, C_{12} (rotamer)), 136.51 (C, C_5), 133.07 (CH, C_2), 129.89 (CH, rotamer), 129.56 (CH, rotamer), 128.60 (CH), 128.50 (CH), 128.26 (CH), 126.57 (CH, rotamer), 126.46 (CH, rotamer), 117.89 (CH_2, C_1), 114.84 (CH_2, C_{11} (rotamer), 113.95 (CH_2, C_{11} (rotamer), 52.22 (CH_2, C_9 (rotamer), 50.24 (CH_2, C_9 (rotamer), 47.56 (CH_2, C_3 (rotamer), 47.02 (CH_2, C_3 (rotamer),

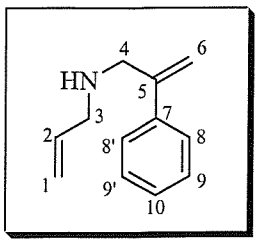
IR (cm-1): 1635 (s), 1457 (m), 1442 (s), 1421 (s), 1258 (s), 774 (s).

LRMS (EI): *m/z* 277 (M, 10 %), 172 (M-Ph-CO, 12 %).

M.P.: 55-57 °C

Microanalysis: Found: C 82.08, H 6.92, N 5.06. Requires: C 82.28, H 6.90, 5.05.

6.4.17. *N-Allyl-(2-phenyl-allyl)-amine*



In a 1 litre Schlenk flask, α-methylstyrene (0.8 mol, 94.4 g), *N*-bromosuccinimide (90 g, 0.5 mol) in CCl_4 (50 mL) were refluxed for 2 hours at 140 °C. Resulting yellow reaction mixture was cooled to r.t., filtered, and CCl_4 was removed *in vacuo* to give an orange oil. GC analysis showed the crude reaction mixture to be approximately 50 % unreacted α-methylstyrene, whilst the rest of the mass was a 7:2 ratio of bromine regioisomers. Acetonitrile (30 mL) was added to the crude reaction mixture before being added dropwise at 0 °C to a stirred solution of allylamine (4 eq, 1.2 M, 69 g), anhydrous K_2CO_3 (2 eq, 0.6 M, 84 g) in acetonitrile (200 mL). The reaction was warmed to r.t. and stirred overnight. Ether (100 mL) and water (100 mL) were added. The organic layer was washed with water (3 X 50 mL) and the aqueous layer was washed with ether (3 X 50 mL). The ether layers were combined and the amine was extracted with 2M HCl (3 X 50 mL). The acidic aqueous layer was basified with NaOH pellets and washed with ether (3 X 50 mL). Ether layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The diene was purified by distillation (0.1 mmHg, 140 °C) to give the title compound as a colourless oil, 54.22 g, 63 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.50 (2H, d, *J*=7.8 Hz, C_8-*H*, $C_{8'}$-*H*), 7.43-7.29 (3H, m, Ar-*H*), 5.96 (1H, ddt, *J*=17.3 Hz, *J*=10.3 Hz, *J*=6.3 Hz, C_2-*H*), 5.46 (1H, s, C_6-*H* (cis to phenyl)), 5.30 (1H, s, C_6-*H* (trans to phenyl)), 5.23 (1H, d, *J*=17.3 Hz, C_1-*H*), 5.15 (1H, d, *J*=10.3 Hz, C_1-*H*), 3.72 (2H, s, C_4-H_2), 3.33 (2H, d, *J*=6.3 Hz, C_3-H_2), 1.43-1.22 (1H, bs, N*H*).

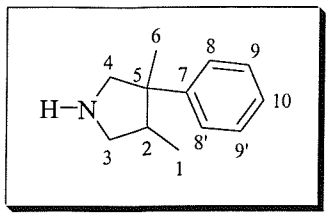
^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm 146.57 (C, C_5), 140.14 (C, C_7), 137.01 (CH, C_2), 128.61 (CH, C_9, $C_{9'}$), 127.82 (CH, C_{10}), 126.36 (CH, C_8, $C_{8'}$), 116.18 (CH_2, C_1), 113.50 (CH_2, C_6), 52.91 (CH_2, C_4), 51.79 (CH_2, C_3).

IR (cm^{-1}): 3080 (w), 2978 (w), 2813 (w), 1642 (w), 1629 (w), 1494 (m), 1444 (m).

LRMS (EI): *m/z* 173 (M, 93 %), 158 (M-15, 28 %), 144 (M-29, 55 %), 118 (M-55, 100 %).

HRMS (ES+): $C_{12}H_{16}N^+$ requires m/z 174.1283, found 174.1279.

6.4.18. *3,4-Dimethyl-3-phenyl-pyrrolidine,* **455**



Bromo-Wang resin (1 mmol, 632 mg) was heated at 60 °C with *N*-allyl-(2-phenyl-allyl)-amine (10 mmol, 1.73 g) in NMP (10 mL) overnight. The reaction mixture was filtered and washed with three cycles of DCM (20 mL), MeOH (20 mL) and THF (20 mL), before finishing with a single wash of DCM (20 mL). The resulting orange coloured amine supported resin (1 mmol, 668 mg) was transferred to a 50 mL Schlenk flask, dried for 3 hours on a high-vacuum and THF (15 mL) was added. In a separate 25 mL Schlenk flask, Cp_2ZrCl_2 (2 eq, 2 mmol, 584 mg) in THF (10 mL) was cooled to -78 °C before BuLi (4 eq, 4 mmol, 1.6 mL) was added dropwise. Reaction was stirred at -78 °C for 40 mins before being added *via* cannular to the resin suspension at -78 °C. The reaction was shaken before warming to r.t.. After 3 hours, the dark brown reaction mixture was quenched with MeOH (10 mL) and aqueous $NaHCO_3$ (10 mL) and the reaction was left overnight at r.t.. The reaction mixture was filtered and washed with three cycles of dichloromethane (20 mL), hot water (20 mL), MeOH (20 mL) and THF (20 mL), before finishing with a single wash of DCM (20 mL). The resulting yellow pyrrolidine supported resin (1 mmol, 675 mg) was suspended in dichloromethane (10 mL) before ACE-Cl (20 mmol, 2.1 mL) was added. The reaction was stirred slowly for 3 hours at r.t. before filtering and washing the resin with DCM (4 X 20 mL). The solvent and volatiles were removed *in vacuo* to give the carbamate as a pale yellow oil, 110 mg, 39 %. The carbamate (0.39 mmol, 110 mg) was dissolved in MeOH (10 mL) and refluxed at 70 °C for 3 hours. This gave the pyrrolidine hydrochloride salt as a brown oil, 81 mg, 38 %. The hydrochloride salt was basified with 2M NaOH and purified by acid/base extraction to give the title pyrrolidine as a yellow oil, 31 mg, 18 % as a 15:1 mixture of diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.32-7.07 (5H, m, Ar-*H*), 3.68-3.46 (1H, bm, C_4-*H*), 3.29-3.10 (2H, m, 2 X C_3-*H*), 2.96 (1H, d, *J*=9.0 Hz, C_4-*H*), 2.67 (1H, t, *J*=10.0 Hz, N-*H*), 2.37 (1H, dq, *J*=9.0 Hz, *J*=7.0 Hz, C_2-*H*), 1.18 (3H, s, C_6-H_3), 0.88 (3H, d, *J*=7.0 Hz, C_1-H_3).

^{13}C NMR (100 MHz, $CDCl_3$): *Trans* Isomer: δ / ppm 147.27 (C, C_7), 128.34 (CH, C_9, $C_{9'}$), 126.03 (CH, C_8, $C_{8'}$), 125.96 (CH, C_{10}), 61.68 (CH_2, C_4), 53.47 (CH_2, C_3), 48.00 (C, C_5), 43.53 (CH, C_2), 20.20 (CH_3, C_6), 12.65 (CH_3, C_1).

^{13}C NMR (100 MHz, $CDCl_3$): *Cis* Isomer: δ / ppm 146.22 (C, C_7), 128.34 (CH, C_9, $C_{9'}$), 126.03 (CH, C_8, $C_{8'}$), 125.96 (CH, C_{10}), 60.58 (CH_2, C_4), 52.66 (CH_2, C_3), 46.97 (C, C_5), 42.06 (CH, C_2), 19.57 (CH_3, C_6), 12.39 (CH_3, C_1).

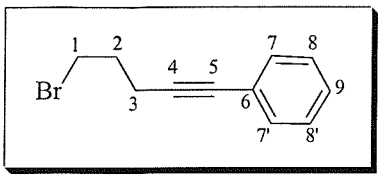
IR (cm^{-1}): 1654 (w), 1600 (w), 1497 (m), 1443 (m), 1407 (s).

LRMS (CI): *m/z* 176 ($M+H^+$, 100 %), 146 (M^+-Me-Me, 3 %), 117 (M-Ph+NH_4^+, 6 %).

HRMS (ES+): $C_{12}H_{18}N^+$ requires m/z 176.1434, found 176.1432.

6.5. Experimental For Chapter 5

6.5.1. (5-bromo-pent-1-ynyl)-benzene



Phenylacetylene (1 eq, 30 mmol, 3.06 g), in THF (40 mL), was cooled to -78 °C before BuLi (1.1 eq, 33 mmol, 13.2 mL) was added. The reaction was stirred for 1 hour at -78 °C before HMPA (1.1 eq, 33 mmol, 5.7 mL) was added. The resulting brown solution was warmed to -30 °C to give a dark green solution before 1,3-dibromopropane (3 eq, 90 mmol, 9.1 mL) was added to give a yellow/orange solution. The reaction warmed to r.t. and stirred overnight. The reaction was quenched with water (30 mL) and ether (30 mL) was added. The aqueous layer was washed with ether (3 X 25 mL) and the organic layer was washed with water (3 X 25 mL). The organic fractions were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a golden yellow oil. The bromide was purified by column chromatography (SiO_2 / 100 % petrol, R_f=0.5) to give the title compound as a colourless oil, 2.76 g, 41 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.45-7.37 (2H, m, Ar-*H*), 7.35-7.24 (3H, m, Ar-*H*), 3.61 (2H, t, *J*=6.6 Hz, C_1-*H*$_2$), 2.63 (2H, t, *J*=6.6 Hz, C_3-*H*$_2$), 2.15 (2H, tt, *J*=6.6 Hz, *J*=6.6 Hz, C_2-*H*$_2$).

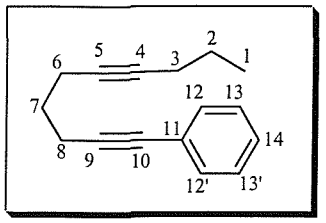
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 131.74 (CH, C_7, $C_{7'}$), 128.41 (CH, C_8, $C_{8'}$), 127.96 (CH, C_9), 123.70 (C, C_6), 88.08 (C, C_4), 81.77 (C, C_5), 32.64 (CH_2, C_2), 31.70 (CH_2, C_1), 18.31 (CH_2, C_3).

IR (cm^{-1}): 2235 (w), 1597 (w), 1489 (w), 1247 (w), 756 (m), 691 (m), 681 (w).

LRMS (CI): *m/z* 242 (M+NH_4, 10 %), 240 (M+NH_4, 10%), 224 (M, 40 %), 222 (M, 40 %), 143 (M-Br, 100 %), 128 (M-Br-Me, 55 %), 115 (M-Br-Et, 85 %), 89 (M+H-Br-Ph, 12 %), 63 (M-Br-Ph-Me, 11 %).

HRMS (EI): $C_{11}H_{15}NBr$ requires m/z 240.0388, found 240.0383

6.5.2. *Deca-1,6-diynyl-benzene*



1-pentyne (1.5 eq, 1.5 mL, 15 mmol,) in THF (15 mL) was cooled to -78 °C before BuLi (1.5 eq, 6.0 mL, 15 mmol) was added dropwise. The reaction was stirred at -78°C for 1 hour before HMPA (1.5 eq, 15 mmol, 2.7 mL) was added. The reaction was then warmed to -30 °C before (5-bromo-pent-1-ynyl)-benzene (1 eq, 10 mmol, 2.23 g) in THF (10 mL) was added slowly to the deprotonated alkyne *via cannular*. The reaction was warmed to r.t. and stirred overnight to afford a dark purple solution. The reaction was quenched with water (30 mL) and ether (30 mL) was added. The aqueous layer was washed with ether (3 X 30 mL) and the organic layer was washed with water (3 X 30 mL). The organic fractions were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. The diyne was purified by column chromatography (SiO_2 / 100 % petrol, R_f=0.4) to give the title compound as a colourless oil, 918 mg, 44 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 7.45-7.37 (2H, m, Ar-*H*), 7.34-7.25 (3H, m, Ar-*H*), 2.54 (2H, t, *J*=7.0 Hz, C_8-*H*$_2$), 2.35 (2H, tt, *J*=7.0Hz, *J*=2.2 Hz, C_6-*H*$_2$), 2.15 (2H, tt, *J*=7.0Hz, *J*=2.2 Hz, C_3-*H*$_2$), 1.81 (2H, quintet, *J*=7.0 Hz, C_7-*H*$_2$), 1.53 (2H, sextet, *J*=7.3 Hz, C_2-*H*$_2$), 1.00 (3H, t, *J*=7.3 Hz, C_1-*H*$_3$).

