DOCTOR OF PHILOSOPHY

Studies in indene and indole synthesis

Swinburn, Steven James

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May this thesis keep some poor student warm
on a cold winters day.

Steven

Dedicated to my parents,

David and Linda Swinburn,

without whom...

"Time is come round.
And where I did begin,
there shall I end."

Julius Caesar
Act V. Scene III

Studies in Indene and Indole Synthesis

A thesis submitted to the University of Wales, Bangor
in candidature for the degree of
Doctor of Philosophy

by

Steven James Swinburn

2004

Abstract

This PhD thesis describes the laboratory scale preparation of a number of indenes and indoles, specifically the methodologies applied for the synthesis of these.

Firstly the generation of 1,2-dichlorocyclopropenes from tetrachlorocyclopropanes upon reaction with 1.3 molecular equivalents of methyl lithium, which ring open to vinylcarbenes at low temperatures, were quenched with several carbonyl containing compounds to form a new carbon-oxygen bond. A series of 1,2-dichloro-3-phenyl-cyclopropenes were synthesised, which ring opened to the vinylcarbene and trap intramolecularly with the benzene ring to give a mixture of two indene regioisomers. The benzene ring substituents was studied as to the affect on this reaction.

The second half of the thesis examined methods of indole synthesis. Firstly the Heck reaction with the coupling of iodoaniline and alkynes gave limited results and involved harsh conditions and lengthy reaction times. The Okuro modification of the copper catalysed Castro reaction was found to give an indole intermediate cleanly in low yield with short reaction times. These alkynes were then easily cyclised to indoles in quantitative yield. The Sonogashira reaction gave the same intermediates in higher yield through quick reaction at room temperature.

A modified Madelung reaction was used to convert a wide range of functionalised toluidines to indoles with short reaction times through deprotonation with *tert*-butyl lithium. A range of quenching reagents were developed to effectively insert alkyl and aryl groups onto the 2-position of the indole.

Acknowledgements

I would like to thank Professor Baird for this opportunity to further my education in his research group and for all his help and extreme patience in what must be beyond what any of us could expect.

This work was supported by a Smart award and carried out in collaboration with Menai Organics. One of the purposes of the work was to test their catalysts. I would like to thank Dr. David Potter for his help and advice, and to the rest of the staff of Menai Organics; Mrs. Potter, Dylan, Elinor, Helen, Sarah and Will for making my time there an enjoyable experience.

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And I would especially like to thank my friends, without whom life in Bangor wouldn't have been half the experience it has been, for drawing out my burgeoning sense of childishness. After all, what's the point of being grown up if you can't be childish, at least some of the time. They are the guardians of my well-being, my alcoholic advisors and a shoulder to cry on.

There have been many in Bangor over my time here: Declan J. Lengley O'Connor (for broadening my horizons), Kevin Fortune (for requested photographs, mutual interests and all his parties), Graham Bromley (the coolest student in Bangor), Louise Hall (for constant support and answers), Spencer Jones (for a different perspective than Louise and for the barbeques), Rachel White (for taking an interest), Claire Gravil (for looking after us), Gianna Toschi, Agnes Roudaut, Paula Bertolli and Leda Favro (for giving a continental perspective), Adam Scott, Kerri Hook, and Amiee Chadderton (wherever they all got to). Thanks to them all, I'm a different person.

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Thanks finally to the Doctor. Wherever, whoever and whenever he may be.

Steven Swinburn

Abbreviations and Acronyms

aq.	aqueous
BOC	*tert*-butoxycarboxylic acid
BuLi	butyl lithium
cetrimide	hexadecyl-trimethyl ammonium bromide
CFC	chlorofluorocarbon
cm	centimetre
d	doublet
D	deuterium
DEAD	diethylazodicarboxylate
DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl
g	grams
GC	gas chromatography
h	hours
HMPA	hexamethylphosphoramide
Hz	hertz
IR	infrared
LDA	lithium di-*iso*-propylamide
m	multiplet
M	molar
m.p.	melting point
Me	methyl
MeLi	methyl lithium
min	minutes
ml	millilitres
mmol	millimoles
mol. eq.	molecular equivalents
mol	moles
NaOMe	sodium methoxide

NMR	nuclear magnetic resonance
petrol	petroleum ether
Ph	phenyl
PPh_3	triphenylphosphine
ppm	parts per million
PTC	phase transfer catalyst
q	quartet
s	singlet
sat.	saturated
t	triplet
TCNE	tetracyanoethene
Tert	tertiary
TFA	trifluoro acetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
tlc	thin layer chromatography
TMG	tetramethylguanidine
TMSCl	trimethylsilyl chloride
UV	ultra violet

Table of Contents

1. Introduction

This thesis involves the reactions of cyclopropenes and the synthesis of indenes from them. This introduction will therefore cover cyclopropanes and cyclopropenes; the background to both the reactions of and the synthesis of these species are covered in **Sections 1.1** and **1.2**, respectively. The thesis will also include synthetic approaches to the production of indoles, so the introduction will conclude with a section on the chemistry and common approaches to the synthesis of indoles.

1.1 Cyclopropanes

Cyclopropanes are three membered rings of carbon. Because of the number of ring atoms involved, ring strain is the predominant feature in the reactions of cyclopropanes, with the facile ring opening of the molecule.

Saturated carbon bonds are formed by hybridisation of one s-orbital and three p-orbitals to give four equivalent sp^3 orbitals. In the case of molecules free of ring strain, such as methane, the four bond angles are 109.5°. In cyclopropane, the bond angle would be drastically reduced to an interatom angle of only 60° if the bonds lay directly between the atoms, hence the concept of strain. This is alleviated by the electron density of the bonds lying outside the imagined triangular lines joining carbon atoms, to produce bent or banana bonds which may be seen in **Figure 1.1**.

Figure 1.1 The bonding in cyclopropane

The hybrid orbitals of carbon in cyclopropane are not all equivalent. The orbitals that take part in the bonding of the ring resemble p-orbitals, which naturally have a bond angle of 90° and the bond forming orbitals outside the ring therefore have greater s-character and resemble sp^2 orbitals. This has been supported by examination of the $^{13}C - {}^{1}H$ coupling constants in molecules with different types of bonding as shown in **Table 1.1**, which shows that as s character increases in the bond, the coupling constant also increases.[1]

Molecule	Bonding	^{13}C-^{1}H Coupling / Hz
CH_4	sp3	125
C_2H_4	sp^2	157
C_2H_2	sp	245

Table 1.1 The ^{13}C – ^{1}H coupling constants for different types of bonding

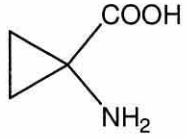
The ^{13}C – ^{1}H coupling constant for cyclopropane has been measured as 161 Hz, making it an approximate sp^2 bond. More precise calculations that take into account the coupling constant and the bond angle for cyclopropane predict that the carbon – carbon bond has a $sp^{3.7}$ hybrid and the carbon – hydrogen bond has a $sp^{2.3}$ hybrid.[2]

1.1.1 Cyclopropanes in nature

There are a large number of naturally occurring compounds found in animals, plants and micro-organisms that contain a cyclopropane group or derivatives thereof. This is due to the wide ranging biological properties that can be affected by a cyclopropane ring due to its high reactivity. The properties of cyclopropane containing groups includes enzyme inhibition, plant growth and fruit ripening control, insecticidal, antifungal and herbicidal activities, antibiotic and antiviral activities, hormonal activities, carcinogenic and neurochemical activities.[3]

1.1.1.1 Aminocyclopropanecarboxylic acids

1-Amino-1-cyclopropanecarboxylic acid **(1)**, commonly abbreviated to ACC, is a unique form of a constrained amino acid that is present in the tissue of many plants[4] and citrus fruits where it is a biosynthetic precursor to ethylene,[5] the hormone that initiates and regulates plant growth and fruit ripening.[6] ACC and its derivatives are attracting a lot of current research interest due to the wide range of its biological activity.[5]



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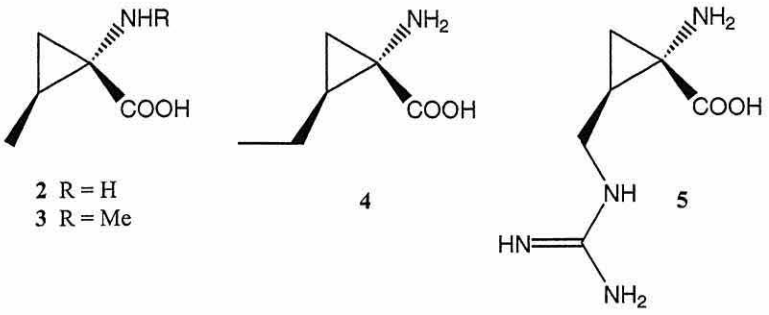
There are four naturally occurring ACC derivatives and countless synthetic ones which have been produced to determine their biological properties.



2 R = H
3 R = Me

4

5

The natural derivatives of ACC include norcoronamic acid **(2)** which has been isolated from norcoronatine[7] and its *N*-methyl derivative **(3)** which has been found to be a constituent of antibiotics of the quinomycin family.[8] Coronamic acid **(4)** is found in liquid cultures of plant pathogens[9-11] and carnosadine **(5)** has been isolated from red algae.[12, 13]

1.1.1.2 Fatty acids

Fatty acids usually contain long unbranched chains with functionality contained within monounsaturated and polyunsaturated fatty acids. Cyclopropane fatty acids are another group of common fatty acids which are widely distributed in nature and often occur in the membranes of various bacteria.

1.1.1.2.1 Lactobacillic acid

The first of the cyclopropane fatty acids, lactobacillic acid, with both its enantiomers shown in **Figure 1.2**, was discovered in 1950 by Hofmann and Lucas.[14, 15] Lactobacillic acid was found to be a major constituent of the lipids of *Lactobacillus arabinosus* and is found in everyday dairy products like yoghurt. Lactobacillic acid is thought to be present in the membrane of *Oenococcus oeni* as a factor against the toxic effect of ethanol which increases the fluidity of membrane walls and therefore allows the bacteria to maintain their activity, which is performing malolactic fermentation in wine.[16]

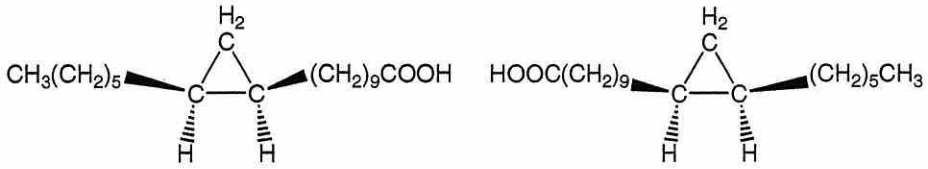


Figure 1.2 The enantiomers of lactobacillic acid

Investigation of *Lactobacillus arabinosus* showed the composition of lactobacillic acid to be $C_{19}H_{36}O_2$,[15, 17] whilst further studies established the *cis*-cyclopropane ring at the C_{11}-C_{12} position.[18-20] In 1972 the absolute configuration was established by comparison with related cyclopropyl ketones,[21] whilst both enantiomers were recently synthesised by Coxon *et al.*.[22]

1.1.1.2.2 Cascarillic acid

Cascarillic acid **(6)** is a C_{11} *trans*-cyclopropane fatty acid which is an oil that is obtained from the oil of *croton eluteria*, a tree like shrub found in the West Indies. The structure of cascarillic acid was determined in 1972 and the synthesis of the racemate was published by Wilson and Prodan in 1976.[23]

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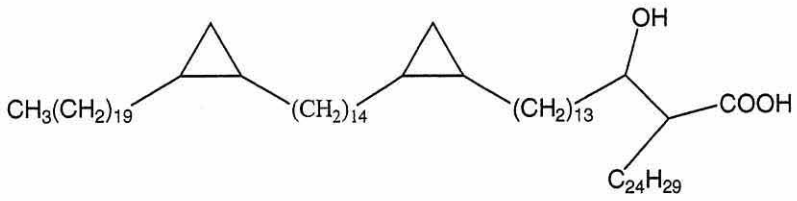
1.1.1.2.3 Mycolic acid

Mycobacterium tuberculosis is the organism responsible for the disease tuberculosis (TB) and the infection is still an epidemic in the third world with 8 million new cases estimated for 1997 on top of the existing 16 million cases of the infection that has a fatality rate of up to 50 %.[24] However, the infection is treatable over a period of time with courses of modern drug therapy, but these are not widely available in poorer countries. Therefore new vaccines to prevent the *M. tuberculosis* infection with shorter drug treatment times are desperately needed.

The cell envelope of *M. tuberculosis* is a complex array of lipids and glycolipids which are greatly studied for the interaction with human hosts.[25-27] The organism is known to synthesise three different types cyclopropane fatty acids; methoxy-

mycolates, keto-mycolates and α-mycolates, the latter of which contains two cyclopropane groups, e.g., **7**. These are known collectively as mycolic acids.[28, 29]



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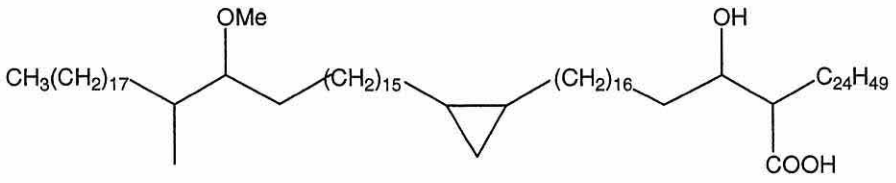
The mycolic acids exist as mixtures of homologues, with variations in the length of the four carbon chains. It is known that in α-mycolates, such as **7**, the cyclopropane stereochemistry is *cis* in each case; however the absolute stereochemistry is not known.

The other groups of mycolic acids exist with a single cyclopropane group. There are α-methoxy β-methyl mycolic acids that contain a *cis*-cyclopropane group **(8)** or the same type of methoxy-mycolates with a *trans*-cyclopropane and an α-methyl group.[30]



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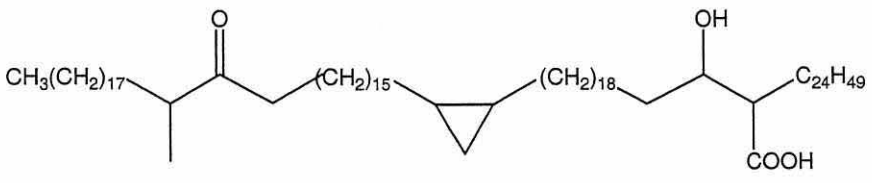
The third type of mycolic acid also contains a single cyclopropane unit with α-keto β-methyl groups, such as for that shown in **9** for the *cis*-cyclopropyl containing structure. As with the methoxy-mycolates, the *trans*-cyclopropyl containing keto-mycolates contains an α-methyl group.[30]



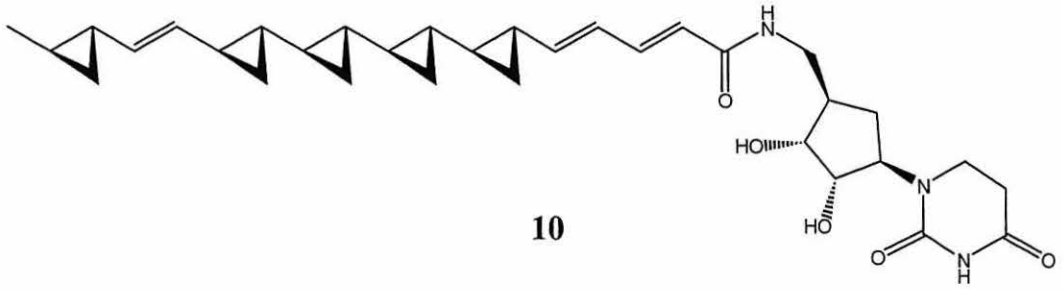
9

The problem with the development of new drugs to combat TB is these getting through the cell wall of *M. tuberculosis*, therefore the synthesis of mycolic acids is being undertaken to understand why the membrane is so impermeable.[31, 32]

1.1.1.3 Polycyclopropanes

As has been shown, many fatty acids and their derivatives contain a single cyclopropane group which is thought to be biosynthetically formed from the corresponding unsaturated fatty acid by the addition of a C-1 unit. However in the 1990s, two remarkable natural compounds with a polycyclopropane fatty acid side chain, were isolated from fungal sources; their stereochemistry was elucidated and the molecules were synthesised using multiple Simmons-Smith reactions,[33, 34] which will be covered briefly later in the introduction. These compounds have led to a great amount of interest due to their novel structures.

The polycyclopropane **10**, termed FR-900848, contains four contiguous cyclopropane units. It was isolated from the fungus *Streptoverticillium fervens* by Yoshida *et al.*.[35]



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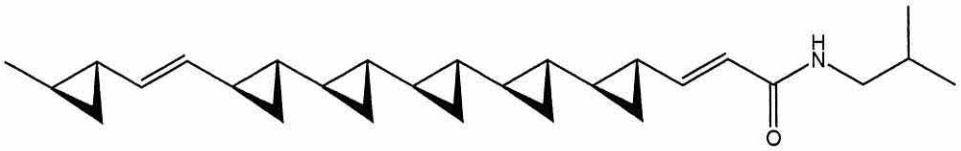
FR-900848 has been shown to have a potent and selective activity against filamentous fungi such as *Aspergillus niger, Mucor rouxianus* and *Aureobasidium pullulans*. It therefore represents a major lead in the synthesis of antifungal agents that are active against human pathogens.

The polycyclopropane **11**, termed U-106305, was isolated from the fermentation broth of *Streptomyces sp.* UC 1136 by Kuo *et al.*.[36] The structure of U-106305 is similar to that of FR-900848 but contains six cyclopropane units, five of them contiguous.

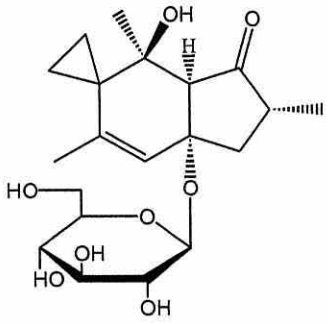


11

U-106305 has been shown to inhibit one of the enzymes that redistributes cholesteryl esters and research is being undertaken with the treatment of coronary heart disease.

1.1.1.4 Cyclopropanes in terpenes and related compounds

Bracken fern is widely distributed throughout the world. Consumption of bracken fern by cattle has been shown to lead to haemorrhaging, anorexia, intestinal damage and ulcers, whilst tests on rats has shown the carcinogenic properties of bracken fern.[37] The fraction with this carcinogenic property was isolated by Niwa *et al.*; who isolated the unstable norsesquiterpene glucoside, ptaquiloside **(12)** which was proven to be the carcinogen of bracken fern[38, 39] and the compound responsible for cattle bracken poisoning, as well.[40]



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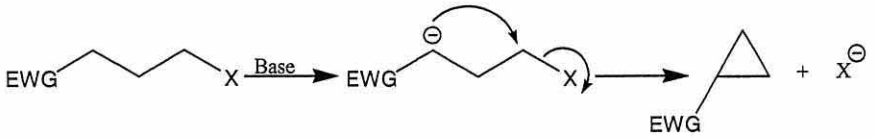
1.1.2 Preparation of cyclopropanes

Cyclopropanes can be obtained via a number of reactions that have been well documented in the literature over the past century.

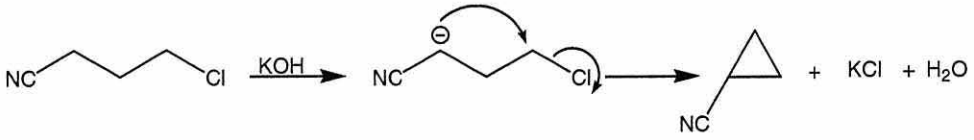
1.1.2.1 The 1,3-elimination of HX

An old method for the synthesis of cyclopropanes is a base promoted ring closure which proceeds with the anionic elimination of a β-leaving group through an intramolecular S_N2 displacement.