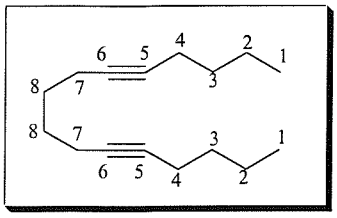
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 131.72 (CH, C_{12}, $C_{12'}$), 128.35 (CH, C_{13}, $C_{13'}$), 127.73 (CH, C_{14}), 124.06 (C, C_{11}), 89.62 (C, C_9), 81.15 (C, C_5), 81.05 (C, C_{10}), 79.36 (C, C_4), 28.51 (CH_2, C_7), 22.67 (CH_2, C_2), 20.93 (CH_2, C_3), 18.74 (CH_2, C_6), 18.23 (CH_2, C_8), 13.67 (CH_3, C_1).

IR (cm^{-1}): 2960 (m), 2930 (m), 2904 (w), 2868 (w), 2832 (w), 2067 (w), 1598 (w), 1490 (s), 1440 (m), 1434 (m), 1337 (w), 755 (s), 691 (s).

LRMS (CI): *m/z* 228 ($M+NH_4$, 42 %), 211 (M+H, 67 %), 195 (M+H-Me, 16 %), 181 (M+H-Et, 100 %).

HRMS (EI): $C_{16}H_{18}$ requires m/z 210.1409, found 210.1408

6.5.3. *Hexadeca-5,11-diyne*



1-hexyne (3 eq, 7.39 g, 90 mmol,) in THF (70 mL) was cooled to -78 °C before BuLi (3.2 eq, 38.4 mL, 96 mmol) was added dropwise. The reaction was stirred at -78°C for 1 hour before HMPA (3.2 eq, 96 mmol, 16.6 mL) was added. The reaction was then warmed to -30 °C to give a yellow solution. 1,4-dibromobutane (1 eq, 30 mmol, 3.6 mL) was added slowly to the deprotonated alkyne whereby the solution immediately went colourless. The reaction was warmed to r.t. and stirred overnight. The reaction was quenched with water (30 mL) and ether (30 mL) was added. The aqueous layer was washed with ether (3 X 25 mL) and the organic layer was washed with water (3 X 25 mL). The organic fractions were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. The diyne was purified by column chromatography (SiO_2 / 100 % petrol, R_f=0.4) to give the title compound as a colourless oil, 1.47 g, 23 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 2.22-2.10 (8H, m, C_4-$\underline{H_2}$, C_7-$\underline{H_2}$), 1.64-1.54 (4H, m, C_8-$\underline{H_2}$), 1.53-1.33 (8H, m, C_2-$\underline{H_2}$, C_3-$\underline{H_2}$), 0.91 (6H, t, *J*=7.0 Hz, C_1-$\underline{H_3}$).

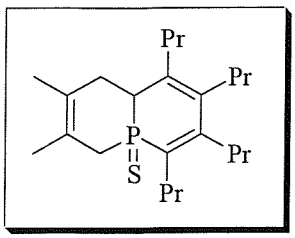
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 80.61 (C, C_6), 79.918 (C, C_5), 31.42 (CH_2, C_3), 28.43 (CH_2, C_8), 22.11 (CH_2, C_2), 18.61 (CH_2, C_4), 18.50 (CH_2, C_7), 13.82 (CH_3, C_1).

IR (cm^{-1}): 2956 (s), 2932 (s), 2861 (m), 2340 (w), 2326 (w), 1470 (m), 1434 (m).

LRMS (CI): *m/z* 236 ($M+NH_4$, 66 %) 219 (M+H, 73 %), 189 (M-Et, 42 %), 175 (M-Pr, 100 %), 161 (M-Bu, 63 %), 147 (M+H-Bu-Me, 40 %), 133 (M+H-Bu-Et, 75 %).

HRMS (ES+): $C_{16}H_{30}N$ requires m/z 236.2378, found 236.2375

6.5.4. *2,3-dimethyl-5,6,7,8-tetrapropyl-1,8a-dihydro-4H-4a-phospha-naphthalene 4a-sulfide*, **526a**



Cp_2ZrCl_2 (1 eq, 1 mmol, 292 mg) in THF (5 mL) was cooled to -78 °C before BuLi (2 eq, 2 mmol, 0.8 mL) was added dropwise. After 30 minutes, 4-octyne (2.1 eq, 2.1 mmol, 231 mg) in THF (5 mL) was added and the reaction was warmed to r.t. and stirred for a further 2 hours. Me_3SiCH_2Cl (1.2 eq, 1.2 mmol, 147 mg), TMEDA (1.2 eq, 1.2 mmol, 140 mg) in THF (5 mL) were cooled to -78 °C before ^{s}BuLi (1.2 eq, 1.2 mmol, 0.92 mL) was added dropwise. The reaction was stirred for an hour at -78 °C. The red zirconacycle solution was cooled down to -78 °C before being added *via cannular* to the carbenoid solution at -78 °C. After an hour at -78 °C, PCl_3 (2.5 eq, 2.5 mmol, 0.25 mL) was added. The reaction was stirred for 1 hour before warming to r.t. and stirred overnight. All volatile materials and solvent were removed *via* low pressure evaporation. The solid was washed with hexane (8 X 50 mL) and the hexane solution containing the phosphinine was filtered through celite under a flow of argon. The hexane was removed *via* vacuum transfer to afford 178 mg of **512a** as a yellow oil. The oil was 55% pure (calculated by ^{1}H NMR), to give a yield of 37 % of **512a**. In a sealed tube, **512a** (178 mg, 55 % purity, 0.37 mmol, 1 eq), sulphur (1.6 eq, 0.61 mmol, 20 mg), 2,3-dimethylbutadiene (10.7 eq, 4.1 mmol, 0.46 mL) in toluene (2 mL) were refluxed for 24 hours at 105 °C. Purification by column chromatography (SiO_2, 1:9 ether to petrol (R_f=0.3), gave the title compound as a pale yellow oil, 33 mg, 9 % over 4 steps.

^{31}P NMR (121 MHz, $CDCl_3$): δ / ppm 22.27

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 2.88-2.57 (1H, m, C-*H*), 2.56-2.26 (4H, m, 2 x C-H_2), 2.25-2.02 (4H, m, 2 x C-H_2), 2.01-1.83 (2H, m, C-H_2), 1.81-1.05 (10H, m, 5 x C-H_2), 1.68 (3H, s, C-H_3), 1.59 (3H, s, C-H_3), 1.03-0.80 (12H, m, 4 x C-H_3).

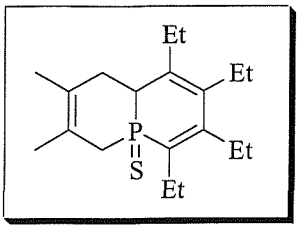
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 148.63 (C, J_{PC}=4.0 Hz), 135.25 (C, J_{PC}=10.2 Hz), 132.81 (C, J_{PC}=18.7 Hz), 128.48 (C, J_{PC}=9.0 Hz), 123.82 (C, J_{PC}=76.9 Hz), 120.92 (C, J_{PC}=6.8 Hz), 38.11 (CH, J_{PC}=54.8 Hz), 37.88 (CH_2, J_{PC}=4.5 Hz), 37.41 (CH_2, J_{PC}=5.6 Hz), 35.41 (CH_2, J_{PC}=50.3 Hz), 32.00 (CH_2, J_{PC}=11.3 Hz), 31.32 (CH_2, J_{PC}=2.3 Hz), 30.82 (CH_2, J_{PC}=10.2 Hz), 23.85 (CH_2, J_{PC}=3.4 Hz), 23.24 (CH_2, J_{PC}=2.8 Hz), 23.09 (CH_2, J_{PC}=2.8 Hz), 21.40 (CH_3, J_{PC}=11.3 Hz), 21.06 (CH_2, J_{PC}=2.3 Hz), 20.15 (CH_3, J_{PC}=1.7 Hz), 14.54 (CH_3), 14.42 (CH_3), 14.41 (CH_3), 14.36 (CH_3).

IR (cm^{-1}): 2958 (m), 2930 (m), 2865 (m), 2364 (s), 2335 (s), 1456 (m), 1076 (m), 818 (m), 791 (m), 699 (s).

LRMS (EI): *m/z* 378 (M, 12%), 349 (M-Et, 8%), 317 (M-Pr-Me, 12%), 296 (M-C_3H_8, 7%), 235 (M-C_3H_8-Pr-Me, 17%), 207 (M-171, 19%), 133 (M-245, 15%), 91 (M-287, 18%)

HRMS (EI): $C_{23}H_{39}PS$ requires m/z 378.2510, found 378.2499

6.5.5. *2,3-dimethyl-5,6,7,8-tetraethyl-1,8a-dihydro-4H-4a-phospha-naphthalene 4a-sulfide,* **526b**



Cp_2ZrCl_2 (1 eq, 1 mmol, 292 mg) in THF (5 mL) was cooled to -78 °C before BuLi (2 eq, 2 mmol, 0.8 mL) was added dropwise. After 30 minutes, 3-hexyne (2.1 eq, 2.1 mmol, 173 mg) in THF (5 mL) was added and the reaction was warmed to r.t. and stirred for a further 2 hours. Me_3SiCH_2Cl (1.2 eq, 1.2 mmol, 147 mg), TMEDA (1.2 eq, 1.2 mmol, 140 mg) in THF (5 mL) were cooled to -78 °C before ^{s}BuLi (1.2 eq, 1.2 mmol, 0.92 mL) was added dropwise. The reaction was stirred for an hour at -78 °C. The red zirconacycle solution was cooled down to -78 °C before being added *via cannular* to the carbenoid solution at -78 °C. After an hour at -78 °C, PCl_3 (2.5 eq, 2.5 mmol, 0.25 mL) was added. The reaction was stirred for 1 hour before warming to r.t. and stirred overnight. All volatile materials and solvent were removed *via* low pressure evaporation. The solid was washed with hexane (8 X 50 mL) and the hexane solution containing the phosphinine was filtered through celite under a flow of argon. The hexane was removed *via* vacuum transfer to afford 113 mg of **512b** as a yellow oil. The oil was 60 % pure (calculated by ^{1}H NMR), to give a yield of 33 % of **512b**. In a sealed tube, **512b** (113 mg, 60 % purity, 0.33 mmol, 1 eq), sulphur (1.6 eq, 0.53 mmol, 17 mg), 2,3-dimethylbutadiene (10.7 eq, 3.5 mmol, 0.40 mL) in toluene (2 mL) were refluxed for 24 hours at 105 °C. Purification by column chromatography (SiO_2, 1:4 ether to petrol (R_f=0.3), gave the title compound as a pale yellow oil, 65 mg, 20 % over 4 steps.

^{31}P NMR (121 MHz, $CDCl_3$): δ / ppm 22.55

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 3.40-1.78 (13H, m, C-*H*, 6 x C-H_2), 1.68 (3H, s, C-H_3), 1.60 (3H, s, C-H_3), 1.13 (3H, t, *J*=7.7 Hz, C-H_3), 1.08 (3H, t, *J*=7.7 Hz, C-H_3), 0.98 (3H, t, *J*=7.4 Hz, C-H_3), 0.95 (3H, t, *J*=7.7 Hz, C-H_3).

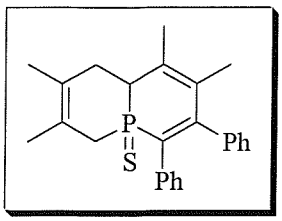
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 149.52 (C, J_{PC}=4.0 Hz), 136.22 (C, J_{PC}=10.2 Hz), 133.32 (C, J_{PC}=18.1 Hz), 128.38 (C, J_{PC}=9.0 Hz), 124.91 (C, J_{PC}=76.9 Hz), 121.12 (C, J_{PC}=6.2 Hz), 37.07 (CH, J_{PC}=54.8 Hz), 36.76 (CH_2, J_{PC}=4.5 Hz), 34.55 (CH_2, J_{PC}=50.3 Hz), 27.18 (CH_2, J_{PC}=5.7 Hz), 21.80 (CH_2, J_{PC}=11.3 Hz), 21.23 (CH_2, J_{PC}=1.7 Hz), 20.67 (CH_2, J_{PC}=10.7 Hz), 20.56 (CH_3, J_{PC}=11.3 Hz), 19.42 (CH_3, J_{PC}=1.1 Hz), 14.24 (CH_3, J_{PC}=4.0 Hz), 13.96 (CH_3, J_{PC}=2.8 Hz), 13.66 (CH_3, J_{PC}=2.8 Hz), 11.65 (CH_3, J_{PC}=2.1 Hz).

IR (cm^{-1}): 2966 (m), 2932 (m), 2869 (w), 2357 (w), 2344 (m), 1450 (m), 1376 (m), 1261 (w), 1122 (w), 1094 (w), 1043 (m), 928 (w), 821 (m), 793 (m), 756 (s), 693 (s).

LRMS (EI): *m/z* 322 (M, 100%), 307 (M-Me, 12%), 289 (M-Et, 33%), 275 (M-47, 37%), 240 (M-C_6H_8, 29%), 208 (M-C_6H_8-S, 21%), 177 (M-C_6H_8-S-Et, 91%), 161 (M-C_6H_8-S-Et-Me, 23%), 147 (M-C_6H_8-S-Et-Et, 32%), 133 (M-C_6H_8-S-Et-Et-Me, 33%), 91 (M-231, 34%)

HRMS (EI): $C_{19}H_{31}PS$ requires m/z 322.1884, found 322.1893

6.5.6. *2,3,7,8-tetramethyl-5,6-diphenyl-1,8a-dihydro-4H-4a-phospha-naphthalene 4a-sulfide,* **526e**



Cp_2ZrCl_2 (1 mmol, 292 mg) in THF (5 mL) was cooled to -78 °C before BuLi (2 mmol, 0.8 mL) was added dropwise and stirred for 30 minutes. DMAP (2 mmol, 245 mg) in THF (3 mL) was added to the Negishi's reagent, warmed to r.t. and stirred for 1.5 hours. The reaction was cooled to 0 °C before diphenylacetylene (1 mmol, 179 mg) in THF (3 mL) was added. The reaction was warmed to r.t., stirred for 1.5 hours before the reaction was cooled to 0 °C and 2-butyne (1.1 mmol, 59 mg) in THF (3 mL) was added. The reaction was warmed to r.t. and stirred for 1.5 hours. Me_3SiCH_2Cl (1.2 mmol, 147 mg), TMEDA (1.2 mmol, 140 mg) in THF (5 mL) were cooled to -78 °C before ^{s}BuLi (1.2 mmol, 0.92 mL) was added dropwise. After stirring for 1 hr, the zirconacycle solution was added *via cannular* to the carbenoid solution at -78 °C. After an hour, PCl_3 (2.5 mmol, 0.25 mL) was added. The reaction was stirred for 1 hour at -78 °C before warming to r.t. and stirring overnight. All volatiles and solvent were removed *via* low pressure evaporation. The product was washed with hexane (8 X 50 mL) and the hexane solution containing the phosphinine was filtered through celite under a flow of argon. The hexane was removed *via* vacuum transfer to afford 187 mg of a 1:1 mixture of **512e** and **513e** as a yellow oil. The residue was 50% pure (calculated by ^{1}H NMR), to give a yield of 34 % of **512e**. In a sealed tube, **512e** (187 mg, 50 % purity, 0.34 mmol, 1 eq), sulphur (1.6 eq, 0.54 mmol, 18 mg), 2,3-dimethylbutadiene (10.7 eq, 3.6 mmol, 0.41 mL) in toluene (2 mL) were refluxed for 24 hours at 105 °C. Purification by column chromatography (SiO_2, 1:4 ether to petrol (R_f=0.3), gave the title compound as a yellow solid, 51 mg, 13 % over 4 steps.

^{31}P NMR (162 MHz, $CDCl_3$): δ / ppm 23.44

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm 7.25-6.75 (10H, m, Ar-*H*), 2.71-2.60 (1H, m, C-*H*), 2.59-2.46 (1H, m, (1H, m, HC-*H*), 2.38-2.05 (3H, m, HC-*H*, C-H_2), 1.98 (3H, s, C-H_3), 1.59 (3H, s, C-H_3), 1.51 (3H, s, C-H_3), 1.27 (3H, s, C-H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 148.27 (C, J_{PC}=4.8 Hz), 138.14 (C, J_{PC}=12.2 Hz), 134.90 (C, J_{PC}=7.3 Hz), 133.01 (C, J_{PC}=9.2 Hz), 128.26 (C, J_{PC}=4.9 Hz), 128.12 (CH), 127.01 (CH, J_{PC}=9.2 Hz), 126.80 (CH), 126.72 (CH), 126.18 (C, 16.0 Hz), 125.94 (CH), 125.82 (CH, J_{PC}=1.0 Hz), 125.21 (C, J_{PC}=74.8 Hz), 120.34 (C, J_{PC}=7.3 Hz), 40.62 (CH, J_{PC}=55.4 Hz), 36.30 (CH_2, J_{PC}=4.9 Hz), 34.20 (CH_2, J_{PC}=53.5 Hz), 21.57 (CH_3, J_{PC}=6.8 Hz), 19.93 (CH_3, J_{PC}=10.7 Hz), 19.04 (CH_3, J_{PC}=1.9 Hz), 17.24 (CH_3, J_{PC}=1.9 Hz).

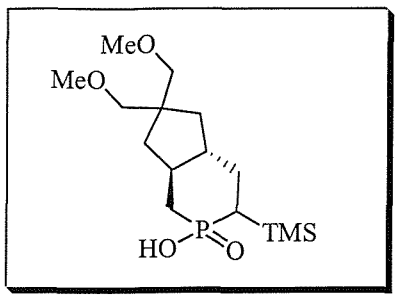
IR (cm^{-1}): 2367 (m), 1598 (s), 1489 (s), 1441 (m), 1264 (m), 1107 (m), 1036 (m), 853 (s), 833 (m), 696 (s).

LRMS (EI): *m/z* 390 (M, 100 %), 357 (M-S, 42 %), 329 (M-Me-Me-Me-Me, 12 %).

HRMS (EI): $C_{25}H_{27}PS$ requires m/z 390.1571, found 390.1561

M. P.: 117-119 °C

6.5.7. *6,6-bis-methoxymethyl-2-oxo-3-trimethylsilanyl-octahydro-2λ^5-cyclopenta[c]phosphinin-2-ol*, **533**



Cp_2ZrCl_2 (1 eq, 1 mmol, 292 mg) in THF (5 mL) was cooled to -78 °C before BuLi (2 eq, 2 mmol, 0.8 mL) was added dropwise. The reaction was stirred for a further 30 minutes before 4,4-bis-methoxymetyl-hepta-1,6-diyne (2.1 eq, 2.1 mmol, 190 mg) in THF (5 mL) was added *via* syringe. The reaction was allowed to warm to r.t. and stirred for a further 2 hours to give a yellow solution. Me_3SiCH_2Cl (1.6 eq, 1.6 mmol, 196 mg), TMEDA (1.6 eq, 1.6 mmol, 186 mg) in THF (5 mL) were cooled to -78 °C before ^{s}BuLi (1.6 eq, 1.6 mmol, 1.15 mL) was added dropwise to give a pale yellow solution. The reaction was stirred for a further hour at -78 °C, before being added *via cannular* to the carbenoid solution at -78 °C. The solution was stirred for a further hour at -78 °C before warming to r.t. and stirring overnight. Excess solvent and volatiles were removed *via* low pressure evaporation, before freshly distilled THF (5 mL) was added. The reaction was cooled to -78 °C before PCl_3 (3 eq, 3 mmol, 0.30 mL) was added. The reaction was stirred for 1 hour at -78 °C before warming to r.t. and stirring for a further 6 days. The reaction mixture was cooled to 0 °C before H_2O_2 (3 eq, 3 mmol, 0.3 mL) was added. The reaction was warmed to r.t. and stirred for a further 40 mins. The reaction was cooled back to 0 °C before being quenched with 2M HCl (20 mL). The reaction mixture was filtered and washed with ether (3 X 15 mL) and 2M HCl (3 X 15 mL). The phopshinic acid was purified by base/acid extraction to give the title compound as a viscous dark brown oil, 120 mg, 36 %. The product was isolated as a 1:1 mixture of diastereoisomers.

^{31}P NMR (121 MHz, $CDCl_3$): δ / ppm 61.94 (s), 61.70 (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm 10.90-9.60 (2H, bs, 2 x O-*H*), 3.18-3.14 (12H, bs, 4 x OC-*H*$_3$), 3.04-3.00 (8H, bs, 2 x MeOC-*H*$_2$), 2.50-1.76 (6H, bm, 3 x C-*H*), 1.75-0.65 (16H, bm, 8 x C-*H*$_2$), 0.03 (9H, s, Si(C-*H*$_3$)$_3$, 0.00 (9H, s, Si(C-*H*$_3$)$_3$.

^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm 78.13 (CH_2), 78.05 (CH_2), 77.97 (CH_2), 77.82 (CH_2), 58.43 (4 x CH_3), 46.16 (C), 46.01 (C), 45.68 (CH, *J*=7.3 Hz), 42.28 (CH, *J*=7.7 Hz), 41.48 (CH) 41.30 (CH), 40.68 (CH_2, *J*=15.6 Hz), 40.57 (CH_2, *J*=15.1 Hz), 38.51 (CH_2), 38.25 (CH_2), 33.45 (CH_2, *J*=76.3 Hz), 31.67 (CH_2, *J*=81.2 Hz), 28.92 (CH_2), 28.70 (CH_2), 25.35 (CH, *J*=89.4 Hz), 24.71 (CH, *J*=72.4 Hz), 0.05 (3 x CH_3), -1.30 (3 x CH_3).

IR (cm^{-1}): 2921 (w), 2869 (w), 2358 (w), 1451 (w), 1251 (m), 1200 (m), 1108 (s), 1051 (s), 959 (m), 837 (s).

LRMS (ES-): *m/z* 333 (M-H, 100%).

HRMS (ES-): $C_{15}H_{31}O_4PSi$ requires m/z 334.1729, found 334.1722

CHAPTER 7

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CHAPTER 8

APPENDIX

8. APPENDIX

8.1. Chapter 1: No appendix data

8.2. Chapter 2: X-Ray Data for *N*-allyl cinnamides

Further information: http://www.soton.ac.uk/~xservice/strat.htm

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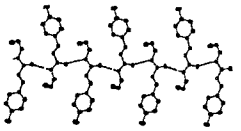
Table 1. Crystal data and structure refinement.