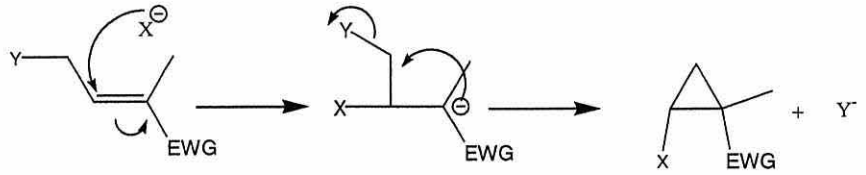
EWG = electron withdrawing group

The reaction utilises an electron withdrawing group such as an ester, ketone or cyanide group on the α-carbon to aid deprotonation by the base, and a leaving group on the γ-carbon such as a halide or tosylate.[41, 42] Cloke *et al.* used this reaction as a viable method to produce cyclopropyl cyanide in the early 1930s.[41]



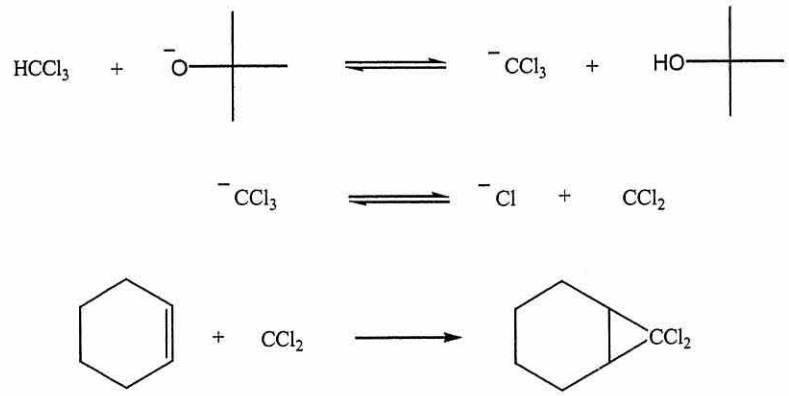
1.1.2.2 Nucleophilic addition

A similar method for the production of cyclopropanes is the addition of a nucleophile to an electron poor alkene to give an anionic species which, similar to the elimination reaction above, will then cyclise to a cyclopropane with attack at the β-carbon and the ejection of an anionic leaving group.[43]



1.1.2.3 Carbene addition to an alkene

A common method of cyclopropane synthesis is the addition of a carbene across an electron rich alkene. This was first reported by Doering and Hoffmann in 1954,[44] with one of the original examples shown in **Scheme 1.1** with *tert*-butoxide used to reversibly deprotonate chloroform.[44]



Scheme 1.1 The generation of cyclopropane from addition of a carbene to an alkene

The derived anion then loses the chloride ion to give the neutral carbene, nowadays shown as $:CCl_2$, before this adds across the double bond to give 7,7-dichlorobicyclo[4.1.0]heptane. Doering and Hoffmann also produced dibromocyclopropanes using bromoform and simpler alkenes, e.g., using 2-methylpropene instead of cyclohexene. As addition to the π-bond of an alkene is now one of the most studied reactions of carbenes, an introduction to the structure and reactivity of carbenes and their cyclopropane forming reactions will follow.

1.1.2.3.1 The structure and reactivity of carbenes

Carbenes are neutral, short lived electron deficient reactive intermediates. They comprise a carbon atom with two covalent bonds and two orbitals that hold the remaining two bonding electrons between them.

These non-bonding electrons can be arranged in two ways, either with their spins paired or with parallel spins. If the electrons are spin paired then the carbene is a singlet species (spin multiplicity = 1) with an empty p orbital and an sp^2 structure **(13)** as shown in **Figure 1.3**. If the electrons have parallel spins, both the orbitals contain one electron each, so that the carbene is a triplet (spin multiplicity = 3) and will generally have a linear sp structure **(14)**. It was Skell who first suggested the idea of singlet and triplet states.[45]

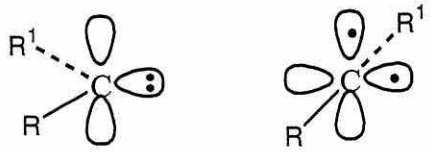


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Figure 1.3 The structure of singlet and triplet carbenes

The singlet carbene is similar in shape and in some ways reactivity to a carbenium ion, whilst the carbene in the triplet state resembles a free radical.

Electron spin resonance (ESR) has been used to observe carbenes at low temperatures, but the high reactivity of carbenes means that often their existence can only be deduced from reaction products. The simplest carbene, methylene (**Figure 1.3**, R = H, R^1 = H), was shown to exist in a ground state as a non-linear triplet with a bond angle of 136° when generated in a low temperature matrix. The difference in energy between the singlet and triplet states of methylene has been calculated as 35 KJ mol^{-1} but when generated from the photolysis of diazomethane, the excited singlet can react before degenerating to the ground state triplet.

In contrast, if the carbene has substituents containing lone pairs that can interact with the carbene centre, then the energy gap between different states is reduced and the singlet state can be stabilised. Dihalocarbenes show this effect due to the lone pairs of electrons on the halogens that overlap with the vacant p-orbital of the singlet state as shown in **Figure 1.4**.[46] Dihalocarbenes generally therefore have singlet ground states.

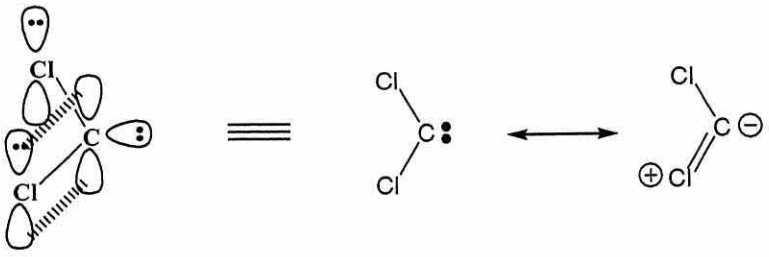
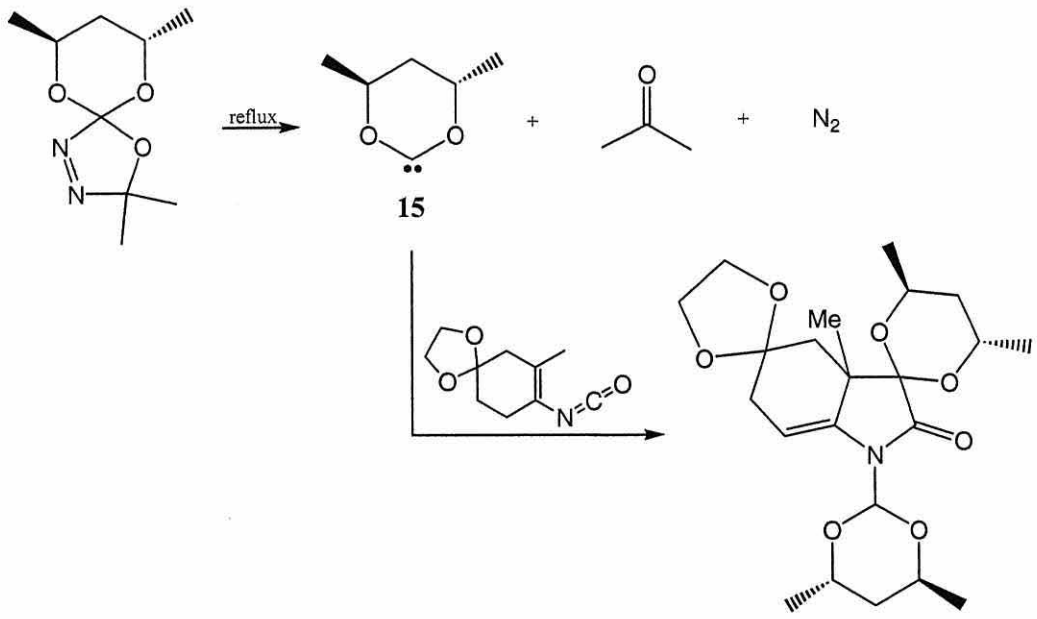


Figure 1.4 The stabilisation of singlet dichlorocarbenes

In general, carbenes are highly electrophilic, due to the carbon atom being electron deficient as it has only six electrons in its outer shell. The substituents on the carbene

affect the reactivity, as electron withdrawing ones will make the carbene more electrophilic. It is also possible to have strong π-donor substituents, such as oxygen, nitrogen or sulfur, to produce nucleophilic carbenes;[47, 48] an example of which is shown in **Scheme 1.2**, where the resultant carbene **(15)** reacted with vinyl isocyanates to form 5-membered heterocycles.[49]



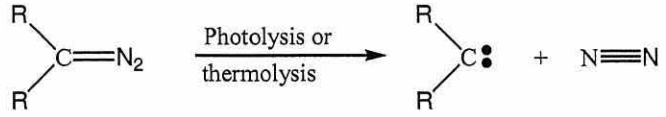
Scheme 1.2 The generation and reaction of nucleophilic carbenes

1.1.2.3.2 Major methods for the generation of carbenes

Due to their high reactivity, carbenes are generated within a reaction and are not generally isolated. They are generated by the breaking of weak bonds within molecules to form thermodynamically stable by-products, such as nitrogen gas or carbon monoxide that make the reaction energetically viable.

1.1.2.3.2.1 The generation of carbenes from diazo compounds

The production of carbenes from diazo compounds is a long established reaction, with these being the best known carbene precursors. The carbenes are generated by decomposition via photolysis or thermolysis to liberate nitrogen gas.



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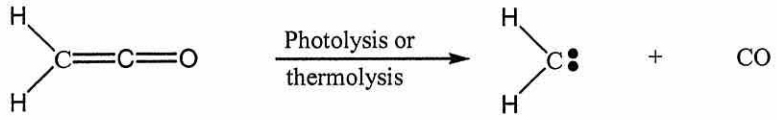
The alkyl groups on the diazo compound affect both the stability and the reactivity of the compounds. Thus a simple diazo-alkane such as diazomethane (**16**, where R = H) is very unstable. However, these reactions were found to suffer from low yields and poor selectivity when using functionalised carbenes. Studies have shown that the reactions are effectively catalysed under mild conditions with rhodium and copper catalysts,[50, 51] such as rhodium (II) carboxylates which have been widely used in cyclopropanation of alkene reactions.[52] Recent studies have shown that asymmetric cyclopropanation reactions with diazo-alkanes and alkenes can be mediated with chiral catalysts.[53]

1.1.2.3.2.2 The generation of carbenes from ketenes

Ketenes produce carbenes upon photolysis or thermolysis, with the formation of carbon monoxide as the stable by-product. The reaction is not common as ketenes are not commonly available precursor molecules.

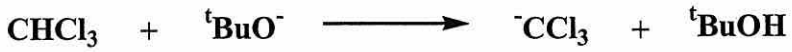


1.1.2.3.3 Major methods for the generation of dihalocarbenes

Electron rich halogens, as has already been stated, will stabilise a carbene and cause it to have the singlet ground state. Many methods have been used to synthesise dihalocarbenes from starting materials that are easier to obtain than those mentioned for the synthesis of carbenes above.

1.1.2.3.3.1 The deprotonation of chloroform with potassium butoxide

The deprotonation of chloroform with a *tert*-butoxide ion to give a trichloromethyl anion was performed by Doering and Hoffman.[54]



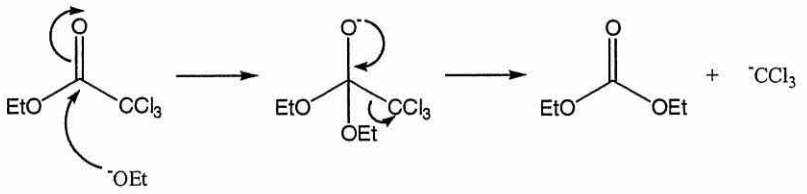
The reversible loss of a chlorine anion from the trichloromethyl anion generates the neutral dichlorocarbene. This then reacts *in situ* with alkenes, e.g. cyclohexene to give 7,7-dichlorobicyclo[4.1.0]heptane.

$$^{-}CCl_3 \rightleftharpoons :CCl_2 + Cl^{-}$$

The drawback with this reaction is that it is carried out under basic conditions and that the *tert*-butanol produced as the by-product can react with the dichlorocarbene.

1.1.2.3.3.2 The modification of the chloroform deprotonation reaction

The reaction in **Chapter 1.1.2.3.3.1** was modified to avoid the production of an alcohol by reacting trichloroacetic acid ethyl ester **(17)**,[55, 56] or hexachloropropanone,[57, 58] with sodium ethoxide to give the diethylcarbonate **(18)** and the trichloromethyl anion.



17 **18**

1.1.2.3.3.3 The dechlorination of carbon tetrachloride

A different approach is to generate dichlorocarbene from dechlorination of carbon tetrachloride with butyl lithium and then trap the carbene *in situ*.[59] This reaction requires not only anhydrous conditions but it has to be carried out under an inert atmosphere.

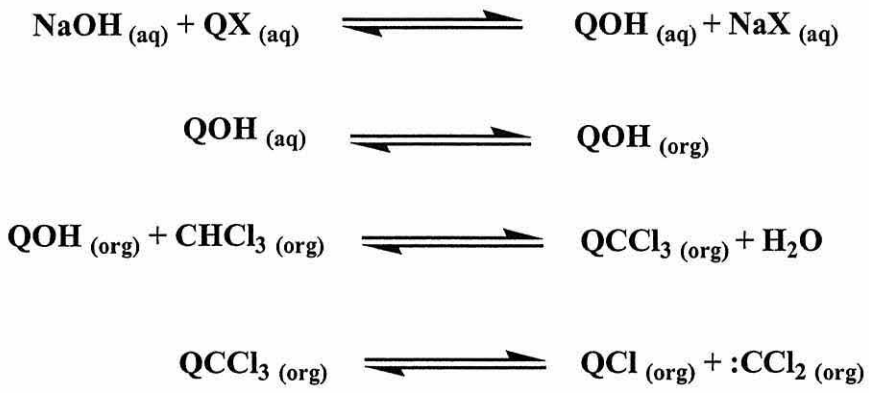
$$CCl_4 + BuLi \longrightarrow :CCl_2 + LiCl + BuCl$$

Carbon tetrachloride is now hard to obtain since it was commercially banned under the Montreal convention. This was set up to control the levels of CFC products produced. This was due to carbon tetrachloride and other CFC's getting into the stratosphere and photo-reacting with UV radiation, therefore interfering with the production of ozone. In addition, butyl lithium is relatively expensive.

1.1.2.3.3.4 The phase transfer reaction

The phase transfer reaction provides a method of dihalocarbene production that does not require anhydrous conditions, as has been necessary for previous reactions. It is

of great importance because the reversibility of each step means that there is a constant supply of dihalocarbene because it is in equilibrium with the carbanion as shown in **Scheme 1.3**. Even though the dihalocarbene is present in a low concentration, its further reaction will drive the equilibrium towards the carbene until the reaction is complete.



Scheme 1.3 The generation of diclorocarbenes with phase transfer catalysis

Phase transfer reactions work as the base that is used to deprotonate the chloroform exists in the aqueous phase and is not soluble in chloroform. The phase transfer catalyst is a quaternary ammonium salt, commonly cetyl trimethyl ammonium chloride (cetrimide).[60] This reacts with the sodium hydroxide in the aqueous phase to produce a sodium halide salt and a quaternary ammonium hydroxide. This is the active part of the phase transfer process which transfers the base into the organic phase.

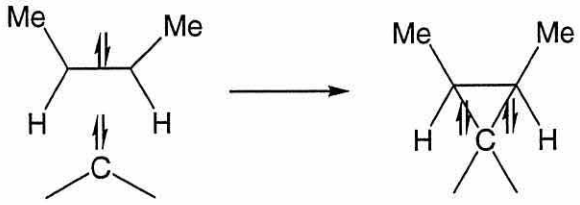
With the base now soluble in the organic phase, the chloroform is deprotonated to give a trichloromethyl anion, which through the loss of a chloride ion will produce the dihalocarbene.

The by-product of the reaction is the regeneration of the cetrimide, which can then be recycled back into the aqueous phase to react with sodium hydroxide and continue the reaction. As all the steps are reversible, a steady state concentration of the carbene is developed that can be trapped, for example by the addition of an alkene to yield a cyclopropane. The water formed transfers to the aqueous phase, reducing the chance of hydrolysis of the cation.

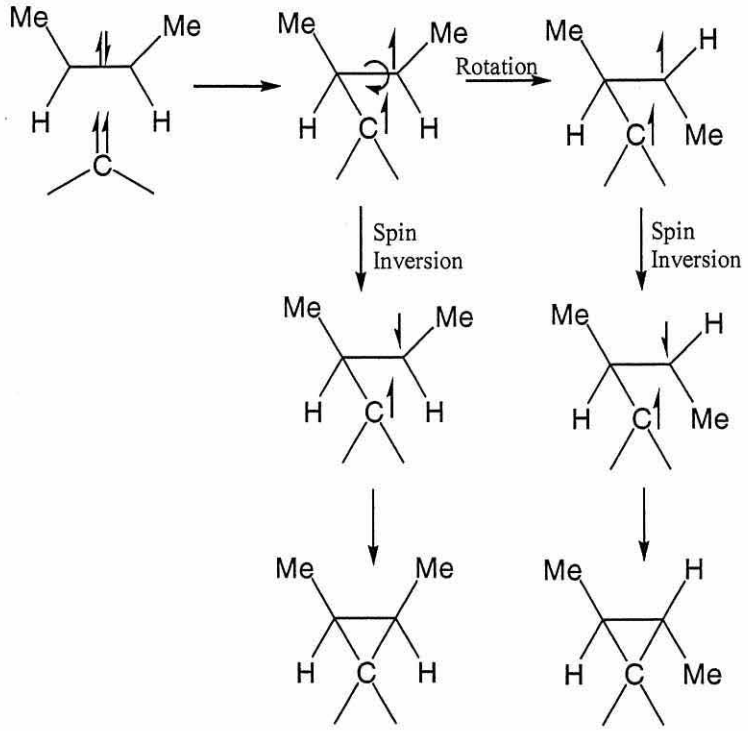
This method was first used by Starks[61] and Makosza[62] who generated dichlorocarbene from aqueous sodium hydroxide with chloroform and triethylbenzyl ammonium chloride as the phase transfer catalyst.

1.1.2.3.4 The mechanism of alkene cyclopropanation by addition of carbenes

In 1956, Skell[45] proposed a mechanism for the addition of a carbene to an alkene, with the stereochemistry of the product being controlled by the spin state of the carbene. He postulated that a spin paired singlet carbene would undergo a stereospecific concerted addition to an alkene, and preserve the stereochemistry.