Identification code	**02SOT151 (RH–3234–169)**
Empirical formula	$C_{13}H_{15}NO$
Formula weight	201.26
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 12.0201(13) Å
	b = 9.5501(8) Å β = 95.847(3)°
	c = 10.0478(8) Å
Volume	1147.42(18) Å^3
Z	4
Density (calculated)	1.165 Mg / m^3
Absorption coefficient	0.074 mm^{-1}
F(000)	432
Crystal	Colourless Plate
Crystal size	0.50 × 0.35 × 0.04 mm^3
θ range for data collection	2.95 – 25.02°
Index ranges	$-11 \le h \le 14$, $-11 \le k \le 10$, $-11 \le l \le 10$
Reflections collected	5729
Independent reflections	1939 [R_{int} = 0.0686]
Completeness to θ = 25.02°	95.9 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9971 and 0.9642
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1939 / 0 / 138
Goodness-of-fit on F^2	1.029
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0623, $wR2$ = 0.1425
R indices (all data)	$R1$ = 0.1143, $wR2$ = 0.1684
Extinction coefficient	0.044(9)
Largest diff. peak and hole	0.152 and –0.140 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement:** *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction:** *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution:** *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement:** *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
N1	9624(2)	2020(2)	6758(2)	59(1)	1
C9	10939(2)	1825(2)	8673(2)	50(1)	1
C10	10155(2)	1164(3)	7647(2)	50(1)	1
O1	9992(2)	–97(2)	7604(2)	76(1)	1
C5	12271(2)	1666(3)	10734(2)	50(1)	1
C8	11447(2)	1138(3)	9688(2)	53(1)	1
C6	12591(2)	3044(3)	10835(3)	62(1)	1
C4	12786(2)	767(3)	11673(3)	65(1)	1
C7	13389(2)	3494(3)	11816(3)	66(1)	1
C11	8860(2)	1542(3)	5656(3)	67(1)	1
C2	13904(2)	2593(3)	12741(3)	63(1)	1
C3	13600(2)	1224(4)	12648(3)	70(1)	1
C12	7697(3)	2039(3)	5673(3)	71(1)	1
C13	7311(3)	2858(4)	6521(4)	94(1)	1
C1	14781(3)	3093(4)	13823(3)	92(1)	1

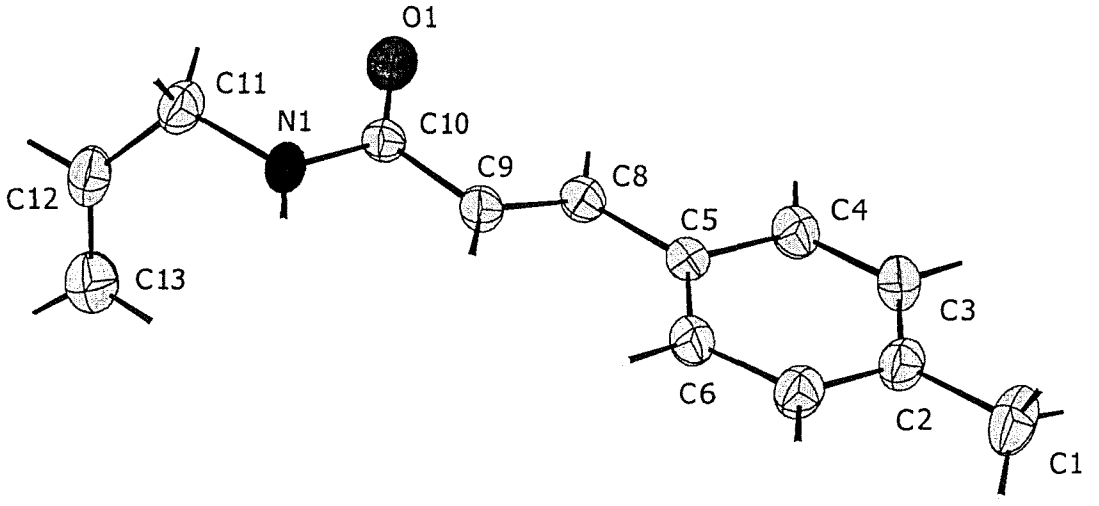


Table 1. Crystal data and structure refinement.

Identification code	**02SOT148 – RH–3427–11**
Empirical formula	$C_{13}H_{15}NO_2$
Formula weight	217.26
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 8.1095(8) Å α = 84.881(5)°
	b = 9.5275(10) Å β = 87.001(4)°
	c = 15.1896(19) Å γ = 80.636(4)°
Volume	1152.5(2) Å^3
Z	4
Density (calculated)	1.252 Mg / m^3
Absorption coefficient	0.084 mm^{-1}
F(000)	464
Crystal	Colourless Plate
Crystal size	0.20 × 0.15 × 0.03 mm^3
θ range for data collection	2.93 – 23.25°
Index ranges	$-8 \le h \le 8$, $-10 \le k \le 10$, $-16 \le l \le 16$
Reflections collected	6024
Independent reflections	3249 [R_{int} = 0.0554]
Completeness to θ = 23.25°	98.4 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9975 and 0.9833
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3249 / 0 / 292
Goodness-of-fit on F^2	1.026
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0719, $wR2$ = 0.1776
R indices (all data)	$R1$ = 0.1190, $wR2$ = 0.2036
Extinction coefficient	0.004(4)
Largest diff. peak and hole	0.679 and –0.269 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement:** *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction:** *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution:** *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A46 467–473). **Structure refinement:** *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
N1	8081(4)	6228(3)	−1175(2)	32(1)	1
O1	14104(4)	7623(3)	−6099(2)	41(1)	1
O2	8375(4)	4209(3)	−1868(2)	46(1)	1
C1	14715(6)	6763(5)	−6811(3)	47(1)	1
C2	13182(5)	7037(4)	−5436(3)	32(1)	1
C3	12833(6)	5665(4)	−5376(3)	39(1)	1
C4	11883(6)	5205(4)	−4658(3)	39(1)	1
C5	11250(5)	6061(4)	−3997(3)	31(1)	1
C6	11602(5)	7457(4)	−4079(3)	36(1)	1
C7	12528(5)	7937(4)	−4780(3)	36(1)	1
C8	10278(5)	5491(4)	−3245(3)	34(1)	1
C9	9645(5)	6138(4)	−2541(3)	32(1)	1
C10	8644(5)	5451(4)	−1847(3)	32(1)	1
C11	7073(6)	5723(4)	−434(3)	41(1)	1
C12	7731(8)	6017(5)	418(3)	61(2)	1
C13	6946(9)	6486(6)	1075(4)	82(2)	1
N1'	9013(5)	1211(3)	−1939(2)	39(1)	1
O1'	4445(4)	2700(3)	3349(2)	38(1)	1
O2'	8844(3)	−954(3)	−1260(2)	35(1)	1
C1'	3531(6)	1875(5)	3963(3)	45(1)	1
C2'	5085(5)	2091(4)	2598(3)	32(1)	1
C3'	4660(5)	857(4)	2322(3)	32(1)	1
C4'	5388(5)	353(4)	1546(3)	33(1)	1
C5'	6544(5)	1018(4)	1038(2)	30(1)	1
C6'	6960(5)	2258(4)	1340(3)	32(1)	1
C7'	6239(5)	2797(4)	2097(3)	34(1)	1
C8'	7277(5)	432(4)	223(3)	31(1)	1
C9'	8058(5)	1063(4)	−435(3)	30(1)	1
C10'	8688(5)	363(4)	−1234(3)	31(1)	1
C11'	9508(6)	705(5)	−2805(3)	43(1)	1
C12'	11244(6)	870(4)	−3056(3)	42(1)	1
C13'	11724(6)	1420(4)	−3839(3)	45(1)	1

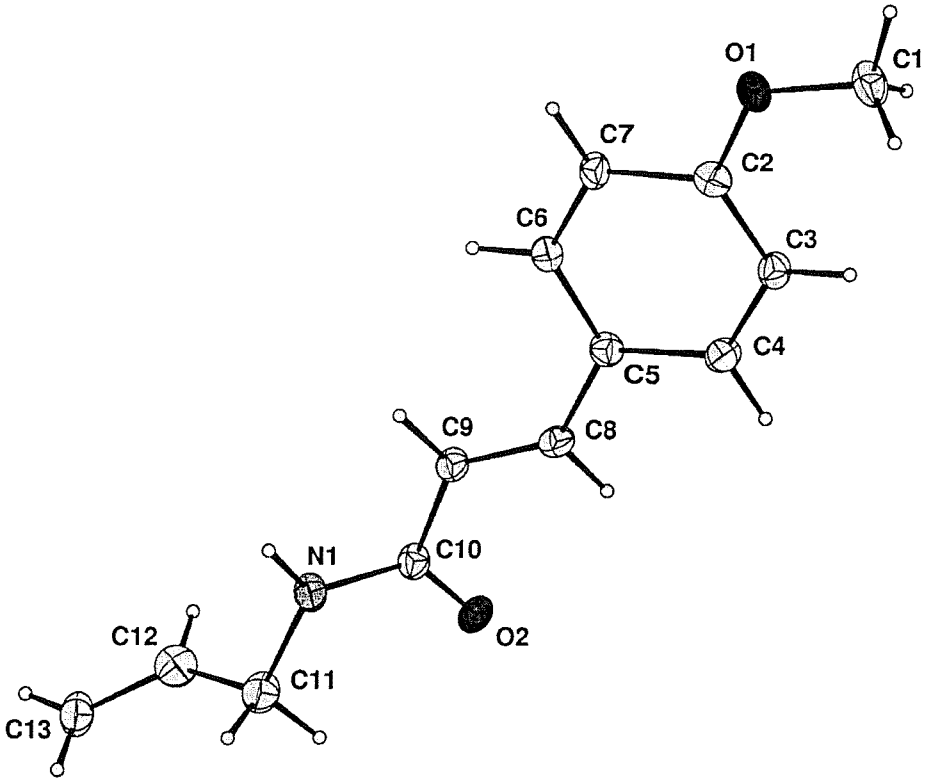

O1
C1
C7
C2
C6
C3
C5
C4
C9
C8
N1
C10
O2
C12
C11
C13

Table 1. Crystal data and structure refinement.

Identification code	**02SOT150 (RH–3427–9)**
Empirical formula	$C_{12}H_{12}FNO$
Formula weight	205.23
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$Pna2_1$
Unit cell dimensions	$a = 23.2350(11)$ Å $b = 4.9677(2)$ Å $c = 9.3339(4)$ Å
Volume	1077.36(8) Å^3
Z	4
Density (calculated)	1.265 Mg / m^3
Absorption coefficient	0.092 mm^{-1}
F(000)	432
Crystal	Colourless plate
Crystal size	1.40 × 0.60 × 0.04 mm^3
θ range for data collection	3.51 – 25.00°
Index ranges	$-27 \le h \le 19, -5 \le k \le 5, -11 \le l \le 9$
Reflections collected	5239
Independent reflections	1768 [$R_{int} = 0.0445$]
Completeness to $\theta = 25.00°$	99.3 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9963 and 0.8814
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1768 / 1 / 136
Goodness-of-fit on F^2	1.046
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0442$, $wR2 = 0.0977$
R indices (all data)	$R1 = 0.0682$, $wR2 = 0.1081$
Absolute structure parameter	1.4(13)
Extinction coefficient	none
Largest diff. peak and hole	0.103 and –0.135 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	2117(1)	13998(5)	5316(4)	57(1)	1
C2	2085(1)	13172(6)	3942(4)	62(1)	1
C3	1696(1)	11174(5)	3606(3)	57(1)	1
C4	1336(1)	10060(6)	4629(3)	45(1)	1
C5	1391(1)	10967(5)	6017(3)	61(1)	1
C6	1784(1)	12970(6)	6370(4)	64(1)	1
C7	923(1)	7974(5)	4194(3)	50(1)	1
C8	554(1)	6670(5)	5014(3)	48(1)	1
C9	163(1)	4594(5)	4422(3)	48(1)	1
C10	−564(1)	1219(5)	5029(3)	56(1)	1
C11	−1179(1)	2110(6)	4921(3)	56(1)	1
C12	−1387(2)	4403(7)	5247(5)	79(1)	1
N1	−163(1)	3355(4)	5394(3)	50(1)	1
O1	144(1)	4037(4)	3137(2)	67(1)	1
F1	2500(1)	15997(3)	5651(2)	82(1)	1

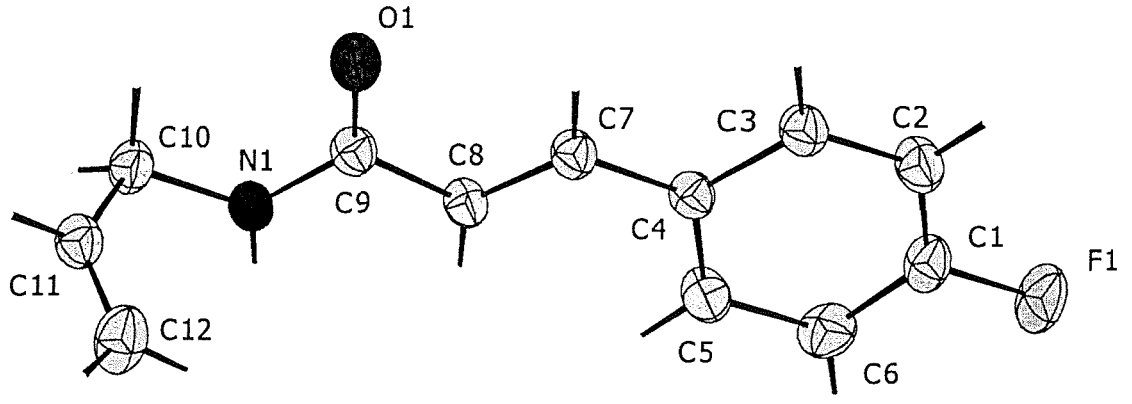


Table 1. Crystal data and structure refinement.