However, a spin parallel triplet state carbene would produce an intermediate that could only complete ring closure after spin inversion of one electron. As spin inversion is relatively slower than rotation around a C-C bond, this intermediate may exist for enough time for the molecule, now free from the previous bond constraints of the alkene, to alter its stereochemistry before ring closure. This would lead to a non-stereospecific reaction as shown in **Scheme 1.4**.[44, 63]

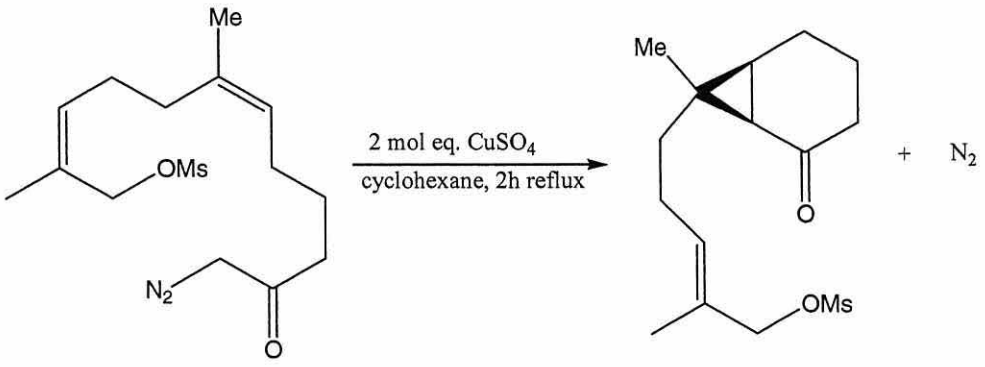


Scheme 1.4 The two reaction pathways of the addition of a triplet carbene to an alkene

1.1.2.3.5 The generation of cyclopropanes from carbene reactions

1.1.2.3.5.1 Cyclopropanes from diazoketones

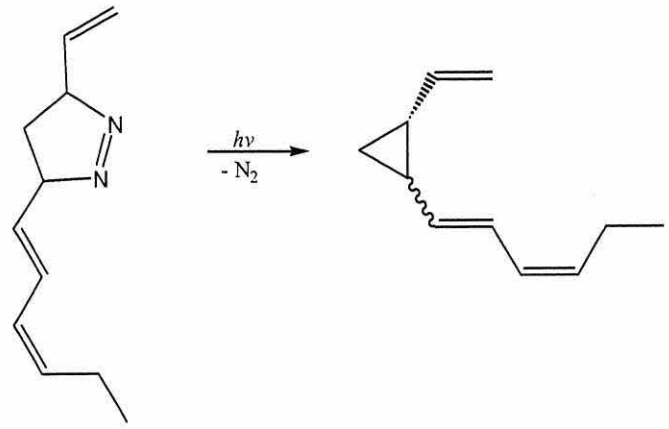
Cyclopropanes can be generated by the irreversible decomposition of diazoketones when heated in the presence of copper sulfate. Copper metal and other copper compounds have also been found to start the cyclisation process which proceeds with the loss of nitrogen gas. An example of the reaction that was performed by Corey can be seen in **Scheme 1.5**.[64]



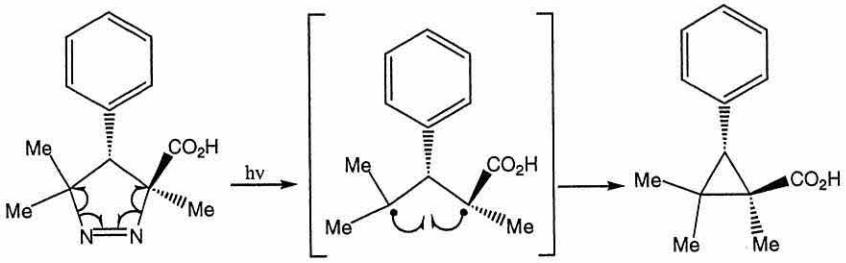
Scheme 1.5 A cyclopropane generated from a diazoketone

1.1.2.3.5.2 Cyclopropanes from pyrazoline photolysis

Cyclopropanes can also be synthesised from a pyrazoline with a 2-atom ring contraction.

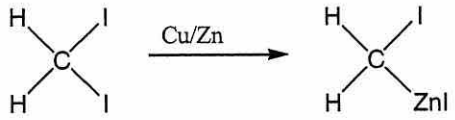


The mechanism for the ring contraction to the more highly strained cyclopropane is driven by the production and removal from the reaction of the very stable nitrogen gas. Radiation with ultra-violet light leads to the cleavage of both the carbon-nitrogen bonds[65] to give nitrogen gas and a diradical species that will rearrange to form the new carbon-carbon bond of the cyclopropane as shown by Karatsu *et al.*.[66]

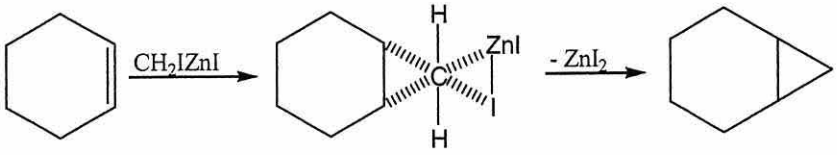


1.1.2.3.5.3 Cyclopropanes from the addition of carbenoids

A carbenoid is a molecule that contains an electropositive and an electronegative group on the same atom that are lost during the reaction. They react similarly to carbenes but are more stable. The most common carbenoid is formed by the reaction of diiodomethane with copper/zinc.



A common carbenoid reaction is the addition to an alkene in the cyclopropane forming Simmons-Smith reaction[67] which was first observed in 1959. The reaction proceeds via the organo-zinc compound and is completed with the loss of zinc (II) iodide.



1.2 Cyclopropenes

1.2.1 Structure, strain and bonding of cyclopropenes

Cyclopropenes, like cyclopropanes, have ring strain as their prominent feature, the strain energy being calculated as *ca* 219 $Kjmol^{-1}$ for cyclopropene[68] compared to *ca* 115 $KJmol^{-1}$ for cyclopropane.[69] This greater strain in cyclopropene is due to the large deviation in the bonding of the alkene from that in ideal sp^2 bonding found in unconstrained alkenes. The deviation is accounted for and the strain partly relieved by changes to the nature of the bonding, with the carbon contribution to the external carbon-hydrogen bond being equivalent to $sp^{1.19}$ and the internal carbon-carbon bonding having $sp^{2.68}$ hybridisation.[70] In effect, this means that the external cyclopropene bonding is more similar to sp than sp^2 bonding, whilst internal bonding resembles sp^3 with the interatom angles shown in **Figure 1.5.**[71] This makes the existence of such strained molecules viable.

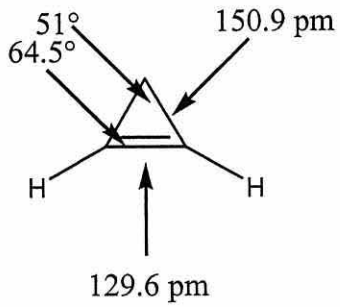


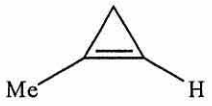
Figure 1.5 The bond lengths and angles in cyclopropene

1.2.2 Cyclopropenes in nature

Cyclopropenes, having greater ring strain than the corresponding cyclopropane, take part in a large range of biological processes[3, 5] and compounds containing cyclopropenes are indeed found in nature.

1.2.2.1 1-Methylcyclopropene

1-Methylcyclopropene or MCP **(19)** is a growth hormone blocker that is used commercially to retard the ripening process of fruit. Positive studies have been carried out to slow ripening with a large variety of fruit and vegetables including avocadoes,[72] broccoli,[73] plums,[74] pears[75] and strawberries.[76] MCP, sold commercially under the name of Smartfresh, blocks ethylene receptors in the fruit and lowers the rate of respiration.[75]



19

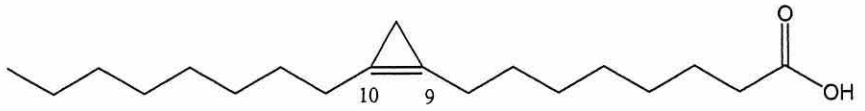
MCP's effect is to decrease fruit softening, maintaining high levels of juice acidity and to extend the storage life of fruit that had previously been considered to have a short shelf life, by up to a factor of four times.[77]

1.2.2.2 Cyclopropene fatty acids

Fatty acids are the most abundant form of reduced carbon chain available in nature.[78] There are a large number of natural fatty acids, most contain long straight carbon chains, but some contain other functionalisation including two common cyclopropene containing fatty acids.

1.2.2.2.1 Sterculic acid

Sterculic acid **(20)** is a naturally occurring fatty acid found in several species of seed oil and the common cotton plant,[79, 80] that has now been synthetically produced.[81]



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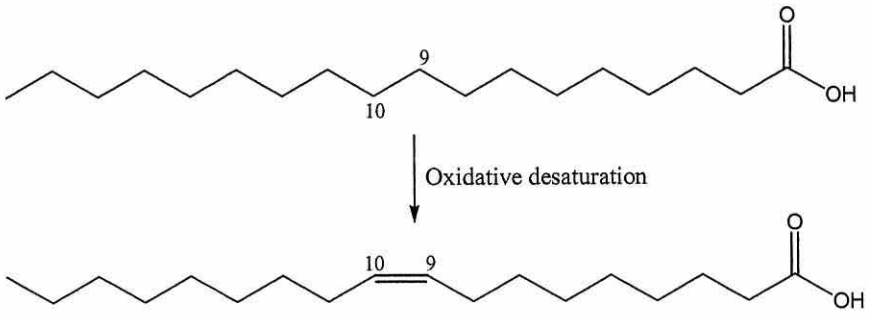
Sterculic acid inhibits the enzyme Δ^9-desaturase which controls the production of unsaturated fatty acids, particularly the desaturation of stearic acid to oleic acid as shown in **Scheme 1.6**. Whilst work has shown that sterculic acid will inhibit the Δ^9-desaturase of aliphatic acids of various chain length,[82] it has been shown that it is important to have the cyclopropene ring in the C9 and/or C10 position for it to be an effective inhibitor of Δ^9-desaturase.[83, 84]

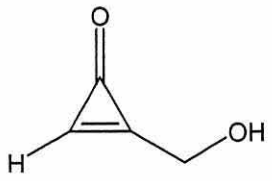


Scheme 1.6 The desaturation of stearic acid

Malvalic acid is the lower homologue of sterculic acid with one CH_2 unit less on the acid chain and is also found within seed oils.[79, 80] Sterculic acid in diet has a marked effect on a range of processes, e.g. it causes growth problems and the cessation of egg laying in hens.[85] Similar growth problems have been observed in mammals, but no effect has been found on humans, with communities in Malaysia eating a range of nuts that contain high levels of cyclopropene fatty acids, with no ill effect.[86] Therefore cyclopropene fatty acids are under investigation for use as insecticides, as they have been found to have a short term sterilising effect on the females of some common pests.[87, 88]

1.2.2.3 Penitricin

Penitricin **(21)** is an antibiotic cyclopropenone[89-91] that is obtained naturally from a species of fungi, although it has been synthetically produced by Isaka *et al.*[92] within the past fifteen years.

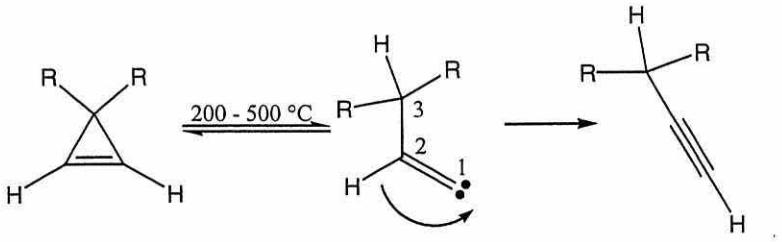


21

1.2.3 The ring opening of cyclopropenes

It has been shown that cyclopropenes will often ring open to vinyl carbenes to relieve the high level of ring strain This reaction is, however, reversible, until the carbene can react with a second species or the molecule rearrange to a stable unsaturated compound. A comprehensive overview of cyclopropene-carbene rearrangements has recently been compiled by Baird.[93]

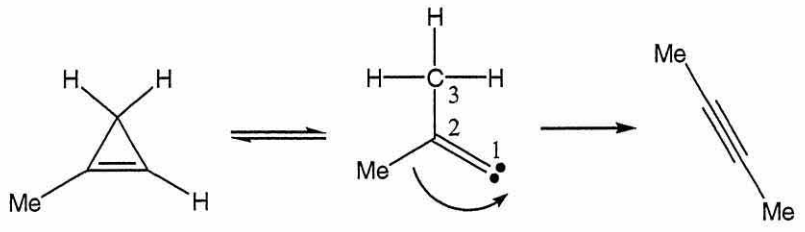
The ring opening of cyclopropenes that contain a proton on the carbon-carbon double bond have been found to be induced by heating to temperatures of 200 - 500 °C. In these cases, the cyclopropene ring opens by a hydrogen shift to give a vinylidene **(22)** that rearranges with a second 1,2-hydrogen shift to give a terminal alkyne[94] as shown in **Scheme 1.7.**



22

Scheme 1.7 The ring opening and rearrangement of a cyclopropene

There are examples of this reaction with 3-methylcyclopropene,[95] and 3,3-dimethylcyclopropene,[95, 96] but with ring opening of 1-methylcyclopropene **(23)** a 1,2-alkyl shift takes place in the methylenecarbene[97] with the migration of the methyl group to give but-2-yne **(24)** as shown in **Scheme 1.8.**

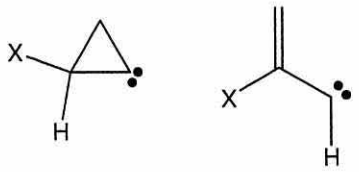


23 **24**

Scheme 1.8 The ring opening and methyl shift of 3-methylcyclopropene

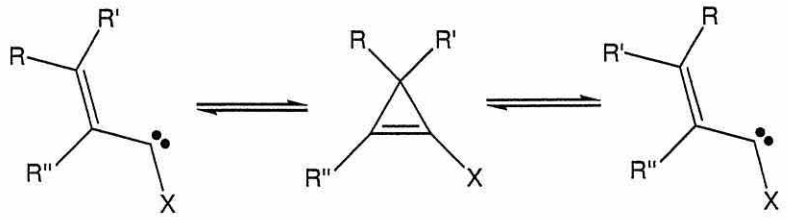
Singly and doubly halogenated cyclopropenes, with hydrogens at the C3 position, have been shown under low pressure and at temperatures of 400 – 650 °C to ring open and rearrange to allenes. Likewise tetrahalocyclopropene was found to convert into tetrahaloallene.[98]

The mechanism of this reaction is not discussed in detail, but may involve a migration of X or H to form a cyclopropylidene **(25)**, followed by rearrangement to the allene, or alternatively the reaction may occur by ring-opening to a vinylcarbene **(26)**, followed by rearrangement.

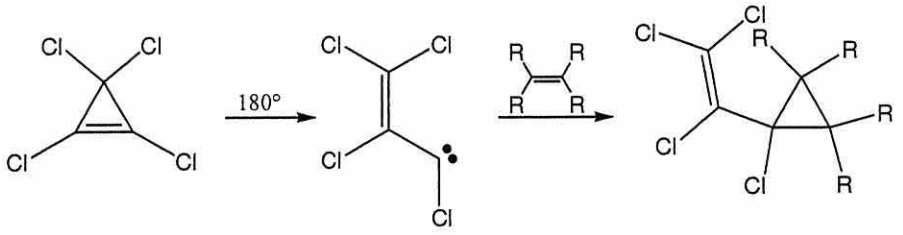


25 **26**

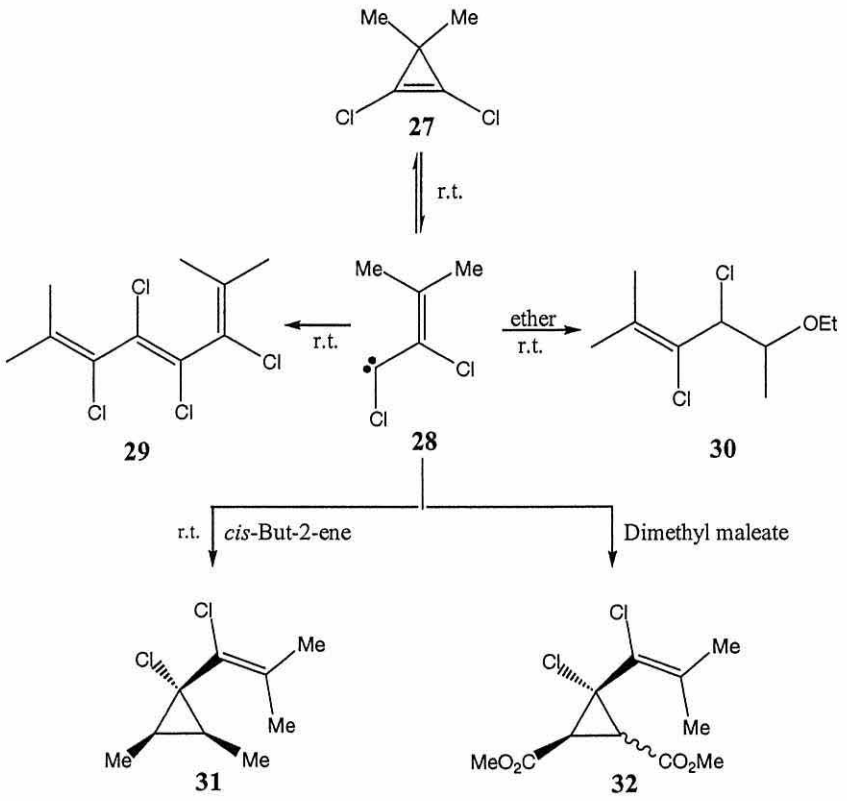
It has been shown that the ring opening of some cyclopropenes does lead to vinylcarbenes in a process that involves monorotation at the C3 position, that can therefore lead to E or Z isomers of the alkene, e.g. where X = R'' = H, R = Ph and R' = Me at 180 °C where both the E and Z carbene isomers have been trapped.[99]



The ring opening of tetrahalocyclopropenes has been found to take place at 150 - 170 °C to give the vinyl carbene which has been trapped with a range of alkenes to give cyclopropanes.[100-102]



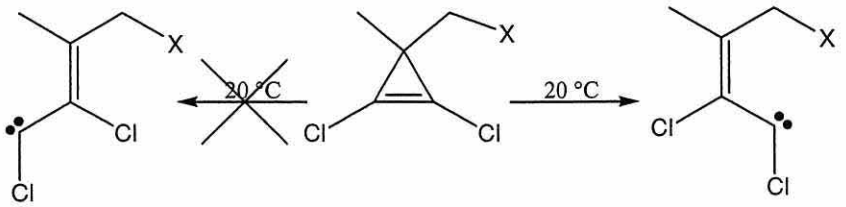
There are however many examples of 1,2-dihalocyclopropenes that ring open to vinyl carbenes at room temperature. Examples of these reactions for 1,2-dichloro-3,3-dimethylcyclopropene **(27)** are shown in **Scheme 1.9.** The carbene **(28)** generated from ring opening will decomposes to a triene **(29)** by an apparent dimerisation, or if in ether solution, the carbene will insert into the ether C-H bond adjacent to oxygen to give the corresponding ether product **(30)**.[103] The vinyl carbene can also be trapped through addition of an electron rich alkene,[104] or an electron poor alkene[105] to give cyclopropanes **31** and **32**, respectively.



Scheme 1.9 The reactions of vinyl carbenes

It is worth noting that the addition to *cis*-but-2-ene leads only to the retention of the relative stereochemistry of the two methyl groups, suggesting a singlet carbene addition. However the stereochemistry is lost in the addition of the electron poor ester.

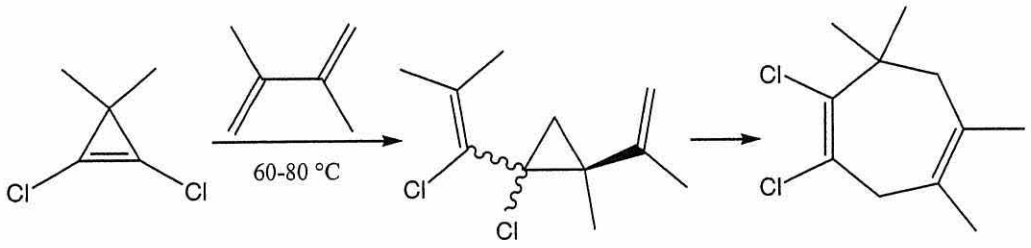
Different functionalisation introduced at the C3 position of a cyclopropane, such as **33** (X = OMe, Ph, Cl), can lead to highly stereoselective ring opening to the vinyl carbene and can therefore lead to stereospecific trapping of the carbene.