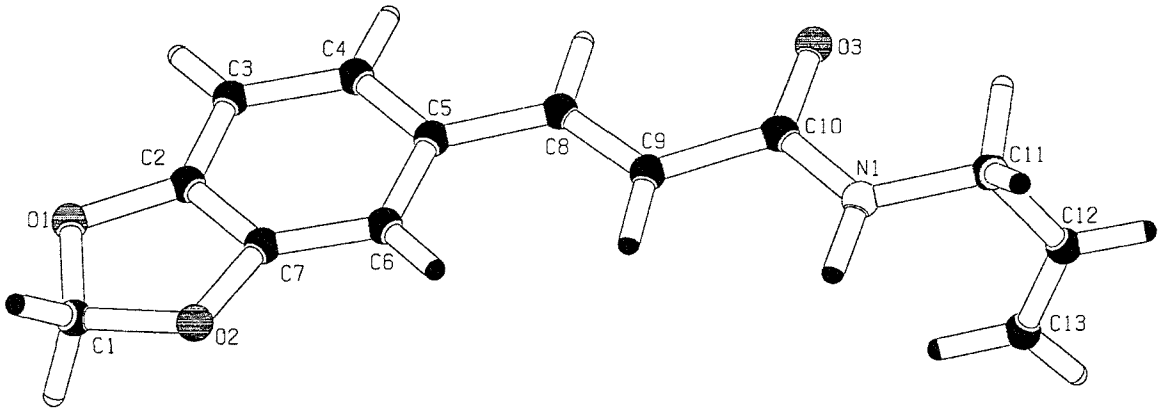
Identification code	**02sot149**	
Empirical formula	$C_{13}H_{13}NO_3$	
Formula weight	231.24	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	$a = 6.80780(10)$ Å	$\alpha = 90°$
	$b = 9.3184(2)$ Å	$\beta = 90°$
	$c = 17.5481(3)$ Å	$\gamma = 90°$
Volume	1113.21(3) Å^3	
Z	4	
Density (calculated)	1.380 Mg / m^3	
Absorption coefficient	0.099 mm^{-1}	
F(000)	488	
Crystal	Block; colourless	
Crystal size	0.30 x 0.18 x 0.14 mm^3	
θ range for data collection	3.19 – 27.47°	
Index ranges	$-8 \le h \le 8, -12 \le k \le 11, -22 \le l \le 22$	
Reflections collected	13466	
Independent reflections	2538 [$R_{int} = 0.0450$]	
Completeness to $\theta = 27.47°$	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9863 and 0.9710	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2538 / 0 / 159	
Goodness-of-fit on F^2	1.010	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0310$, $wR2 = 0.0848$	
R indices (all data)	$R1 = 0.0337$, $wR2 = 0.0870$	
Absolute structure parameter	-0.6(8)	
Extinction coefficient	0.068(7)	
Largest diff. peak and hole	0.222 and -0.164 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

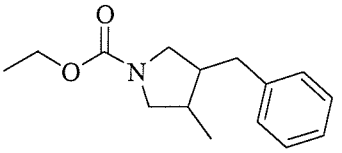
Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	642(2)	399(1)	6846(1)	28(1)	1
C2	743(2)	2510(1)	6251(1)	21(1)	1
C3	737(2)	3935(1)	6067(1)	25(1)	1
C4	792(2)	4261(1)	5290(1)	23(1)	1
C5	830(2)	3204(1)	4731(1)	18(1)	1
C6	864(2)	1745(1)	4941(1)	19(1)	1
C7	825(2)	1450(1)	5703(1)	21(1)	1
C8	835(2)	3649(1)	3935(1)	19(1)	1
C9	568(2)	2810(1)	3329(1)	19(1)	1
C10	658(2)	3397(1)	2551(1)	18(1)	1
C11	607(2)	2789(1)	1194(1)	25(1)	1
C12	−1355(2)	2918(1)	814(1)	27(1)	1
C13	−3063(2)	2720(1)	1146(1)	32(1)	1
N1	508(2)	2413(1)	1994(1)	21(1)	1
O1	732(2)	1911(1)	6964(1)	29(1)	1
O2	909(1)	131(1)	6047(1)	30(1)	1
O3	911(1)	4690(1)	2414(1)	25(1)	1



8.3. Chapter 3: ^{1}H NMR's of Solution & Solid-phase 3-Benzyl Pyrrolidine Syntheses

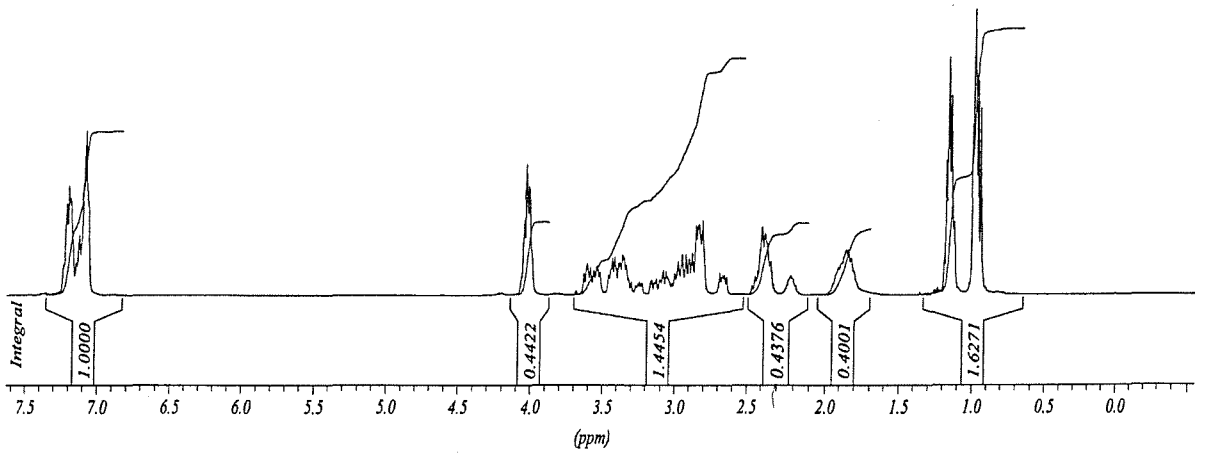
- *Ethyl 3-benzyl-4-methylpyrrolidine-1-carboxylate*
- *Ethyl 3-(4-methylbenzyl)-4-methylpyrrolidine-1-carboxylate*
- *Ethyl 3-(4-methoxybenzyl)-4-methylpyrrolidine-1-carboxylate*
- *Ethyl 3-(4-fluorobenzyl)-4-methylpyrrolidine-1-carboxylate*
- *Ethyl 3-(1,3-benzodioxol-5-ylmethyl)-4-methylpyrrolidine-1-carboxylate*

Ethyl 3-benzyl-4-methylpyrrolidine-1-carboxylate

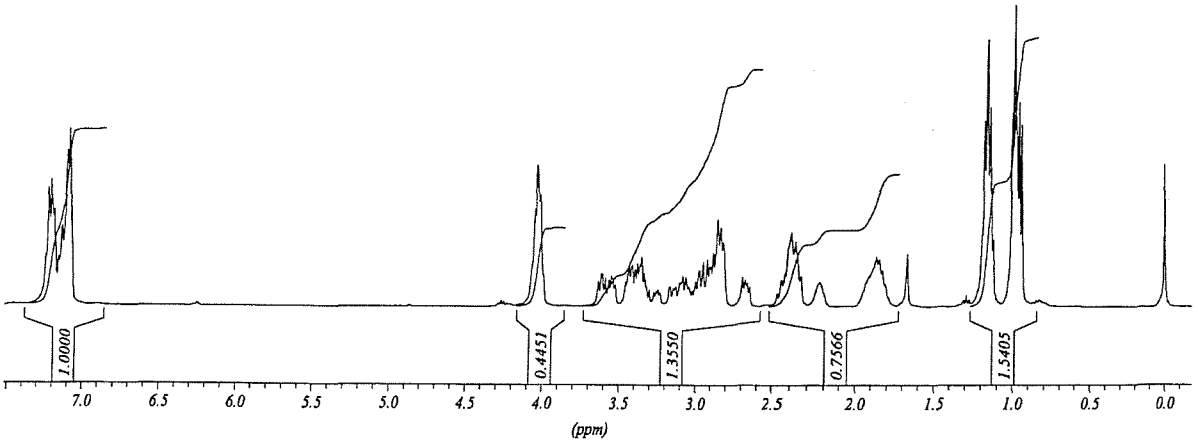


$C_{15}H_{21}NO_2$
Exact Mass: 247.16
Mol. Wt.: 247.33
C, 72.84; H, 8.56; N, 5.66; O, 12.94