33

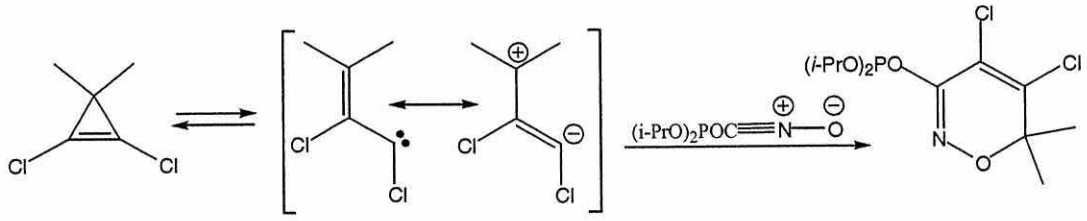
It has been shown that 3,3-dimethyl-dichlorocyclopropene **(27)** is trapped by 1,4-dienes to give divinylcyclopropanes, as with trapping by alkenes above, but Cope

rearrangement of the intermediate cyclopropane **34** gives the corresponding dichlorocyclohepta-1,4-diene **(35)**.[106, 107] Both *cis* and *trans* adducts **(34)** rearrange under these conditions.

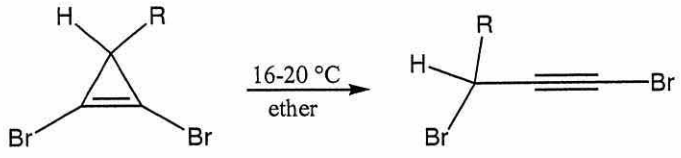


27 **34** **35**

The same dichlorocyclopropane **27** will also cyclise in a three-centre plus three-centre [4 + 2]-cycloaddition with a nitrile oxide to give a six membered heterocycle.[108]

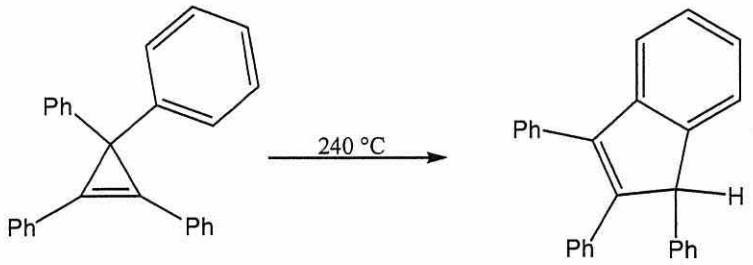


In the case of 1,2-dibromocyclopropenes with a single alkyl substituent at the C-3 position, it has been shown that the compound will ring open at room temperature to the vinyl carbene and can be trapped like previous examples with suitable trapping agents.[93] However, in the absence of a trapping agent, the cyclopropene rearranges to an alkyne.



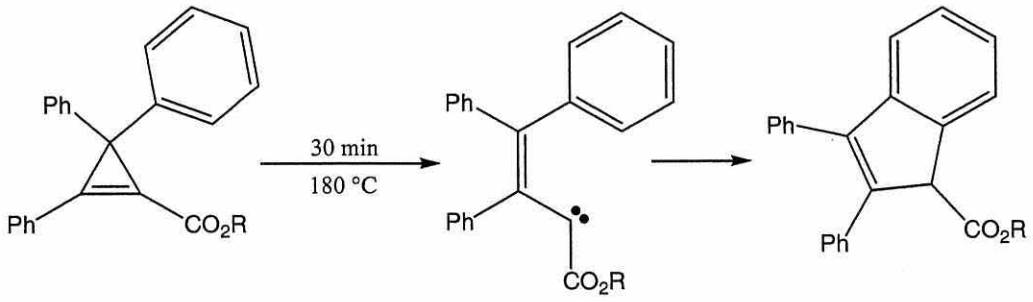
The carbene produced upon ring opening of a cyclopropene can also be trapped intramolecularly if there is an appropriate group in the molecule. Examples of this with an aryl group on the cyclopropene ring are seen in the rearrangement of

tetraphenylcyclopropene **(36)** to the indene **(37)** at 240 °C[109] and a similar reaction for 3,3-diphenylcyclopropene at 200 °C.[110]



36 **37**

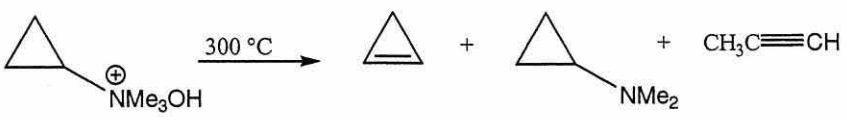
The mechanism for this reaction has been studied with the thermal isomerization of esters of 2,3,3-triphenylcyclopropenecarboxylic acid **(38)** to give the corresponding esters of 2,3-diphenyl-1-indenecarboxylic acid **(39)**. The rate of the reaction was not found to generally increase with use of a polar solvent, although the use of TFA was found to have a considerable affect, increasing the rate, possibly because the reaction proceeds via a cation. However the large negative entropy of activation for the reaction taking place in tetrachloroethylene is more consistent with ring opening of the cyclopropene to a vinyl carbene.



38 **39**

1.2.4 The preparation of cyclopropenes

Cyclopropanes are commonly used in the synthesis of cyclopropenes. The first such synthesis was from the pyrolysis of trimethyl cyclopropyl ammonium hydroxide at 300 °C in 1922, to yield cyclopropene itself amongst the products.[111]



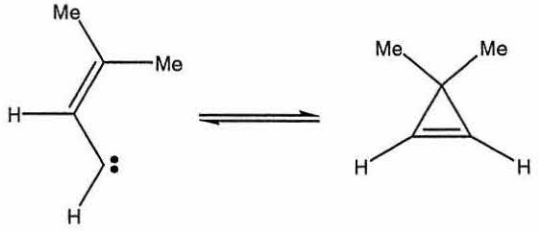
1.2.4.1 Dehydrohalogenation

The dehydrobromination of cyclopropane **(40)** with potassium *tert*-butoxide gives the cyclopropene ester **(41)** which rapidly adds the by-product of the reaction, *tert*-butanol, across the double bond.[112]

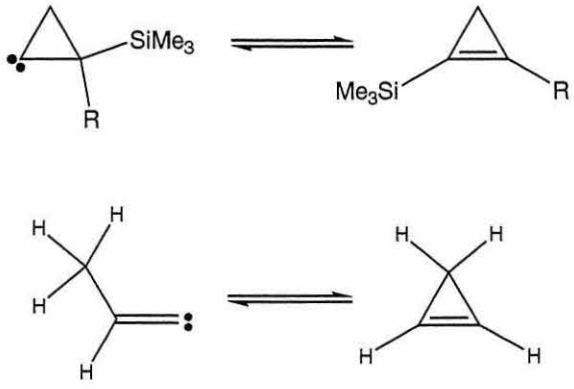
40 **41**

1.2.4.2 Cyclopropenes from carbene precursors

Cyclopropenes can be synthesised from three different types of carbene precursor. The most common of these reactions is from a vinyl carbene. These are commonly generated by the thermolysis of an alkali metal salt of a tosylhydrazone of a ketone.[113]



The other, less common, reactions from cyclopropylidines[114, 115] and vinylidenes[116] are shown in **Scheme 1.10**, respectively.



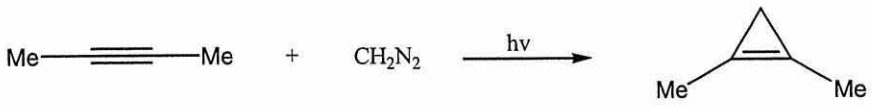
Scheme 1.10 The formation of cyclopropenes from cyclopropylidines and vinylidenes

The cyclopropylidine can be generated from the reaction of the corresponding dibromocyclopropane with methyl lithium,[115] whilst the methylenecarbene is generally generated from the 1,1-dibromo-alkene and methyl lithium or by reaction of a ketone with methyl diazomethylphosphonate.[117, 118]

These reactions are all, in principle, reversible under suitable conditions until the carbene can be trapped through intramolecular rearrangement or through an intermolecular trapping reaction. Therefore cyclopropene generation and cyclopropene reaction mirror each other.

1.2.4.3 The addition of carbenes to alkynes

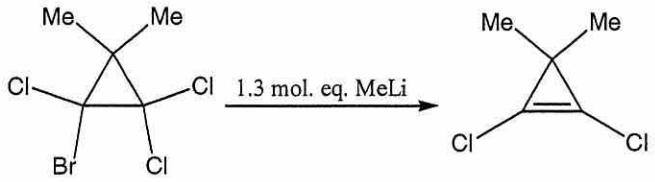
Another method to generate cyclopropenes from carbenes is the addition of carbenes to alkynes in much the same way as the synthesis of cyclopropanes from the addition of carbenes to alkenes, with the formation of two σ-bonds with the concertedness of the reaction dependent on the multiplicity of the carbene, as discussed in **Section 1.1.2.3**. This reaction is illustrated by the photolysis of diazomethane and the subsequent reaction with prop-2-yne to give 1,2-dimethylcyclopropane.[119]



The reaction is limited because with terminal alkynes there is a competing reaction with the insertion of the carbene into the terminal C – H bond. Also this reaction cannot be used produce cyclopropenes with alkyl groups at the C3 position since the required alkylcarbenes rapidly rearrange to form alkenes and cyclopropanes before addition can occur.

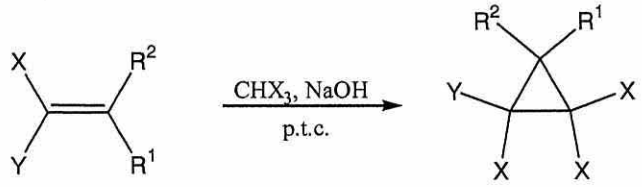
1.2.4.4 The preparation of dihalocyclopropenes

The studies reported in this thesis involve the rearrangement of 1,2-dihalocyclopropenes. These are synthesised via the 1,2-dehalogenation of 1,1,2,2-tetrahalocyclopropanes with methyl lithium.[103]



The 1,2-dehalogenation of the tetrahalocyclopropane is however effectively carried out with treatment with 1.3 mol. eq. of MeLi. The reaction occurs within a few minutes under conditions depending on the halogens present. 1,2-Debromination reactions have been found to take place at – 90 °C, whilst 1,2-dechlorination takes place at 0 – 20 °C.[103]

The tetrahalocyclopropanes required for the above process are synthesised from the reaction of 1,1-dihaloalkenes with dihalocarbenes generated from haloform with an aqueous base and a phase transfer catalyst as previously discussed in **Chapter 1.1.2.3.3.4**.



The cyclopropanation reactions using a phase transfer catalyst provide an effective method for the production of a wide range of tetrahalocyclopropanes,[120] however the reactions occur in low yields in many cases and are generally slow with reactions taking up to five days to run to completion. Other problems with the reaction include competing addition reactions of the carbene to electron poor alkenes[121] and that there is no reaction between dichlorocarbenes and hindered alkenes.[122]

1.3 Indoles

Indoles are widespread in nature and because of their roles in many biological reactions, they are being targeted by drug companies as synthetic solutions to modern day health problems.

1.3.1 Structure and Bonding in Indoles

For symmetrical aromatic structures like benzene there is one carbon-carbon bond length, midway between a normal double and single bond. However, in the fused bicycles of indoles, there is alternation in the values of the bond length of the pyrrole ring that is comparable with none aromatic localised structures.

Even with a fully aromatic system, the lack of symmetry and the electronegative nitrogen would lead to different bond lengths around the ring. A standard carbon - nitrogen single bond length is 1.45 Å, whereas the carbon – nitrogen double bond length is 1.27 Å. The standard carbon – carbon single bond has been measured as 1.54 Å, whilst the double bond is 1.33 Å. Using the bond length data shown in **Figure 1.6** for indole and pyrrole, with comparison to these standard bond lengths, the effect of aromaticity is observed due the bond lengths being averaged but not equal.

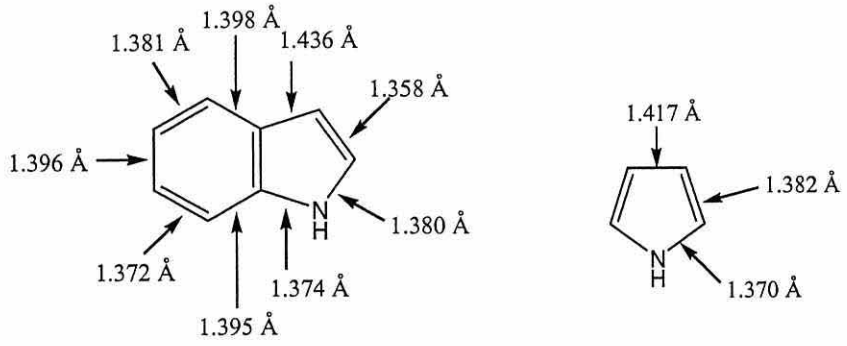


Figure 1.6 Bond lengths in indole and pyrrole

The aromatic effect can also be observed in indoles in the deshielding of signals in the ^{1}H and ^{13}C NMR spectra due to an induced diamagnetic ring current in the external field of the NMR magnet. This is because when a molecule with delocalised π-electrons is placed in an external magnetic field, an internal magnetic field is induced that opposes the applied field within the ring. The protons on the ring are therefore deshielded and the NMR signals are moved downfield, whereas any protons in a molecule which sit over the ring are shielded. The ^{1}H and ^{13}C NMR shifts of indole and pyrrole are shown in **Figures 1.7** and **1.8**, respectively.

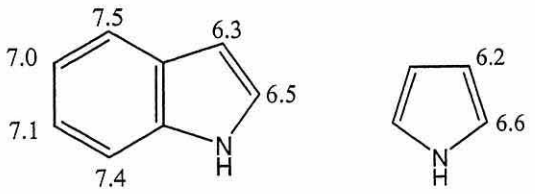


Figure 1.7 ^{1}H NMR chemical shifts in indole and pyrrole

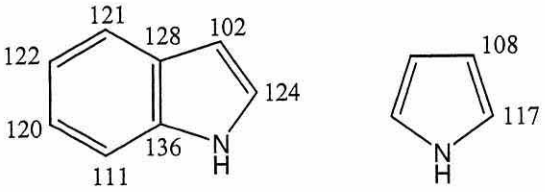
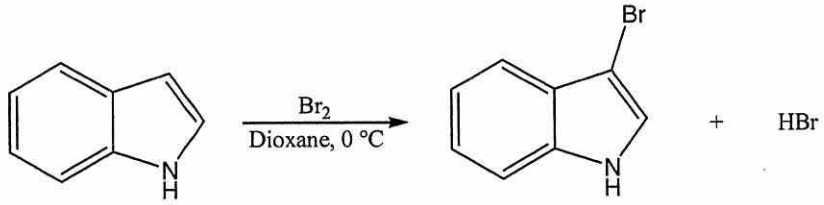
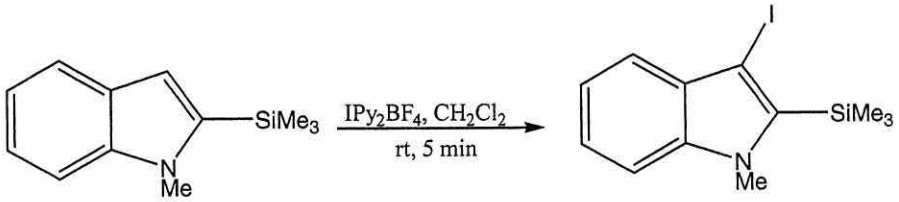


Figure 1.8 ^{13}C NMR chemical shifts in indole and pyrrole

A consequence of the stability gained from aromaticity of the bi-cycle is the reactivity of indoles. Whereas alkenes react with electrophiles by addition, indoles generally do not, as this would destroy the aromaticity. Instead aromatic systems like indoles react via substitution reactions that maintain the aromaticity. Electrophilic substitution is found to take place at the C3 position on the electron rich pyrrole ring for the selective bromination of indole.

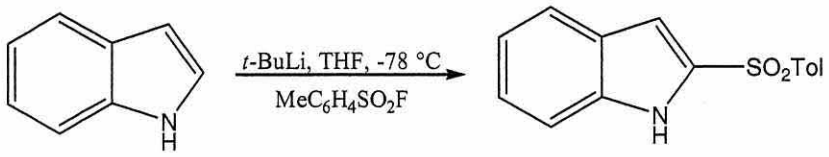


Lewis acid catalysts have been developed for electrophilic substitution reactions at ambient temperatures.[123]



An alternative method to substitute indoles is to deprotonate and then quench the anion in a nucleophilic substitution reaction. This occurs at the 2-position, rather than

the 3-position.[124] These reactions generally require strong base, with *tert*-BuLi commonly used.

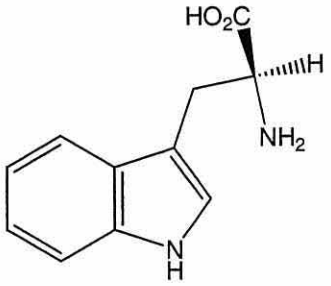


1.3.2 Indoles in nature

As has already been mentioned, indoles are prevalent in nature and therefore have gained a lot of attention from synthetic chemists who are designing modern day drugs. Examples of indoles, both natural and synthetic, are given below.

1.3.2.1 Tryptophan[125]

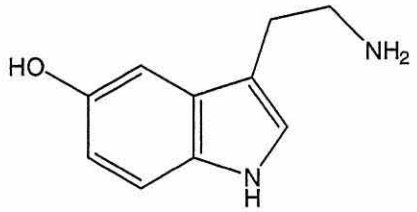
Tryptophan **(42)** is a constituent of many proteins and is an essential nutrient in the diet of vertebrates. It has been used as an antidepressant drug for a long time, but, since it has been linked with cosinophilia-myalgia syndrome,[126, 127] it is now greatly regulated and is only used as a last resort for treating severe depressive illnesses.



42

1.3.2.2 Serotonin

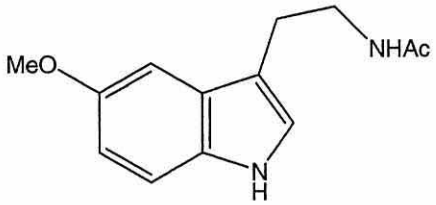
Serotonin **(43)** is found in the blood platelets and serum of warm blooded animals and therefore plays an import role in the central nervous,[128, 129] cardiovascular[130] and gastrointestinal systems.[130, 131] Upon bleeding, serotonin is released from the platelets where it constricts the blood vessels to reduce blood loss. In the tissue lining of the digestive tract, serotonin inhibits gastric secretion and, in the brain, it is involved in the transmission of impulses between nerve cells as well as controlling mood and states of consciousness.[132]



43

1.3.2.3 Melatonin

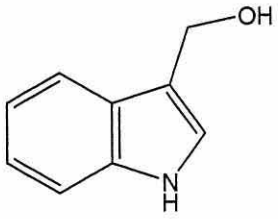
Melatonin **(44)** is a hormone that is secreted by the pineal gland within the brain between the two halves of the cerebrum. It is thought to control bodily rhythm by variation in the amount released to the brain controlled by nerves in the retina.[133, 134] Light inhibits the secretion of melatonin which is greatest during the night, so as a result investigations are being conducted as to whether melatonin can prevent jet lag.[135, 136]



44

1.3.2.4 Indole-3-Carbinol

Indole-3-carbinol **(45)** is a natural compound found in the *Brassica* genus of cruciferous vegetables that includes cabbage, broccoli, cauliflower and Brussel sprouts. It has been shown to be an anticancer agent, stomach acid promoting the formation of a complex with carcinogens in the digestive tract and thus eliminating DNA damage to cell nuclei.[137, 138]

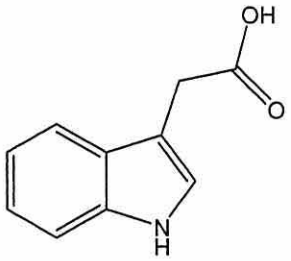


45

It is also thought that **45** is an important compound for preventing breast cancer as it converts dangerous forms of oestrogen to safer forms and inhibits oestrogen-induced growth of cancer cells.[139] Body builders take commercially produced indole-3-carbinol supplements to prevent the build up of oestrogen in their bodies.

1.3.2.5 Indole-3-acetic acid (IAA)

Indole-3-acetic **(46)** acid is one of the most important plant hormones despite only occurring in minute concentrations. It stimulates the division and elongation of cells as well as the production of the hormone ethylene. It has been found that variations of indole-3-acetic acid levels of cherry seed and pulp correspond to changes in the diameter of the cherry. IAA is known to promote root formation as well as fruit development.[140]



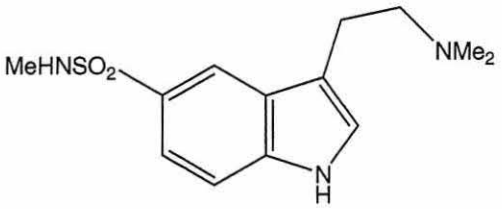
46

Despite its role in fruit ripening, at high concentrations IAA becomes harmful to humans and plants alike. Comparatively small amounts have drastic effects, with leaves wilting rapidly and dropping off, whilst large amounts are fatal. For this reason different ratios of the synthetic mimics of IAA, 2,4-dichlorophenoxy acids (2,4-D) and 2,4,5-trichlorophenoxy acid (2,4,5-T) were used as defoliating agents during the Vietnam war. These were more commonly termed as Agents Purple, Green, Pink, White, Blue and Orange, named according to the colour coding on the 55 gallon drums they were stored in.[141]

1.3.3 Synthetic Indoles

1.3.3.1 Sumatriptan

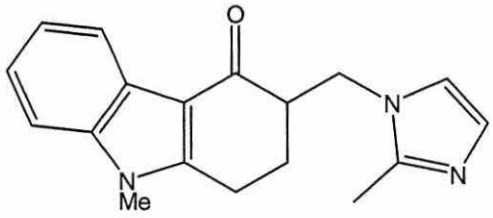
Sumatriptan **(47)** is a synthetic drug used as a pain killer to combat migraines as it is a serotonin receptor. It is produced commercially under the name *Imigran* by Glaxo.[142]



47

1.3.3.2 Ondansetron

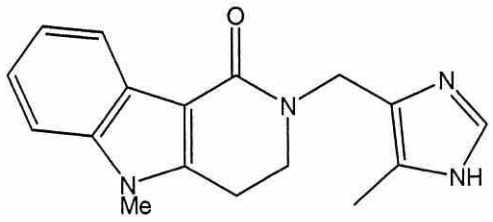
Ondansetron **(48)** is a serotonin blocker that is administered to combat nausea and vomiting during chemotherapy and radiotherapy treatment. It is also widely used in hospitals as an anti-emetic when a general anaesthetic is administered, either as a precaution beforehand or to stop nausea and vomiting afterwards. It has regular side effects of constipation and headaches as well as some wide ranging infrequently reported effects. Ondansetron is commercially produced as *Zofran* by Glaxo.[143]



48

1.3.3.3 Alosetron

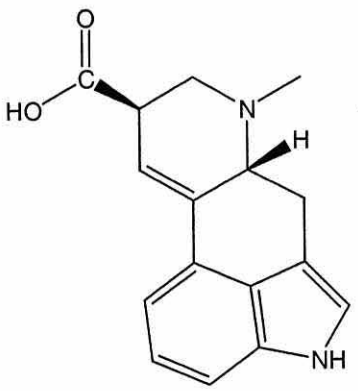
Alosetron **(49)** is a serotonin blocker that administered as a treatment for irritable bowel syndrome.[144, 145]



49

1.3.3.4 Lysergic acid and its derivatives

Lysergic acid **(50)** is a compound found in a parasitic disease that grows on rye and other species of grain called ergot. The infected kernels of the crop develop light brown curved pegs that grow within the husk instead of the grain. It was ergot that was the cause of mass poisonings reported from the Middle Ages onwards due to bread made from flour containing it. Ergotism manifests itself as a convulsive or gangrenous form, the latter termed as Saint Anthony's Fire, with Saint Anthony deemed the patron saint of ergotism sufferers. Present day understanding and improved farming methods mean that there has not been a serious outbreak of ergotism for almost a century.[146]



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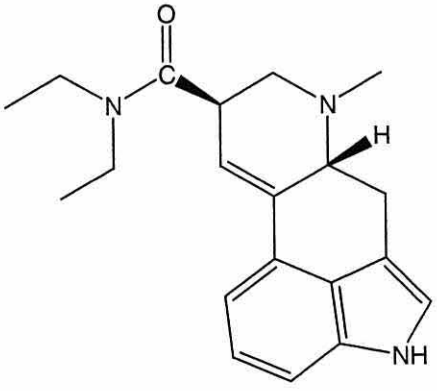


51

Ergot has been used in medicine, first being recorded in the 16th century as a drug used to induce childbirth, although it was not until the early 19th century that this received wide use. Adverse side effects of this process on children led to the use of the process being short lived.

In the 1930s, the chemically active compounds in ergot were isolated, the ergot alkaloids. The common nucleus of these alkaloids was identified and isolated by

Jacobs and Craig who named it lysergic acid **(50)**. A series of derivatives were made of lysergic acid and tested for medical properties. One of these derivatives was lysergic acid diethylamide (LSD) **(51)** but it was discarded for having no properties except a perceived state of insensibility induced in the experimental animals upon testing.

A few years later the pharmacological properties of LSD were investigated and it was found to have the now infamous hallucinogenic affect. It is unknown why this happens, but LSD has a hormone blocking effect, stimulates parts of the brain, causes pupils to dilate and body temperature and blood sugar levels to rise.

LSD has, since the 1960s, been a popular illicit drug due to its psychedelic effects, its non-addictiveness and being non-toxic. Some other hallucinogenic drugs contain a similar indole containing structure, the effects of which were immortalised by the Beatles in their song *Lucy in the Sky with Diamonds.*[147]

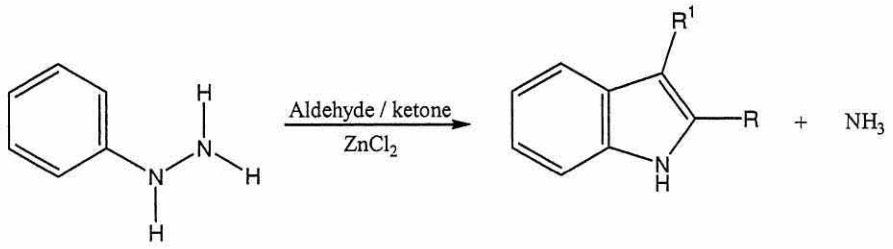
1.3.4 The synthesis of indoles

There are a vast range of indole producing reactions,[148] both traditional and recently developed, with synthesis via the mediation of many different metal catalysts. Two of these reaction, the Fischer and the Madelung indole synthesis will be described below.

1.3.4.1 The Fischer indole synthesis

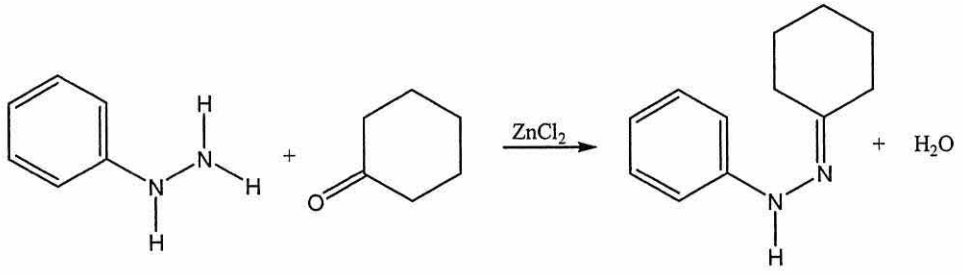
The most renowned of these reactions is the Fischer indole synthesis,[149] as shown in **Scheme 1.11**, which was devised in the late nineteenth century[150, 151] to produce indoles from the aryl hydrazones of aldehydes and ketones, but is still used today as a prominent industrial process.

The method has been adapted over the years from the conventional thermal conditions,[152, 153] to microwave irradiation under pressure,[154] the use of zeolites[155, 156] and solid phase synthesis.[157-159]



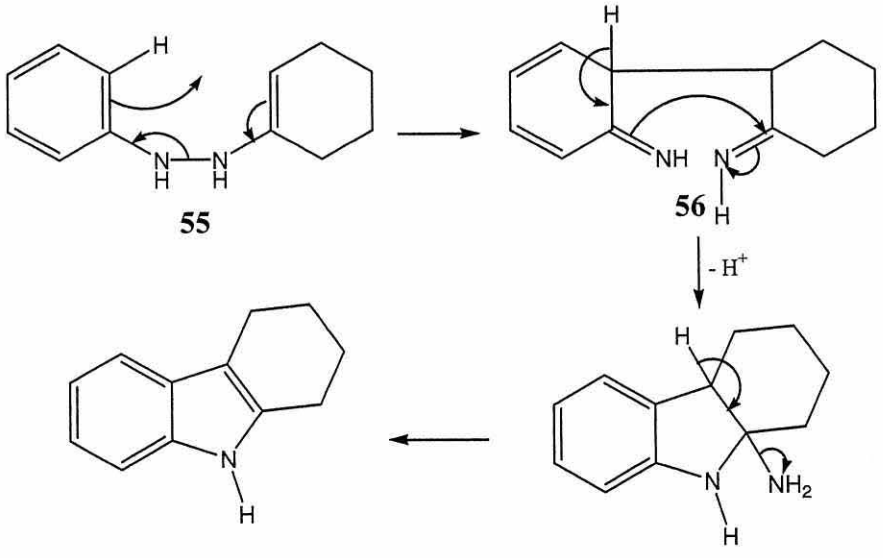
Scheme 1.11 The Fischer indole synthesis

The mechanism of the reaction begins with treatment of a phenyl hydrazine **(52)** with an aldehyde or ketone with a Lewis acid catalyst, such as $ZnCl_2$ to generate a hydrazone **(54)**, for the Fischer indole synthesis using **52** with cyclohexanone **(53)**, though an initial dehydration coupling reaction.



52 **53** **54**

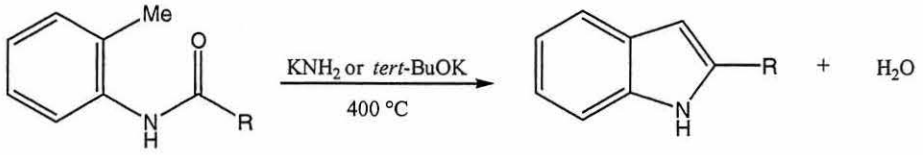
This product is tautomeric with the enamine **(55)**, which through attack of the aromatic ring gives the bis-imine **(56).**[160] Loss of the hydrogen cation leads to re-aromatisation of the benzene ring and the cyclisation reaction that completes the indole synthesis with a hydrogen transfer and loss of the amide ion.



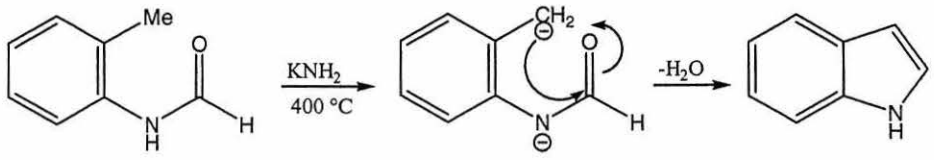
This reaction can be carried out for a range of functionalised aryl hydrazones to produce a wide range of indoles.

1.3.4.2 Madelung synthesis

The Madelung synthesis[161] is a method of producing indoles that was developed in the early twentieth century. The reaction involves the formation of a dianion of an N-acyl-2-alkylaniline by treatment of a strong base, such as potassium *tert*-butoxide or potassium amide, at temperatures up to 400 °C.

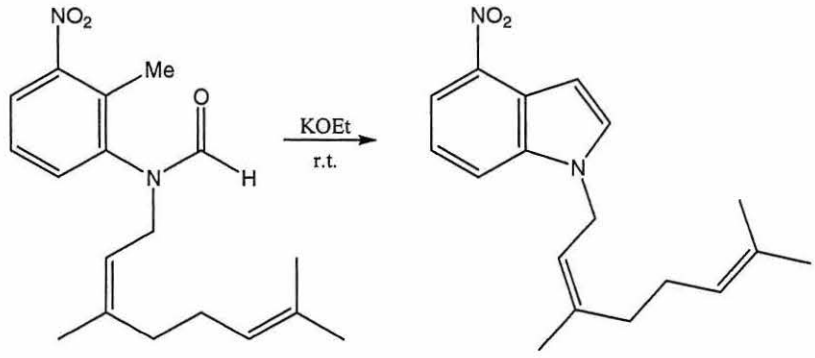


The standard Madelung reaction is the formation of the dianion of formanilide **(57)**, which through attack of the carbonyl group forms a bicyclic alcohol that through a dehydration reaction forms the sp^2 bond in indole **(58).**



57 **58**

There are modifications of the Madelung synthesis, such as the inclusion of a 3-nitro group on the aniline ring and the protection of the amide with an alkyl group, which allows the reaction to proceed at room temperature with potassium ethoxide.



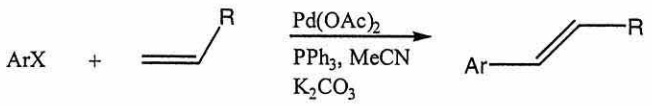
This is due to the activating property of the nitro group and because the replacement of the amide proton means the reaction does not require the formation of a dianion.[162]

1.3.4.3 Transition metal mediated indole formation

Apart from named indole forming reactions, such as those discussed above, it is possible to construct indoles via transition metal catalysed multi-step procedures. The most important step in this procedure is the formation of a new carbon - carbon bond between two different substrates before cyclisation of the product to a molecule containing the indole nucleus. There are various transition metal catalysed bond forming reactions that work because of the variable oxidation states of transition metal compounds, with reactions proceeding under a range of different conditions with different reactants. These reactions include the Stille reaction, which is the palladium catalysed coupling of organic halides or acetates with organostannanes[163] and the Suzuki reaction, which is the palladium catalysed coupling of organic halides with a alkyl and aryl organoboron derivatives.[164] The drawback of Stille coupling is the toxicity of organostannanes, whilst the Suzuki reaction's drawbacks are due to the availability of organoboron derivatives. Two of the wider ranging reactions carbon – carbon bond forming processes, the Heck[165] reaction and the Castro reaction, will be now be described in more detail.

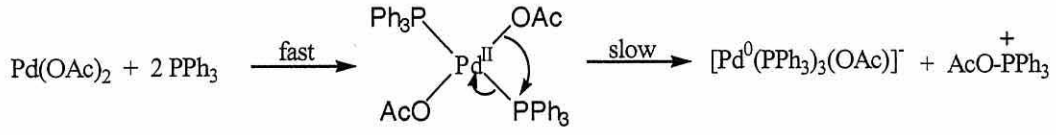
1.3.4.3.1 The Heck Reaction

The Heck reaction is a wide ranging process that will couple aryl or alkenyl halides with alkenes. The standard procedure for Heck arylation[166-171] involves heating an alkene with an aryl bromide, base, a tertiary phosphine [PPh_3 or $P(C_6H_4Me\text{-}o)_3$][172] and 3% palladium acetate in acetonitrile in a sealed tube for several days at 110 °C.



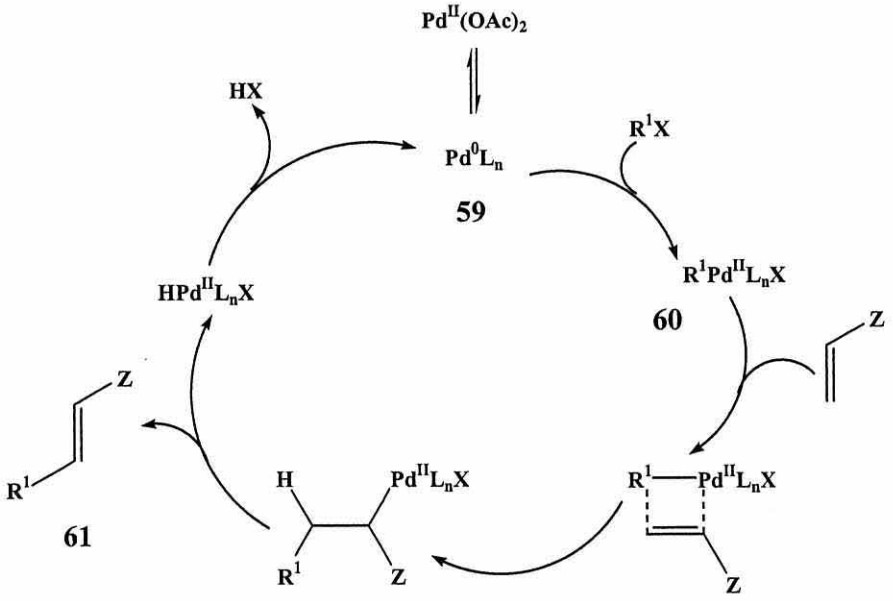
The accepted mechanism for this reaction involves the *in situ* generation of the active palladium catalyst with reduction of the oxidation state of the initial complex from Pd(II) to Pd(0). With a standard catalyst of $Pd(OAc)_2$, the oxidation state is variable through removal of labile acetate ligands by reducing agents such as triphenylphosphine to give a palladium (0) complex.[166] Cyclic voltammetry has

shown that an acetate ion coordinates to the Pd(0) centre to give an anionic species[173] that is in equilibrium with the less ligated but more reactive complex as shown in **Scheme 1.12**.[174]



Scheme 1.12 The proposed generation of the active palladium catalyst

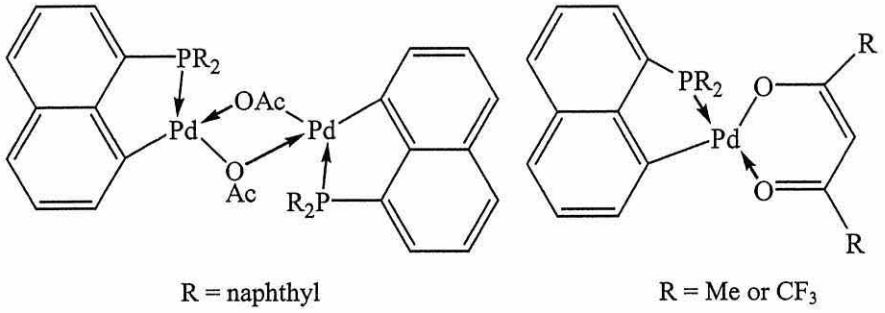
Upon generation of the active catalyst **(59)**, the aryl or alkyl halide (R^1X) then adds via oxidative addition to give the Pd (II) complex **(60)** as shown in **Scheme 1.13**.