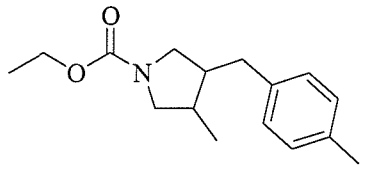
Solution-phase Synthesis



Solid-phase Synthesis

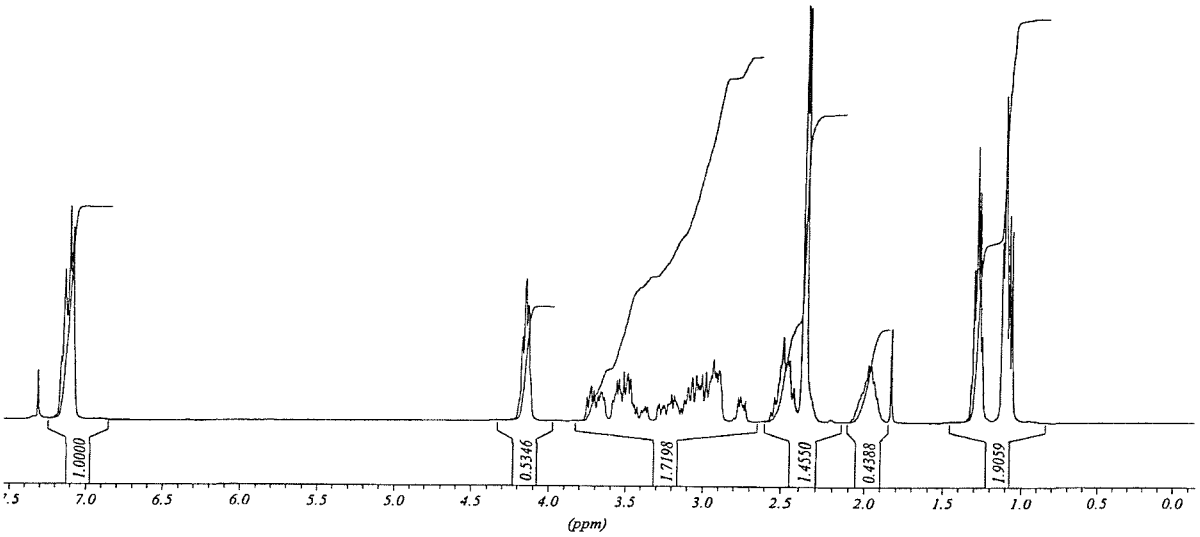


Ethyl 3-(4-methylbenzyl)-4-methylpyrrolidine-1-carboxylate

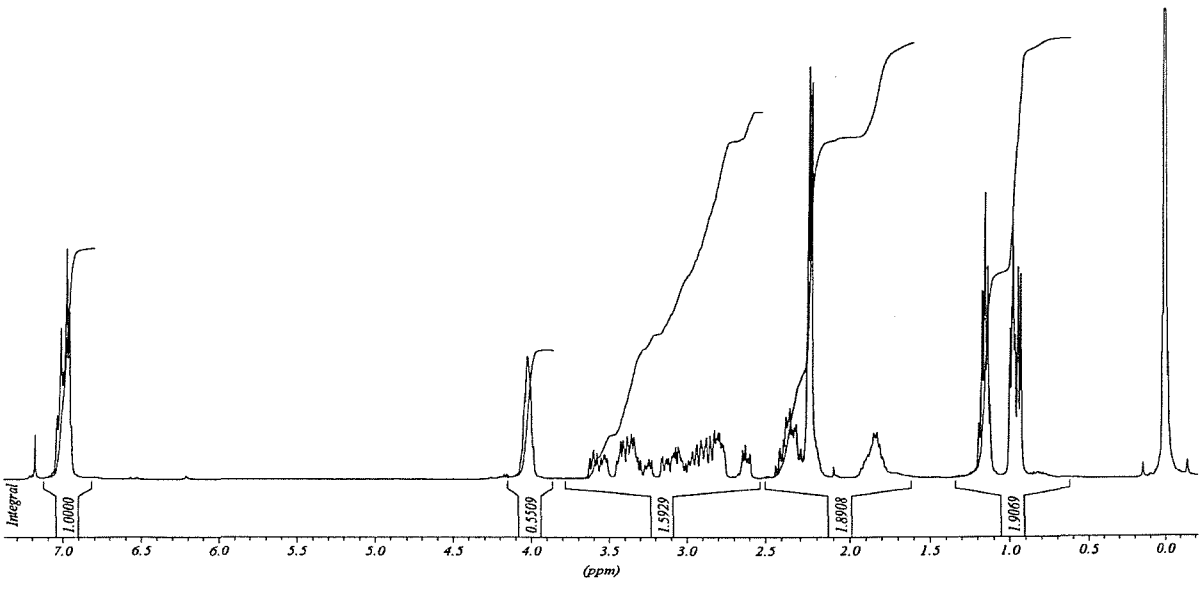


$C_{16}H_{23}NO_2$
Exact Mass: 261.17
Mol. Wt.: 261.36
C, 73.53; H, 8.87; N, 5.36; O, 12.24

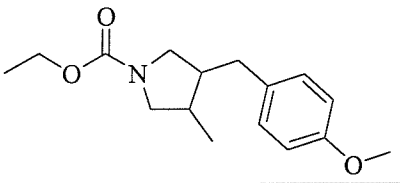
Solution-phase Synthesis



Solid-phase Synthesis

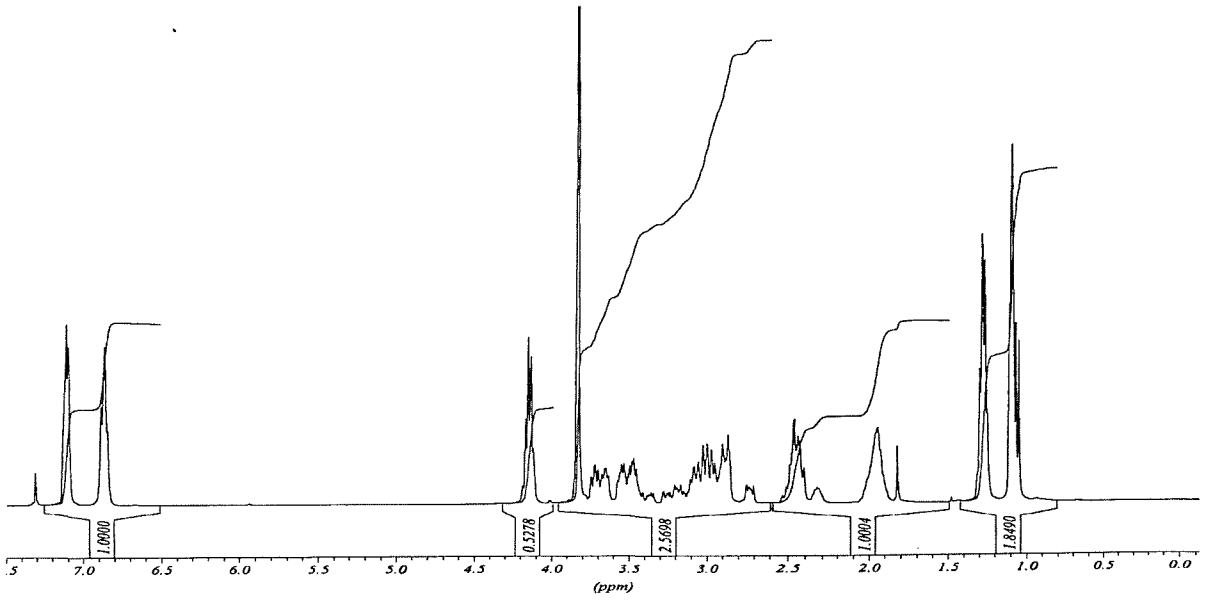


Ethyl 3-(4-methoxybenzyl)-4-methylpyrrolidine-1-carboxylate

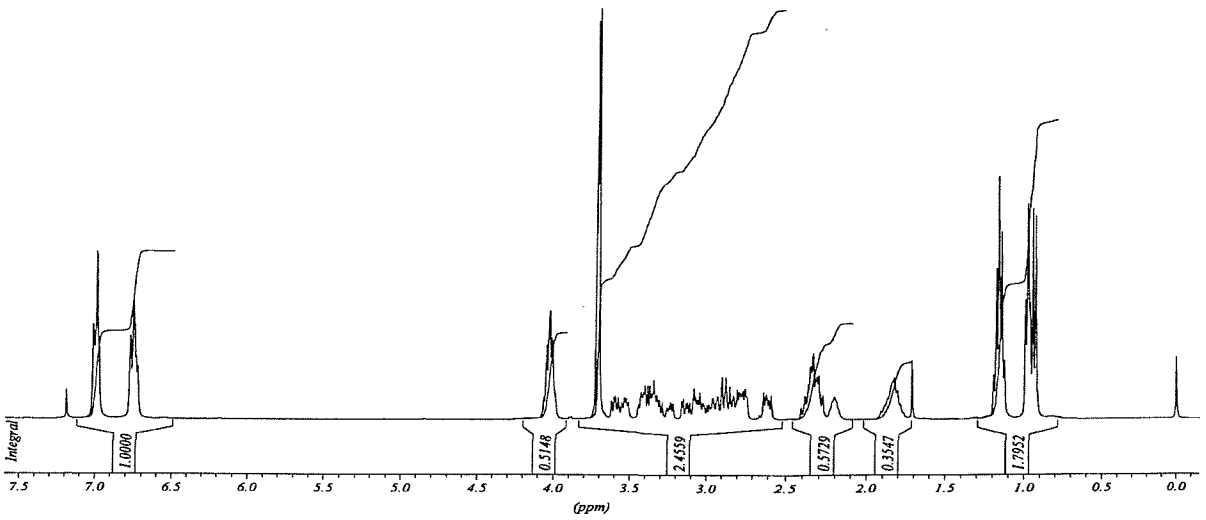


$C_{16}H_{23}NO_3$
Exact Mass: 277.17
Mol. Wt.: 277.36
C, 69.29; H, 8.36; N, 5.05; O, 17.31

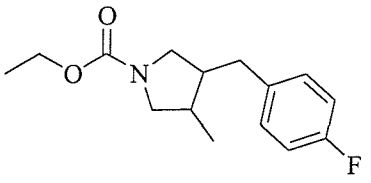
Solution-phase Synthesis



Solid-phase Synthesis

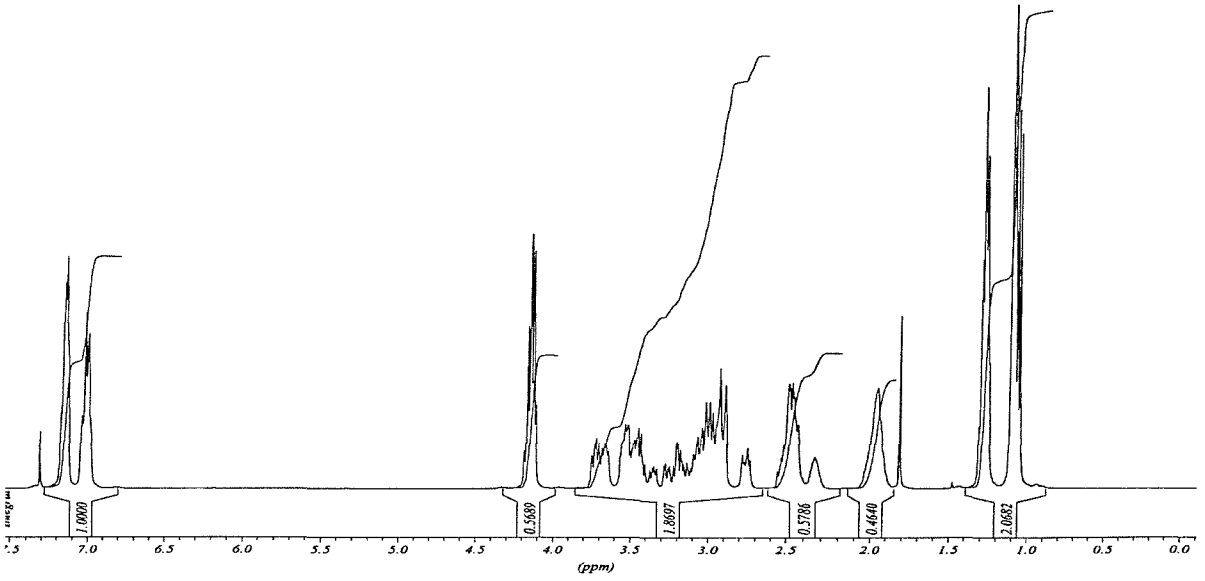


Ethyl 3-(4-fluorobenzyl)-4-methylpyrrolidine-1-carboxylate

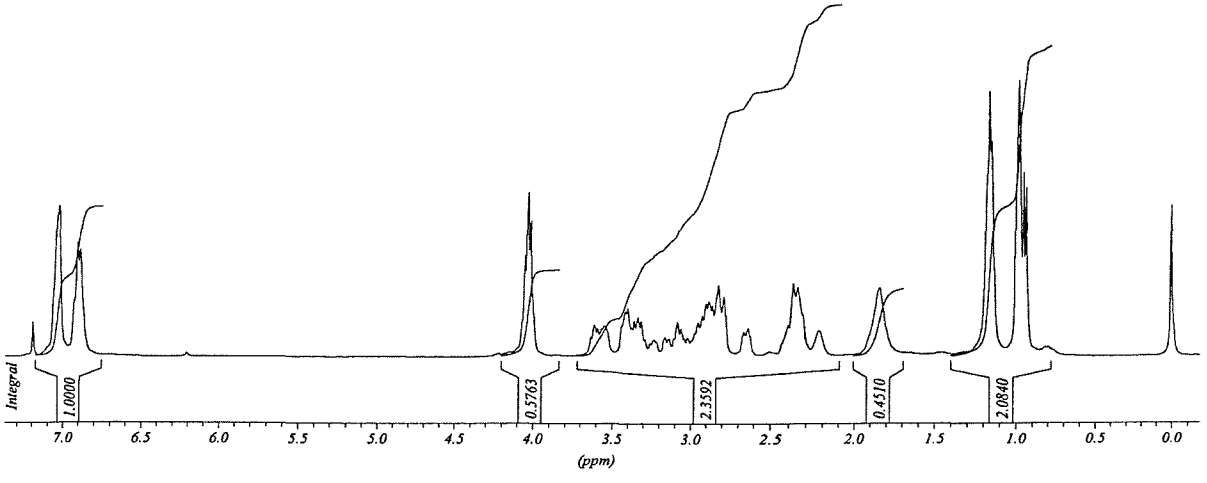


$C_{15}H_{20}FNO_2$
Exact Mass: 265.15
Mol. Wt.: 265.32
C, 67.90; H, 7.60; F, 7.16; N, 5.28; O, 12.06