Scheme 1.13 The catalytic cycle for the Heck reaction

An alkene then coordinates to the metal centre, without affecting the oxidation state, before undergoing a rearrangement to create a palladium - carbon bond and the important new carbon - carbon bond. β-Hydride elimination ejects the product alkene **(61)** from the complex; through reductive elimination with a base there is regeneration of the catalyst within the cycle.

It has been shown that large and bulky palladacycles, two examples of which are shown in **Figure 1.8**, give catalysts that are more thermally stable than simple palladium - phosphine complexes.[172, 175] This more stable catalyst reduces commonly formed by-products in coupling reactions which are formed by breakdown of the catalyst. Also the greater efficiency of palladacycle catalysts allows previously unviable coupling reactions with aryl and alkyl chlorides to proceed.



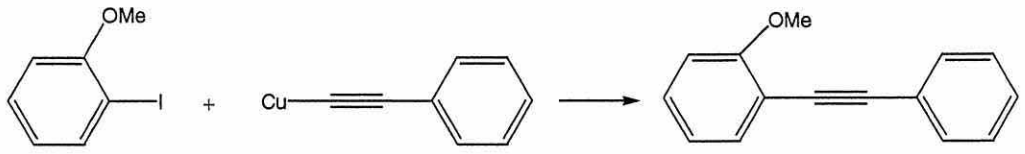
R = naphthyl R = Me or CF_3

Figure 1.8 Examples of palladacyles

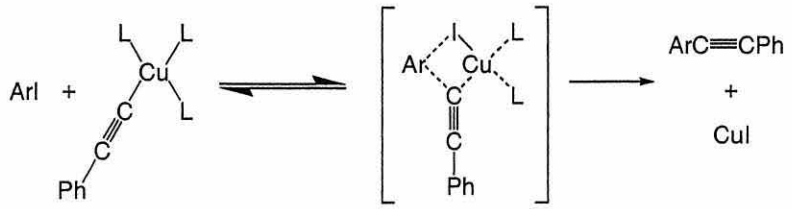
The mechanism proposed with these catalysts involves the variation in the oxidation state of between Pd (II) and Pd (IV), but there is evidence[176] that with one of these palladacycles in the Stille reaction, a Pd (0) complex is the active catalyst. However the same catalyst used in Heck reactions has no Pd (0) detected by NMR experiments and the reaction is thought to proceed through a Pd (II)-Pd (IV) change in the oxidation state of the metal centre or via ligand exchange reactions between Pd(II) intermediates.[175]

1.3.4.3.2 The Castro reaction

The Castro reaction is a copper mediated carbon - carbon bond forming process that was first used in 1963 when Castro and Stephens[177] prepared diarylacetylenes by refluxing aryl iodides and cuprous acetylides in pyridine.



The reaction is thought to involve a concerted mechanism that takes place through coordination to the copper centre as shown in **Scheme 1.14**.[178]

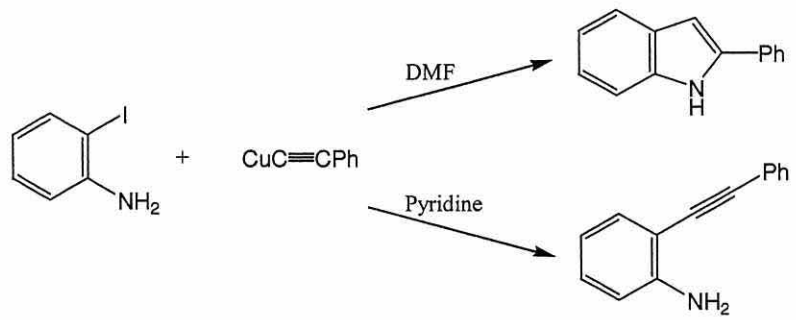


Scheme 1.14 The proposed mechanism for the reaction of the Castro reaction

Castro and Stephens also found that aryl iodides with an *ortho* nucleophilic substituent underwent a further cyclisation reaction to give the corresponding heterocycle in good yield.[178]

The effectiveness of the nucleophile, X, in promoting cyclisation was found to be in the order of $CO_2H > OH > NH_2$.[179] The reaction is thought to occur within the same copper complex as the coupling reaction, as the same reaction cannot be observed with 2-aminodiphenylacetylene upon exposure to cuprous iodide and phenyl acetylide in refluxing pyridine.[180]

The production of indoles via this method was found to be influenced by the solvent used.[179] Copper acetylides are only slightly soluble in DMF at room temperature and therefore the reaction remains heterogeneous and the only product obtained is the cyclised indole.



However, in warm pyridine acetylides are generally soluble and the same reaction gives the uncyclised product or a mixture of the two products.

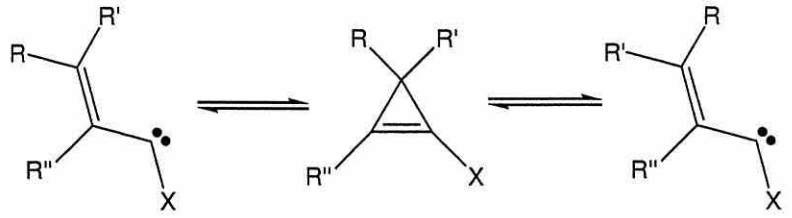
A problem with the Castro reaction is that copper acetylides, precipitated from solutions of copper iodide and terminal acetylenes,[177] are required and are hazardous to the extent that the UK Department of Transport has labelled them as an explosive that is forbidden to be transported through or flown over public thoroughfares.

2. Intra and Intermolecular Reactions of Cyclopropenes

2.1 Intermolecular Reactions

2.1.1 Introduction

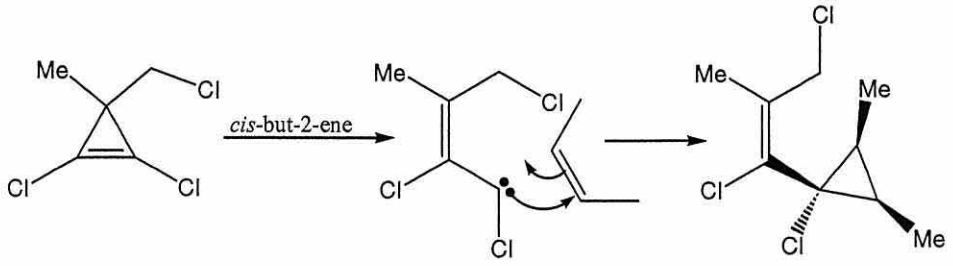
The range of interest in cyclopropene and its derivatives is due to the high ring strain that is involved. Cyclopropenes will typically rearrange to reactive vinyl carbenes at temperatures of 150 – 180 °C, as discussed in **Section 1.2**. This ring opening gives the possibility of different products being formed by a monorotation around the bond to C3.



Thus reactions of vinylcarbenes from cyclopropenes can lead to the trapping of both E and Z isomers for the carbene as shown above. This is known because the carbene can be trapped intramolecularly[109, 110, 181, 182] with appropriate substituents on the cyclopropene ring or intermolecularly[100-102, 183] with suitable reagents. It has been found that 3,3-dialkyl-1,2-dihalocyclopropenes ring open to vinyl carbenes at room temperature[103, 104, 184-186] so one example of this type of cyclopropene was studied in a series of intermolecular carbene trapping experiments.

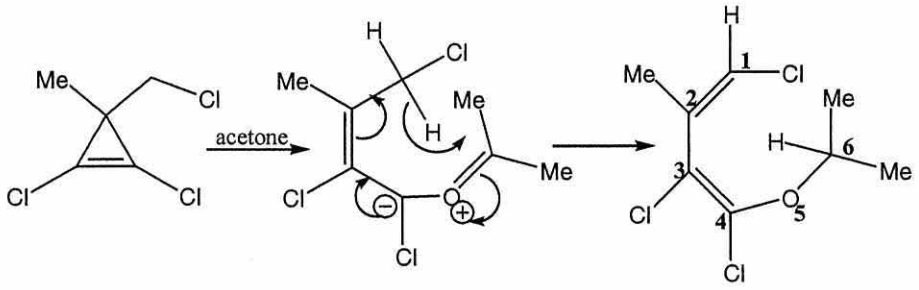
2.1.2 Aim

Previous work[13] has shown that the treatment of 3-chloromethyl-3-methyl-1,1,2,2-tetrachlorocyclopropane **(68)** with 1.3 molecular equivalents of methyl lithium gives the corresponding cyclopropene **(62)** through 1,2-dechlorination; this ring opens at 20 °C to give a vinylcarbene. There are many examples of this vinylcarbene being trapped by addition to a series of alkenes, such as *cis*-but-2-ene to give the resultant cyclopropanes.[99]



62 **63**

There is one example of trapping of the carbene **(63)** with a carbonyl group, as shown in **Scheme 2.1**, which shows the vinyl carbene being trapped by the addition of acetone. This reaction is very unusual because after the addition of acetone, a 1, 6-hydrogen shift occurs within the dipolar intermediate, leading to molecule **(64)**. This 1, 6-shift has not been reported from quenching of the carbene **(63)** with any other carbonyl containing reactant, nor has it been observed with other vinylcarbenes.



62 **64**

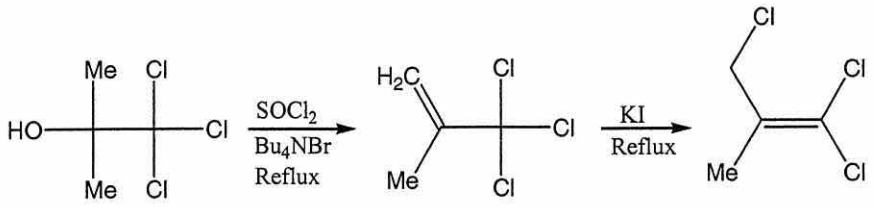
Scheme 2.1 The trapping of acetone and resulting hydrogen shift

This unusual process has only been discussed briefly in review articles, and no details are available.[93] The aim of this part of the work was therefore to investigate the reaction of **62** with other aldehydes and ketones to try and observe the resultant migration of a proton from atom 1 to atom 6 in the molecule.

2.1.3 The preparation of 3-chloromethyl-3-methyl-1,2-dichlorocyclopropene

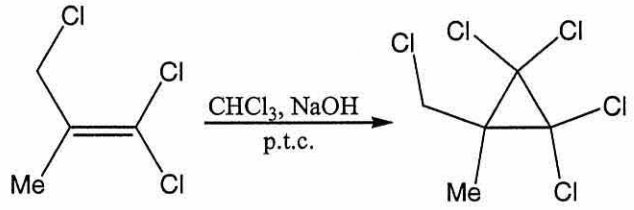
This required the trichlorocyclopropene **62**. In order to prepare this, the required precursor, pentachlorocyclopropane **(68)** was first made by the sequence shown. The initial step was the conversion of readily available 1,1,1-trichloro-2-methylpropan-2-ol **(65)** into the trichloroalkene **67** by reaction with potassium iodide and tetrabutylammonium bromide in refluxing thionyl chloride for 72 h, after which time distillation was required to remove excess thionyl chloride and give **67** in high yield.

The reaction first involved dehydration of the tertiary alcohol of **65** to give an alkene **(66)** which then rearranged by an allylic shift of chloride ion that was catalysed by iodide ion, to give the trichloroalkene **67**.



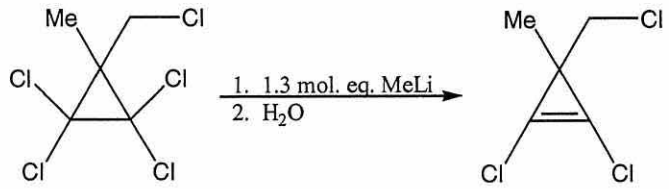
65 **66** **67**

The trichloroalkene **67** was converted into the pentachlorocyclopropane **68** by reaction with dichorocarbene generated from chloroform and base under phase transfer conditions as discussed in **Chapter 1.1.2.3.3.4**; this involved stirring for 5 days at room temperature. This reaction was problematic as, apart from the reaction time, it only gave a 27 % yield. Nonetheless, it could be carried out on a large scale.



67 **68**

The cyclopropane **68** was then effectively converted into the cyclopropene **62** through 1,2-dehalogenation in an almost quantitative yield by reaction with 1.3 molecular equivalents of methyl lithium in dry ether at 0 °C and quenching with water after overnight stirring at room temperature.



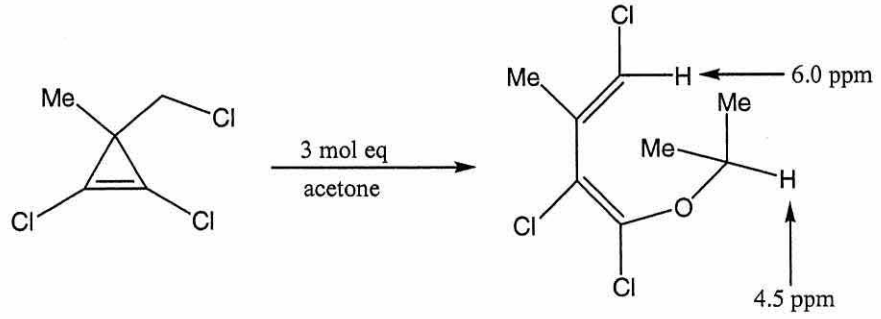
68 **62**

As the cyclopropene decomposes relatively slowly at room temperature in the absence of a carbene trap, it could successfully be stored in a freezer for a period of some days and its reactions studied.

2.1.3.1 The reactions of 3-chloromethyl-3-methyl-1,2-dichlorocyclopropene

2.1.3.1.1 The reaction with acetone

The cyclopropene **62** was reacted with an excess (3 mol. eq.) of acetone at room temperature to try and trap the ring opened carbene with the carbonyl group and produce 1,2,4-trichloro-3-methyl-1-(2-propoxy)-buta-1,3-diene **(64)** described above.[187, 188] The product was obtained in a 35 % yield after purification by column chromatography. Its structure was confirmed due to the shift of the proton signal in the ^{1}H NMR. This was from the methylene group at 3.9 ppm in the cyclopropene **62**, to a septet at 4.5 ppm (J = 6.2 Hz) for the *iso*-propoxy group of **64.** The methine hydrogen at 6.0 ppm corresponded to the olefinic proton in the product; this appeared as a narrow quartet due to allylic coupling to the methyl group. The coupling constant for this quartet of 1.5 Hz would imply that there is *trans*-allylic coupling within the molecule after the 1,6-migration has taken place, in contrast to a coupling constant of 2.0 Hz for the *cis*-coupling.[189] The methyl-groups derived from acetone appeared, as expected, as a six-hydrogen doublet (J = 10.4 Hz).



62 **64**

The stereochemistry of the alkene product **64** was only provisionally assigned on the basis of NMR as being *trans*. As the difference between *cis* and *trans* allylic coupling constants is small, it was hoped that this could be confirmed with the trapping of the diene in a Diels-Alder reaction.

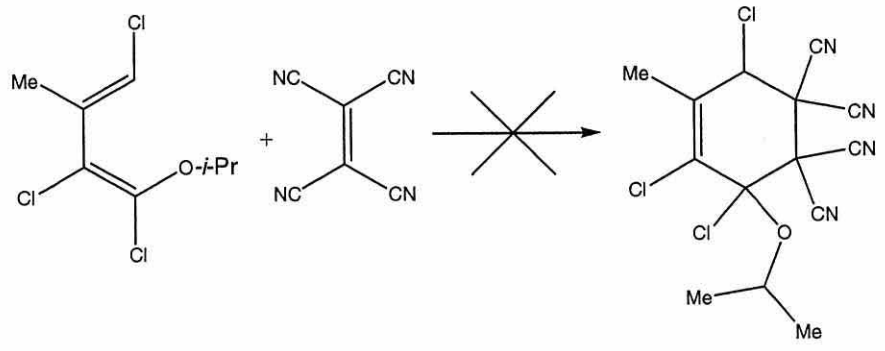
2.1.3.1.2 The reactions with pentan-2-one and benzaldehyde

Other examples of the reaction of the carbene **63**, from the cyclopropene **62**, with carbonyl groups were sought. These reactions could be monitored by observation of the signal for the olefinic hydrogen at 6.0 ppm in the ^{1}H NMR, as in the previous experiment (**Chapter 2.1.3.1.1**). As this proton would be at the opposite end of the molecule from that where the new carbon – oxygen bond forms, its signal at 6.0 ppm should not be altered greatly by reaction of different aldehydes or ketones.

Reactions were carried out by treating the cyclopropene **62** generated as above with an excess of pentan-2-one and benzaldehyde over an hour. Both reactions led to a complex mixture of components as shown in the crude ^{1}H NMR, with no product detected having a signal at δ 6.0.

2.1.3.1.3 A Diels-Alder reaction with TCNE

The stereochemistry of the alkene in the product **64**, of the acetone quenching reaction (**Chapter 2.1.3.1.1**) was only provisionally assigned on the basis of NMR data as being *trans*. It was hoped that this could be confirmed by reaction of diene **64** in a [4 + 2] Diels-Alder reaction with TCNE **(69)** to give a crystalline cyclohexene **(70)**. Analysis via single crystal X-ray diffraction would then prove the stereochemistry.



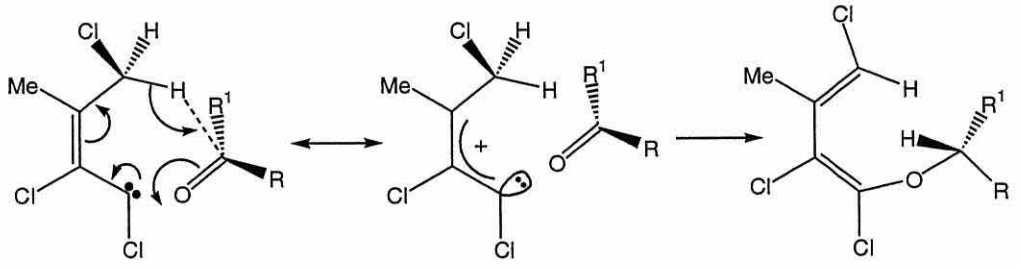
64 **69** **70**

The cyclopropene **62** was generated with 1.3 mol. eq. of methyl lithium as in previous reactions. An excess of acetone was added along with a quantity of TCNE **(69)** based on the predicted yield, based on the previous reaction, and the mixture was stirred overnight at room temperature. NMR analysis of the resultant crude solid

showed many compounds with no evidence that **70** had been produced. Flash chromatography of the crude solid gave a large number of fractions that ^{1}H NMR and tlc showed was due to decomposition of the crude product on the column. This reaction was not examined further.

2.1.4 Conclusions and future work

Only the simplest ketone, acetone, was found to react with the cyclopropene used. Possible reasons why molecules larger than acetone did not trap the carbene could be the size of the groups adjacent to the carbonyl group, R and R^1 as shown in **Scheme 2.2**. This is because the carbonyl group within the molecules must be aligned with the carbene and the alkyl hydrogen to affect the concerted 1, 6-proton shift.

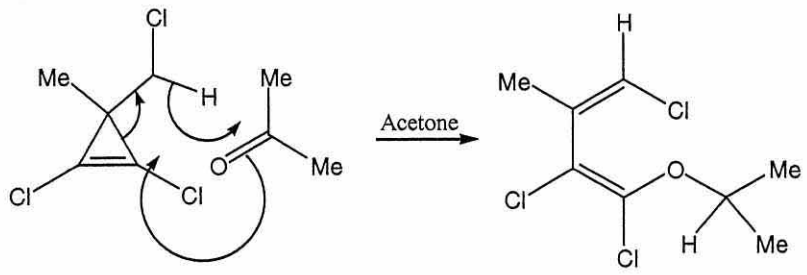


64

Scheme 2.2 The trapping of a carbonyl containing compound

It could therefore be postulated that this would be difficult for molecules larger than acetone because to the rigid structure of the vinyl carbene, due to the delocalised allylic system. The steric bulk of the long alkyl chains of pentan-2-one would therefore prevent alignment of a carbonyl group by not allowing the molecule to get close enough to the carbene and allow the irreversible concerted reaction to take place. In the case of benzaldehyde, either the one large group blocks the transition state, or the reactivity of benzaldehyde is different from a simple ketone and therefore the reaction is not seen.

It is interesting that although the reaction has been rationalised in terms of trapping of the vinylcarbene and then a 1,6-hydrogen shift, as shown earlier in **Scheme 2.2**, an interesting alternative could be a modified ene-reaction as shown in **Scheme 2.3**.

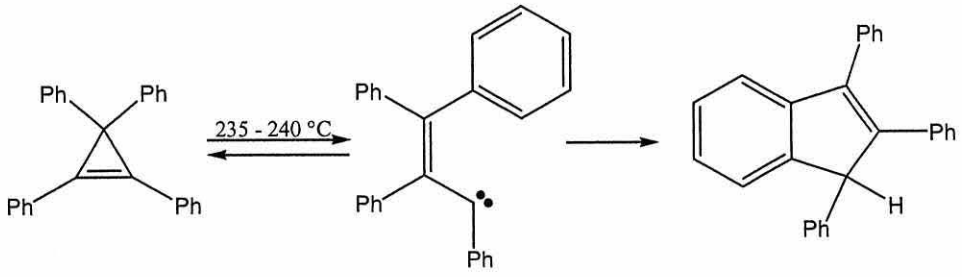


Scheme 2.3 An ene-reaction mechanism for the quenching with acetone

2.2 Intramolecular reactions

2.2.1 Introduction

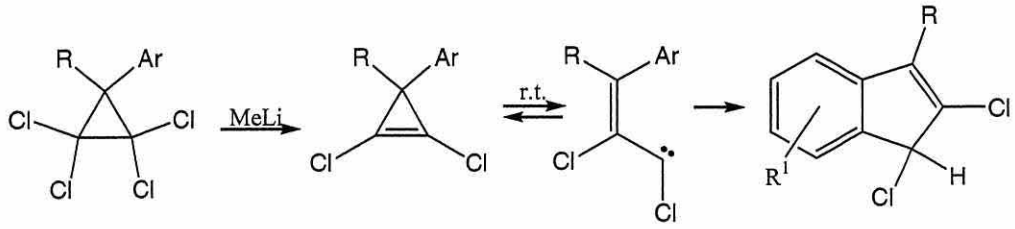
Previous work has shown that under forcing conditions of 200 – 240 °C, 3 - arylcyclopropenes will ring open to vinyl carbenes which react intramolecularly with the aryl group on the 3-position in an irreversible reaction to form a bicyclic system.[109, 110] An example of this is the ring opening of tetraphenylcyclopropene **(71)** at 235 – 240 °C which leads to the formation of triphenylindene **(72).**[109]



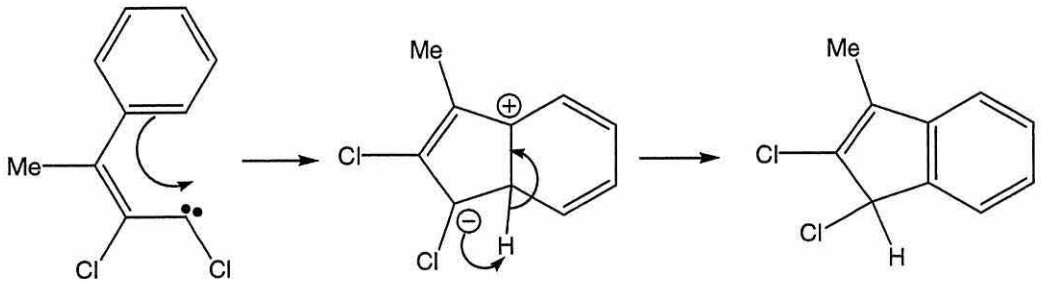
71 **72**

It has been found that this type of reaction generally only occurs for tetrasubstituted cyclopropenes,[188] but has been carried out for a variety of cyclopropenes with different aryl groups[109, 181, 182, 190, 191] and different substituents on the cyclopropene ring that include phenyl,[192] thio-ether,[192, 193] ester[194, 195] and amine groups.[196]

It has been reported briefly that indenes are also formed in the reaction of 3-aryl-1,1,2,2-tetrachlorocyclopropanes with methyl lithium at ambient temperature. This apparently occurs by an initial dechlorination to give the dichlorocyclopropene which rearranges to the corresponding indene.[197]

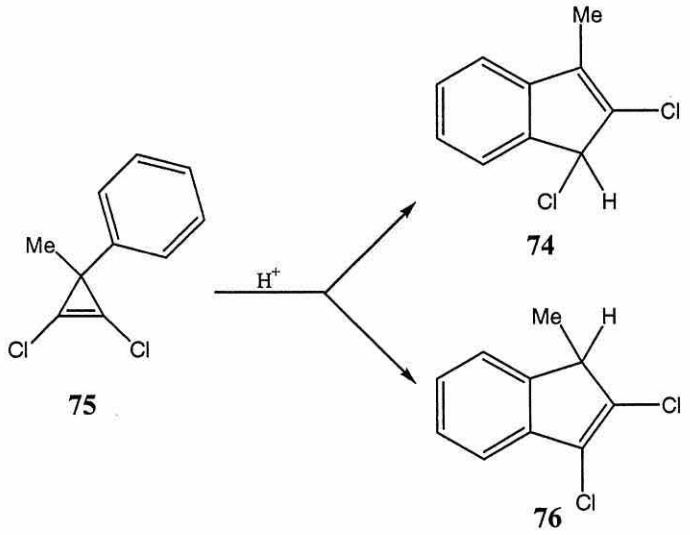


The mechanism for the ring closure has been rationalised as proceeding through a diradical intermediate or through a carbene which inserts into the aryl C – H bond. However an electrocyclic ring closure followed by a proton migration is thought to be more likely.[188]



73 **74**

The reaction with 3-phenyl-3-methyl-1,2-dichlorocyclopropene **(75)** to form indenes has been shown to give 3-methyl-1,2-dichloro-1,2-indene **(76)** as a minor product, together with 2-methyl-1,7-dichloro-1,2-indene **(74)**.[197]

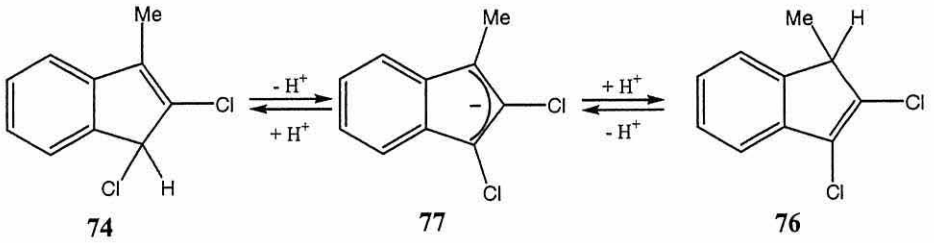


74

75

76

It was not clear whether **76** was formed directly in the reaction, by intramolecular rearrangement of **74**, or by removal of the acidic indene proton from **74** by an excess of methyl lithium to give the anion **(77)** as shown in **Scheme 2.4**. In any event, it was also possible that the anion could be generated deliberately with an appropriate excess of base and then selectively trapped.



74 **77** **76**

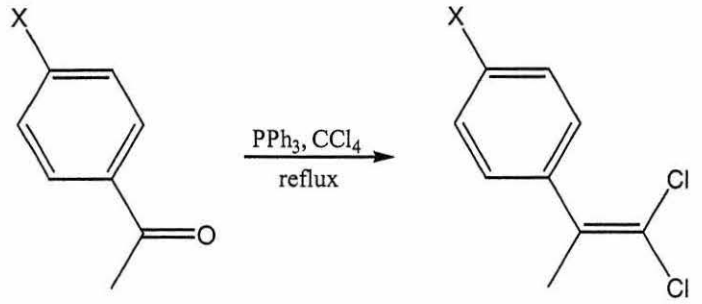
Scheme 2.4 A possible mechanism for the formation of the minor indene product

2.2.2 Aim

The aim of the work was to build on the observations of Al Dulayymi *et al.*,[197] described above, to investigate the facile synthesis of indenes by rearrangement of 3-aryl-1,2-dichlorocyclopropenes derived from 3-aryl-1,1,2,2-tetrachlorocyclopropanes and to investigate the differing ratios of indene isomers formed.

2.2.3.1 The formation of cyclopropane precursors

The first requirement was to make a range of 3-aryl-3-methyl-1,1,2,2-tetrachlorocyclopropanes. The first step was the conversion of *para*-substituted acetophenones (**78,** X = H, OMe, NO_2) into dichloroalkenes **(79)**, by reaction with triphenylphosphine in refluxing carbon tetrachloride for 24 hours through a Wittig reaction. The dichloroalkenes were obtained in a 43 - 92 % yield after a purification that involved thorough stirring with petrol to remove excess triphenylphosphine from the oil and then concentration and distillation of the oil to remove unreacted **78** and leave the alkene product, **79**, as the residue. The alkenes were then identified by observation of the methyl group in the ^{1}H NMR at 2.2 ppm. The yields obtained were 92 % for 1,1-dichloro-2-(4-methoxyphenyl)propene (**79**, X = OMe), 65 % for 1,1-dichloro-2-(4-nitrophenyl)propene (**79**, X = NO_2) whilst the lowest yield of 43 % was obtained for 1,1-dichloro-2-phenylpropene (**79**, X = H).

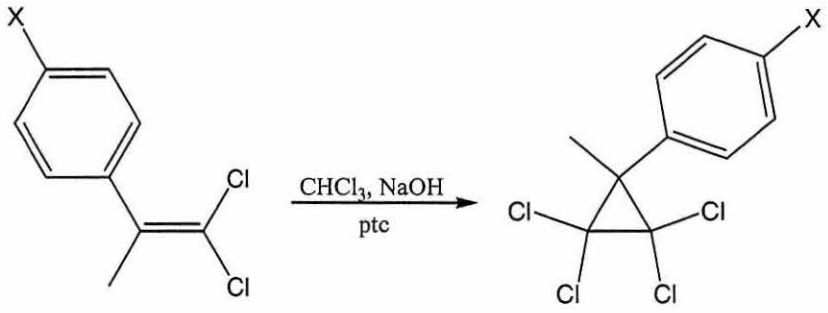


78 **79**

X = H, NO_2, OMe

2.2.3.2 The formation of cyclopropanes

The synthesis of 3-phenyl-3-methyl-1,1,2,2-tetrachlorocyclopropane (**80**, X = H), 3-(4-nitrophenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane (**80**, X = NO_2) and 3-(4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane (**80**, X = OMe) were carried out by Benedetti[197] by addition of dichlorocarbene to the alkene under phase transfer conditions, in the same way as described in **Chapter 2.1.3** for the synthesis of pentachlorocyclopropane **68** from the alkene **67**, with refluxing for 5 days. The cyclopropanes were obtained in yields of 42 %, 59 % and 16 %, respectively.



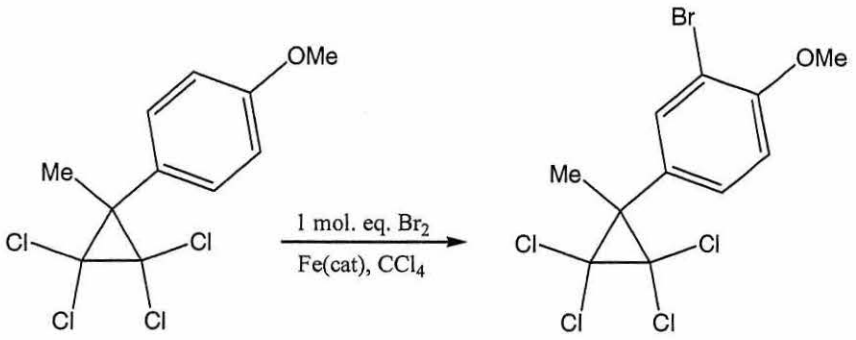
79 **80**

2.2.3.3 The alteration of the substituents on the phenyl ring

The substitution on the phenyl ring was manipulated to extend the range of reactions that could be carried out without the need to used the lengthy phase transfer catalyst approach.

First the number of substituted positions on the phenyl ring was increased by the bromination of 3-(4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(81)** with one molecular equivalent of bromine and using iron filings as catalyst in carbon

tetrachloride for 2 days at room temperature, after an initial heating period of half an hour. This gave the singly brominated 3-(3-bromo-4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(82)**.

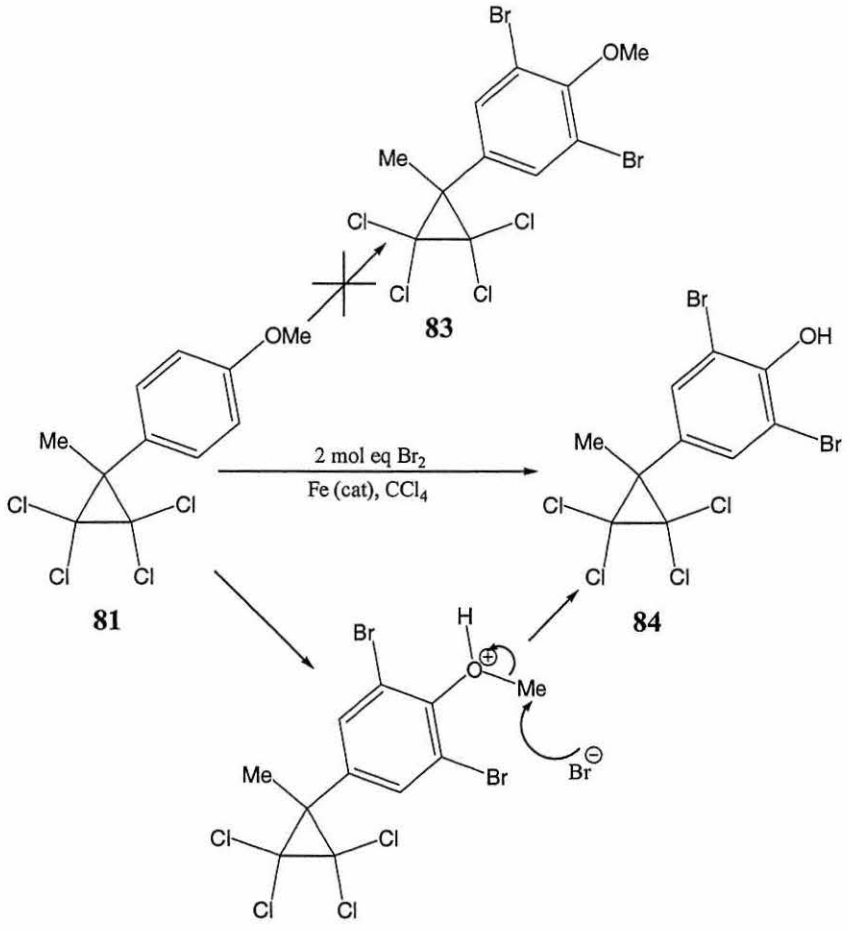


81 **82**

The reaction proceeded through the *in situ* generation of an iron bromide Lewis acid catalyst which mediated the Friedel Craft bromination reaction. Thus the cyclopropane **81** was singly brominated to give 3-(3-bromo-4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(82)** in a yield of 27 %. The product was identified from the signals for a trisubstituted phenyl group with doublets at 6.9 ppm (J = 8.6 Hz) and 7.6 ppm (J = 2.2 Hz) and a double doublet at 7.3 ppm (J = 2.4, 8.7 Hz) in the ^{1}H NMR spectrum with typical ortho / meta coupling values as would be expected for **82**. This is in contrast to the starting material **81**, where due to free rotation of the aryl group, the average conformation had a mirror plane dissecting the methoxy bond. This therefore led to the equivalence of NMR signals and therefore the starting material **81** showed two doublets at 6.9 and 7.3 ppm. The bromine in **82** was assigned as *ortho* to the methoxy-group on the basis of the strong *ortho / para* directing effect of the latter. This was confirmed by its subsequent reaction (see later).

The same reaction was carried out with cyclopropane **81** and two molecular equivalents of bromine to try to obtain the doubly brominated 3-(3,5-dibromo-4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(83)**, under the same conditions as above. The product obtained was shown to be dibrominated as NMR showed a single aromatic singlet at 7.5 ppm. However, it was not the expected product **(83)** as there was an unexpected broad singlet at 6.0 ppm, but no methoxy

group signal at 3.8 ppm in the ^{1}H NMR spectrum and an alcohol absorption in the IR at 3483 cm^{-1}. The product was therefore identified as 3-(3,5-dibromo-4-hydroxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(84)** and was obtained in a 58 % yield.

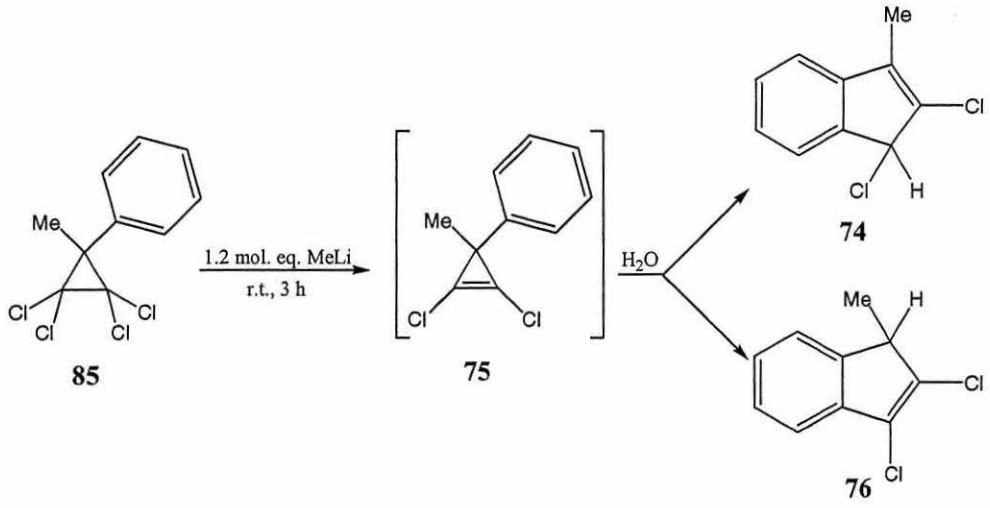


A reasonable approach to **84** would involve protonation of the methoxy-group and then S_N2 attack by a bromide ion generated in the reaction. It is thought that addition of a second electron withdrawing bromine to the phenyl ring weakened the methoxy bond and led to displacement of the methyl group by attack from a bromide anion to give a methyl bromide by-product. As **83** and mono-brominated product **82** were not recovered, it could be hypothesized that such a reaction is facile and takes place after double bromination of the phenyl ring.

2.2.3.4 The formation of indenes

The reaction of 1.2 molecular equivalents of methyl lithium with 3-methyl-3-phenyl-1,1,2,2-tetrachlorocyclopropane **(85)** in dry ether, gave the corresponding

dichlorocyclopropene **75**, that could not be isolated, but ring opened to the carbene at 20 °C and reacted intramolecularly with the phenyl ring to form an indene over a period of three hours at room temperature. The quenching of this reaction with water gave the two different indene isomers, 2-methyl-1,7-dichloro-1,2-indene **(74)** as the major product and 3-methyl-1,2-dichloro-1,2-indene **(76)** as the minor product in the ratio of 10 : 1, respectively, as calculated by ^{1}H NMR..