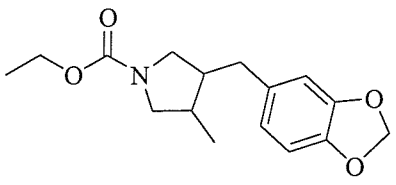
Solution-phase Synthesis



Solid-phase Synthesis

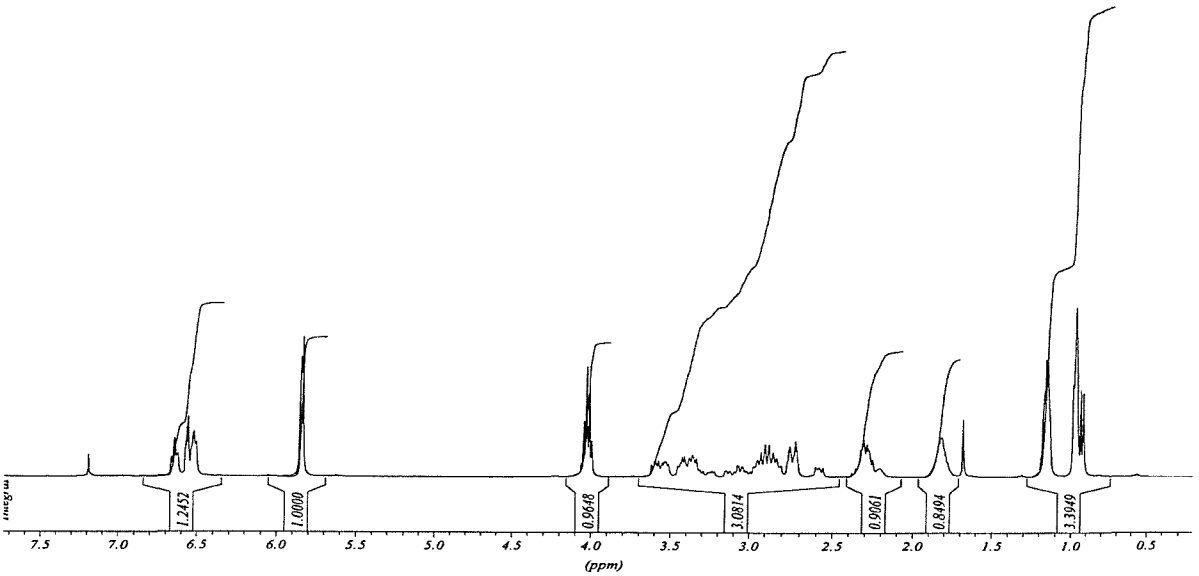


Ethyl 3-(1,3-benzodioxol-5-ylmethyl)-4-methylpyrrolidine-1-carboxylate

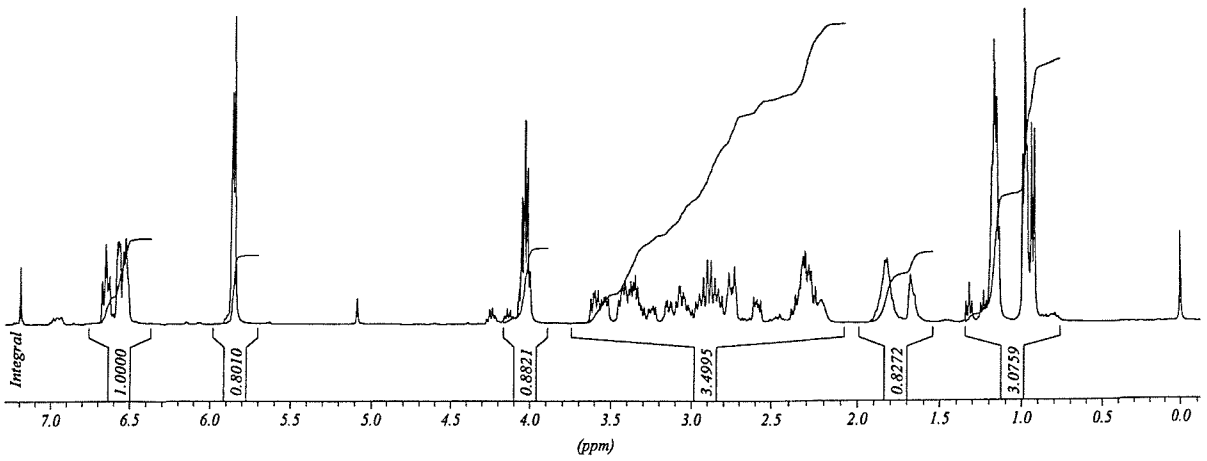


$C_{16}H_{21}NO_4$
Exact Mass: 291.15
Mol. Wt.: 291.34
C, 65.96; H, 7.27; N, 4.81; O, 21.97

Solution-phase Synthesis



Solid-phase Synthesis

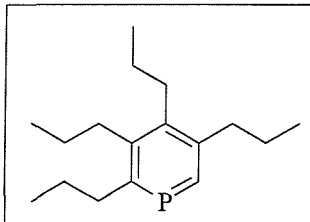


8.4. Chapter 4: No appendix data

8.5. Chapter 5: ^{1}H NMR's of filtered phosphinines

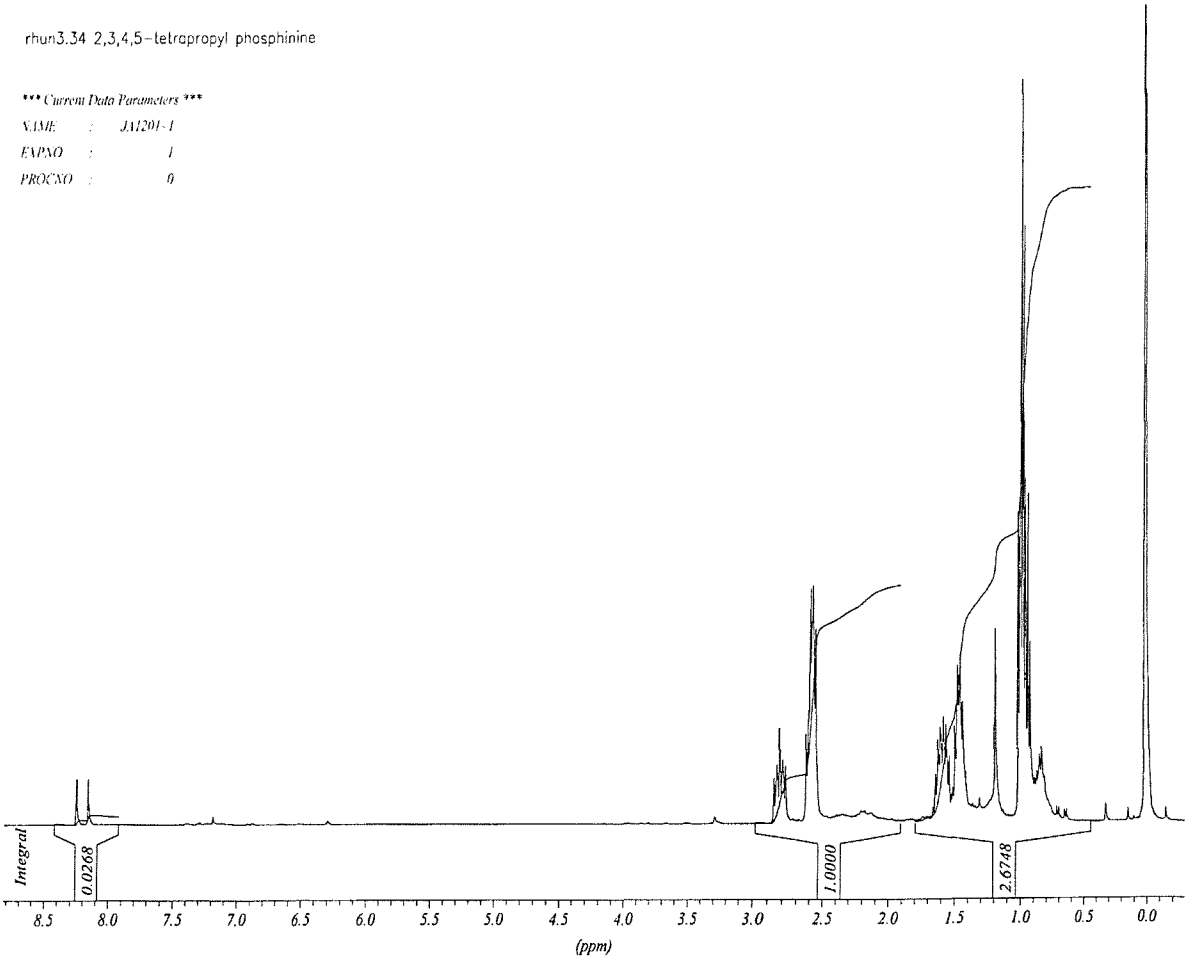
- *2,3,4,5-tetrapropyl phosphinine*
- *2,3,4,5-tetraethyl phosphinine*
- *1:1 mixture of 2,3-diphenyl-4,5-dimethyl phosphinine and 2,3-diphenyl-4,5-dimethyl-6-trimethylsilyl phosphinine*

2,3,4,5-tetrapropyl phosphinine

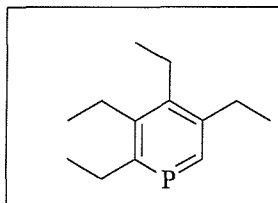


$C_{17}H_{29}P$
Exact Mass: 264.20
Mol. Wt.: 264.39
C, 77.23; H, 11.06; P, 11.72

^{1}H NMR of crude phosphinine

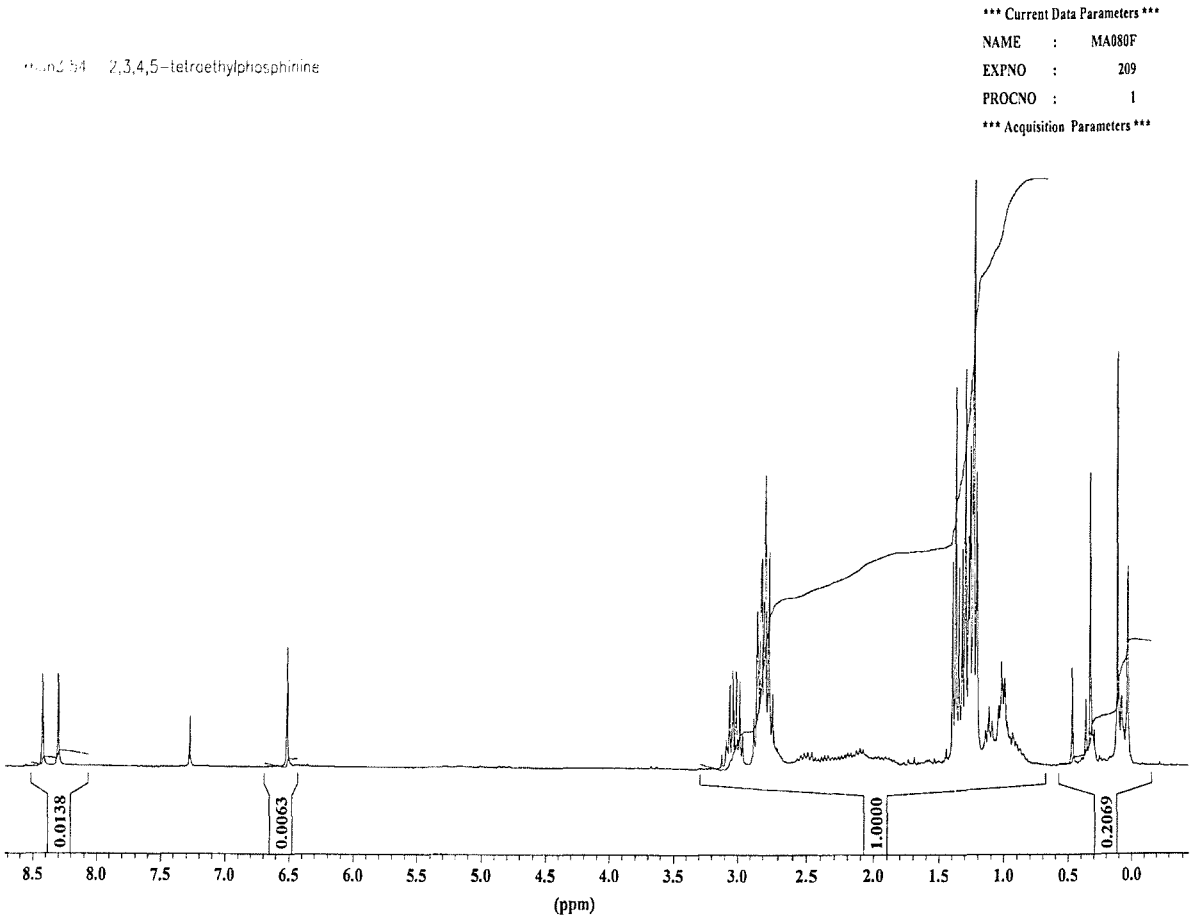


2,3,4,5-tetraethyl phosphinine

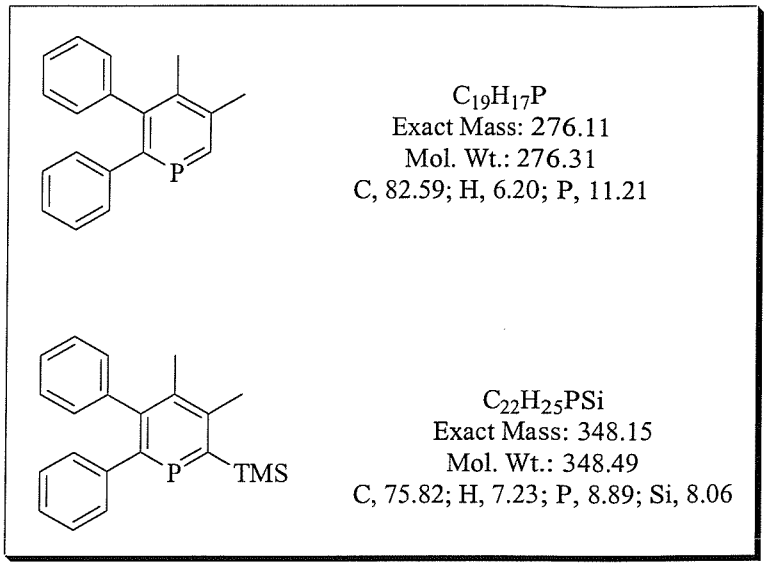


$C_{13}H_{21}P$
Exact Mass: 208.14
Mol. Wt.: 208.28
C, 74.97; H, 10.16; P, 14.87

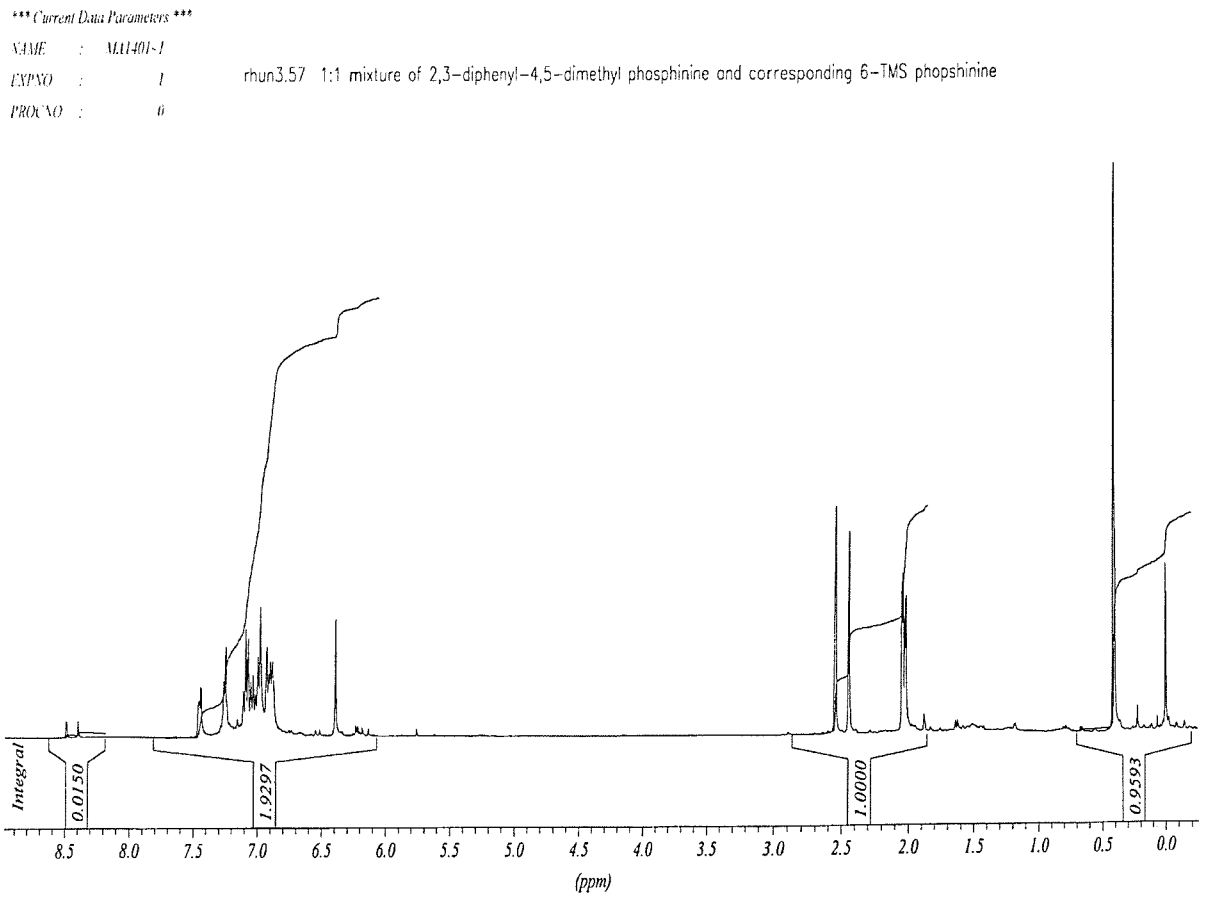
^{1}H NMR of crude phosphinine



1:1 mixture of 2,3-diphenyl-4,5-dimethyl phosphinine and 2,3-diphenyl-4,5-dimethyl-6-trimethylsilyl phosphinine



^{1}H NMR of crude phosphinines



8.5. Chapter 5: X-Ray Data for Diels-Alder Adduct

Further information: http://www.soton.ac.uk/~xservice/strat.htm

University of Southampton · Department of Chemistry

EPSRC National Crystallography Service

Table 1. Crystal data and structure refinement.

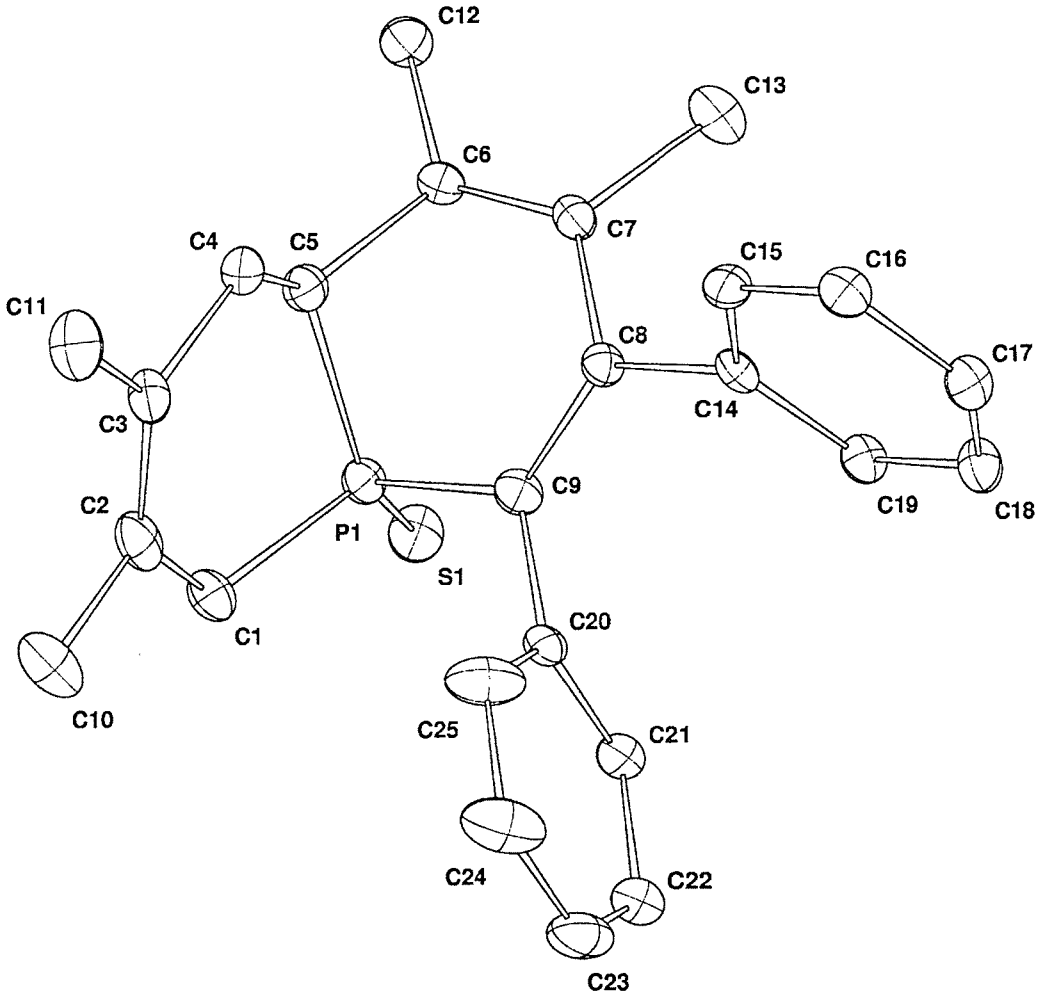
Identification code	**01SOT045**
Empirical formula	$C_{25}H_{27}PS$
Formula weight	390.50
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 9.0048(5) Å
	b = 12.9090(7) Å β = 90.221(3)°
	c = 18.0368(14) Å
Volume	2096.6(2) Å^3
Z	4
Density (calculated)	1.237 Mg / m^3
Absorption coefficient	0.238 mm^{-1}
F(000)	832
Crystal	Colourless Plate
Crystal size	0.20 × 0.20 × 0.02 mm^3
θ range for data collection	2.98 – 23.25°
Index ranges	$-8 \le h \le 10$, $-13 \le k \le 14$, $-19 \le l \le 20$
Reflections collected	9720
Independent reflections	2968 [R_{int} = 0.1065]
Completeness to θ = 23.25°	98.5 %
Max. and min. transmission	0.9953 and 0.9540
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2968 / 0 / 245
Goodness-of-fit on F^2	0.875
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0679, $wR2$ = 0.1913
R indices (all data)	$R1$ = 0.1054, $wR2$ = 0.2250
Extinction coefficient	0.000(2)
Largest diff. peak and hole	0.619 and –0.493 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A46 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C16	491(6)	8653(4)	4099(3)	33(1)	1
C17	−740(6)	9289(4)	4102(3)	33(1)	1
C1	2189(6)	7453(4)	293(2)	37(1)	1
C2	3681(6)	7555(4)	652(3)	39(1)	1
C3	4127(6)	6984(4)	1239(3)	34(1)	1
C4	3185(5)	6231(3)	1659(3)	32(1)	1
C5	1701(5)	5838(3)	1323(2)	30(1)	1
C6	685(5)	5451(3)	1930(2)	27(1)	1
C7	−22(5)	6120(3)	2364(2)	28(1)	1
C8	43(5)	7270(3)	2250(2)	25(1)	1
C9	345(6)	7702(3)	1584(2)	30(1)	1
C10	4669(7)	8354(4)	291(3)	53(2)	1
C11	5639(6)	7112(4)	1596(3)	46(1)	1
C12	614(6)	4288(3)	1987(3)	36(1)	1
C13	−1033(6)	5766(4)	2992(3)	40(1)	1
C14	−266(5)	7972(3)	2906(2)	25(1)	1
C15	734(6)	7996(3)	3494(2)	29(1)	1
C18	−1748(6)	9261(4)	3522(3)	36(1)	1
C19	−1494(5)	8597(3)	2925(2)	29(1)	1
C20	331(6)	8832(3)	1411(2)	29(1)	1
C21	−875(6)	9282(4)	1081(3)	45(1)	1
C22	−865(8)	10313(5)	878(3)	60(2)	1
C23	367(9)	10909(4)	1017(3)	60(2)	1
C24	1588(9)	10462(4)	1340(3)	62(2)	1
C25	1583(7)	9431(4)	1538(3)	51(2)	1
P1	742(2)	6848(1)	820(1)	28(1)	1
S1	−988(2)	6455(1)	228(1)	40(1)	1



Molecular Structure with thermal ellipsoids drawn at the 30 % probablity level