The major product **74**, could be obtained pure by column chromatography. In the ^{1}H NMR crude spectrum the uncoupled methyl group and the single non-aromatic proton are both present as singlets at 2.1 and 5.2 ppm respectively, as shown in **Figure 2.1**, whilst the ^{13}C NMR showed the expected ten signals. The minor product **76** ran very close together to the major product and so it was not isolated by chromatography, but preparative HPLC was not tried. The ratio of the two indenes was measured by analysis of ratio of the areas of the methyl signals in the crude ^{1}H NMR spectrum **(Figure 2.1)**. The minor product showed a doublet for the methyl group at 1.4 ppm **(B)** with the single proton adjacent to it split into a quartet at 3.6 ppm **(A)**, with coupling constants of 7.2 Hz.

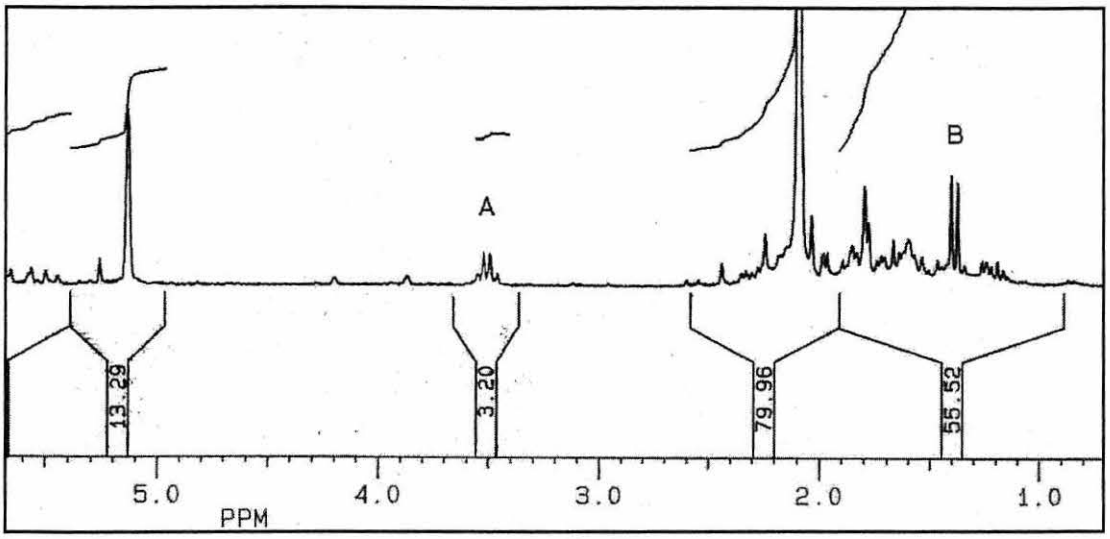
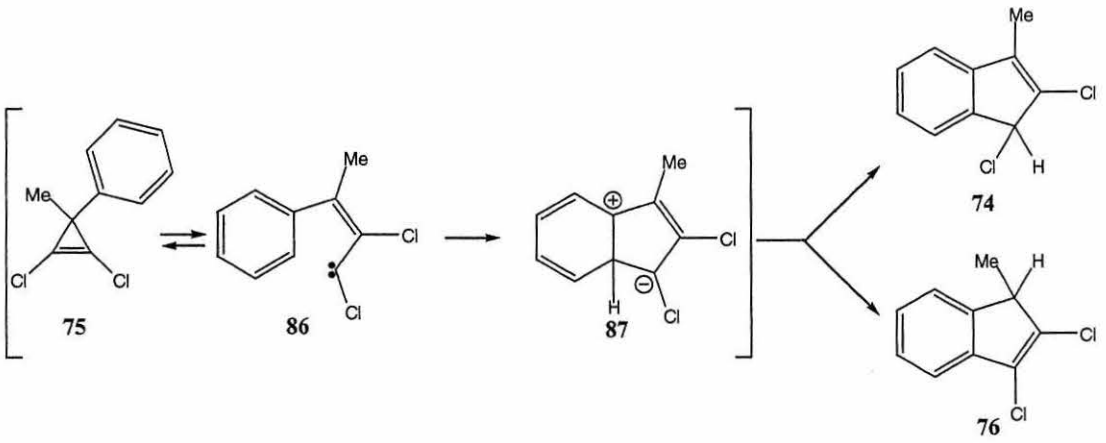


Figure 2.1 The ^{1}H NMR spectrum with characteristic signals of 74 and 76 after reaction of 85

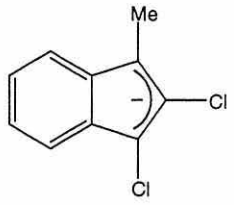
The formation of these isomers can be rationalised in terms of the ring opening of intermediate dichlorocyclopropene **75** to a vinyl carbene which traps intramolecularly with the phenyl group at the C3 position to form a bicyclic dipolar species **87**.



The formation of the major isomer could be explained by the electron withdrawing properties of the chlorine atom being greater than that of the methyl group and therefore having a build up of negative charge adjacent to the chlorine carbon and thus promoting the pathway to the formation of the major isomer 2-methyl-1,7-dichloro-1,2-indene **(74)** by a formal 1,5-hydrogen shift.

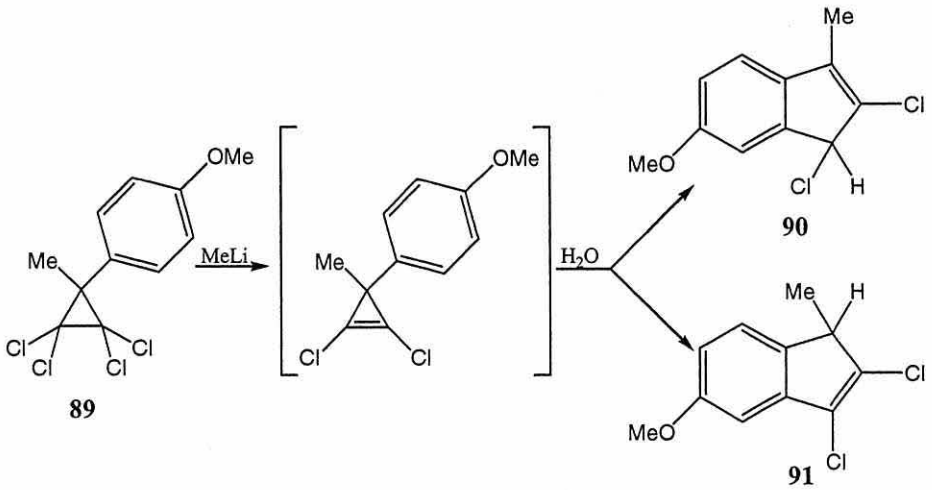
The minor isomer could arise from the major one directly by a 1,3-hydrogen shift, although this is disallowed in orbital symmetry terms. Alternatively, a slight excess

of base might catalyse the rearrangement via the indenyl anion **(88)** followed by reprotonation of the alternative site adjacent to the methyl group.



88

The reaction of 3-(4-nitrophenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane with methyl lithium did not give an indene product, but instead gave a complex mixture of products that ^{1}H NMR showed did not contain the starting material, as the aromatic signals of 3-(4-nitrophenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane at 7.7 and 8.4 ppm were not present. No indene product was present as there was no signal at 5.2 ppm that is characteristic of the major indene isomer. However reaction of 3-(4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(89)** with methyl lithium did react and give a mixture of indenes, this time in the ratio of 2.6 : 1.0. Only the major product 2-methyl-5-methoxy-1,7-dichloro-1,2-indene **(90)** was obtained pure, in this case by crystallisation. It showed singlets in the ^{1}H NMR at 2.1 ppm (3 H) 3.8 ppm (3 H) and 5.1 ppm (1 H) as well as aromatic signals at 6.7, 7.1 and 7.3 ppm. The minor product, 3-methyl-6-methoxy-1,2-dichloro-1,2-indene **(91)**, was observed with a quartet at 3.5 ppm and a doublet at 1.4 ppm in the crude NMR.

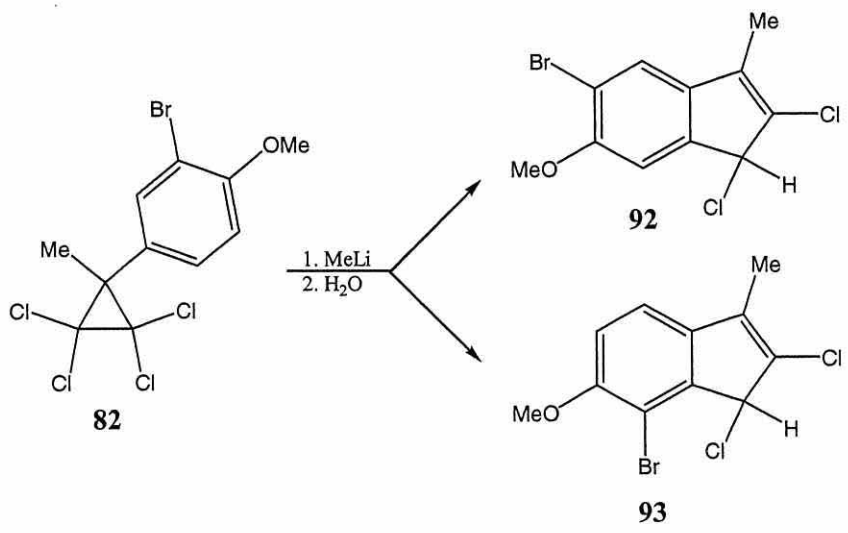


89 **90** **91**

3-(3-Bromo-4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(82)** was treated with 1.3 molecular equivalents of methyl lithium in dry ether for three hours at room temperature as in the previous experiments and the reaction was quenched with water. The products were identified by analysis of the crude ^{1}H NMR, but due to the similar chemical nature of **92** and **93**, despite repeated recrystallisations and column chromatography, the isomers were not successfully separated.

The reaction gave indene isomers of 2-methyl-1,7-dichloro-4-bromo-5-methoxy-1,2-indene **(92)** and 2-methyl-1,7-dichloro-6-bromo-5-methoxy-1,2-indene **(93)** in the ratio of 11 : 9, equivalent to, in structure, the major isomer formed from previous reactions. The products were identified with two singlet signals for the methyl group at 2.1 ppm and two singlet signals for the C3 proton at 5.1 ppm. The spectrum also showed two signals for the methoxy group at 3.9 ppm and an overlapping aromatic region from 6.8 to 7.4 ppm that contained two singlets corresponding to the protons in **92** at 7.1 and 7.4 ppm and two doublets 6.8 and 7.1 ppm for the aromatic protons in **93**. It was through comparison of these signals that the ratio of indenes **92** and **93** were measured.

In previous reactions, the 3-methyl-1,2-dichloro-1,2-indene has been obtained as a minor isomer, however in the reaction with **82** gave none of this isomer with no quartet signals at 3.6 ppm in the ^{1}H NMR.

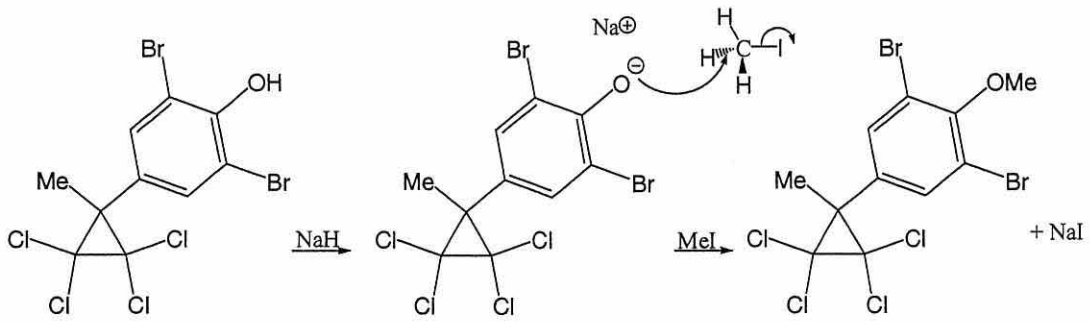


82 **92** **93**

It is due to the loss in the symmetry by bromination of the phenyl group of **82**, that makes the possibility of four different indenes being formed. This is because there are two inequivalent positions on the phenyl ring of **82** that the carbene can attack. This led to the production of almost an equal amount of the two isomers **92** and **93**. It had been hoped that this reaction would be more regioselective, leading to just one of the isomers. If this were the case, then this method could be used to make highly substituted indenes.

3-(3,5-Dibromo-4-hydroxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(84)** was reacted with three molecular equivalents of methyl lithium in dry ether under an argon atmosphere with stirring for three hours at room temperature. During this time the solution turned brown and after quenching with water, only a small amount of organic material was extracted from the solution. It was assumed that the methyl lithium had reacted with the hydroxyl group, thus giving a salt. The aqueous layer was therefore acidified to yield further organic product. NMR analysis of both oils showed that the starting material had reacted to form a number of compounds with no indene product present in the mixture, an observation made due to the lack of characteristic peaks, such as the singlet from the C3-proton at 5.1 ppm.

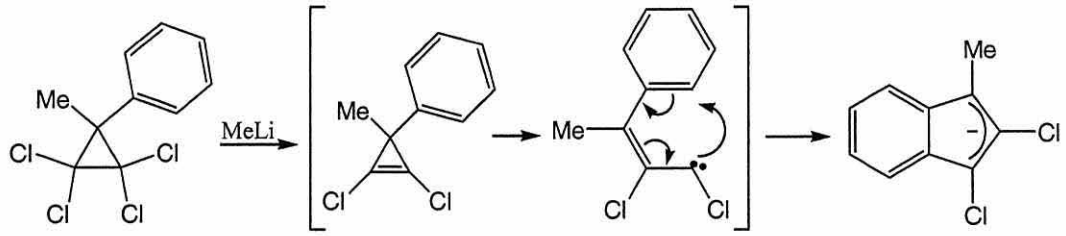
If the reaction were to be repeated, then methylation of the alcohol group should be carried out first. The synthesis of **83** could be completed by reaction of **84** under Williamson ether synthesis conditions.[198, 199] This involves treating the alcohol group with a base, such as sodium hydride or potassium *tert*-butoxide, to form an oxygen anion. The methylation would then be completed with an S_N2 reaction with methyl iodide to give the methylated product **83** and the relevant iodine salt.



84 **83**

2.2.3.5 Indene anion quenching experiments

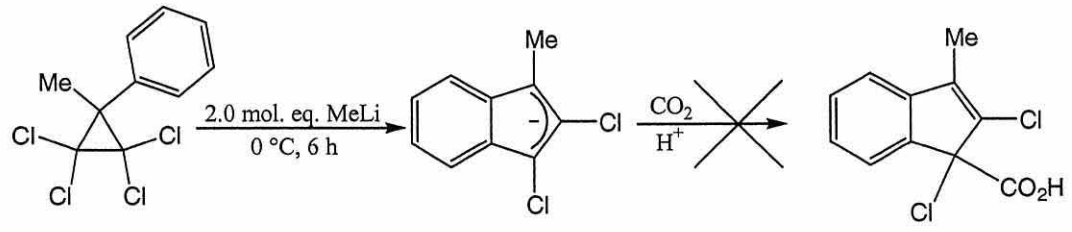
In the previous reactions 3-phenyl-3-methyl-1,1,2,2-tetrachlorocyclopropane **(85)** had been reacted with methyl lithium and then quenched with water. The aim was to see if the work up could be used to insert small molecules into the ring system after treatment with two mol. eq. of methyl lithium. This would then provide evidence that the quenching reaction proceeds through an indene anion **(88)** and lead to a method of producing a range of substituted indenes.



85 **75** **88**

2.2.3.5.1 The quenching of 3-methyl-3-phenyl-1,2-dichlorocyclopropene

The cyclopropene **75** was produced from treatment of 3-methyl-3-phenyl-1,1,2,2-tetrachlorocyclopropane **(85)** in dry ether with two molecular equivalents of methyl lithium and constant stirring at room temperature for six hours to produce the anion **88**. A vast excess of solid carbon dioxide, about one hundred molecular equivalents, was added to the reaction with cooling on a water bath and the reaction was left stirring until all of the carbon dioxide had sublimed in an attempt to form the indene acid **89** in solution.



64 **88** **89**

The reaction mixture was washed with sodium bicarbonate solution, until the aqueous layer was neutral to pH paper, to make the salt of the acid **89** and transfer it to the aqueous layer. The aqueous phase was removed and acidified with HCl and

extracted with ether. The majority of organic material was recovered from the first organic layer, indicating that an acid had not been produced by the reaction.

2.2.4 Conclusions

It has been shown that a range of 1,2-dichloro-3-aryl-3-methyl-cyclopropenes can be used as a route to the synthesis of indenes. Substitution of the phenyl ring was found to affect the ratio of isomers produced, with further examples needed of this reaction to understand why the substitution directs the formation of different isomers with the minor 3-methyl-1,2-dichloro-1,2-indene isomer produced in many cases, but not isolated. Removing the symmetry from the aromatic ring was found to synthesise different indene isomers with no selectivity between them. The attempted quenching of the indene anion was unsuccessful with reactants other than with water, so the mechanism for indene formation occurring via an anion could not be proven with these results.

In conclusion, the reactions to form indenes were carried out successfully in many cases to show that this was an effective method for the synthesis of indenes. However, the real difficulty in these reactions lay in the synthesis of the tetrachlorocyclopropanes via lengthy five day phase transfer reactions that often gave poor yields. It is because of this reaction step that the reactions were not continued and the scope of work not extended.

3. Indole synthesis via the Heck reaction

3.1 Aim

The initial aim of this work was to synthesise a range of indoles with the palladium catalysed Heck reaction, with a secondary aim of using solid state chemistry to produce clean products in high yields.

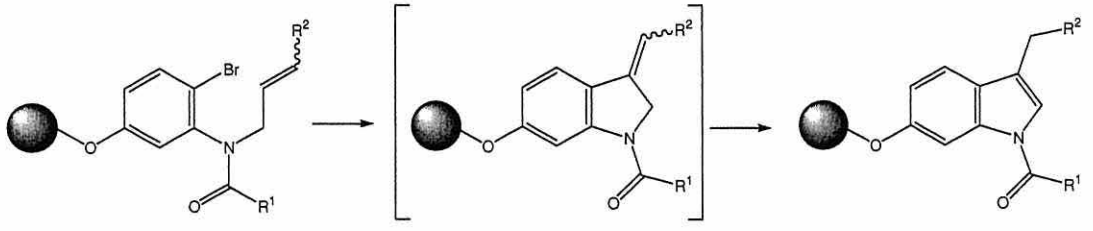
3.2 Introduction

Since the nineties, solid phase synthesis has become increasingly important in the production of catalogues of small molecules. The advantages of resin chemistry include the quicker processing of multi-step reactions due to the avoidance of time-consuming intermediate purification, to yield products of high purity when cleaved from the resin, which is then reusable.

A great effort to increase the variety of chemical reactions involved with solid phase chemistry is currently being undertaken, commonly with the adaptation of established solution phase reactions.

One of the cornerstones in organic chemistry is the formation of a new carbon - carbon bond. These reactions have been the subject of greatly detailed reviews over the past century using solution phase chemistry whilst similar coupling reactions for the solid phase have been described by Andres *et al.*[200] and Franzen, who covered palladium catalysed Heck reactions on resin substrates.[201]

The Heck reaction, covered in **Chapter 1.3.4.3.1**, has been utilised by Yun and Mohan in their solid state synthesis of indoles from resin bound *N*-acyl-*N*-allyl-*ortho*-bromoanilines **(94)**. The reaction proceeds through an intramolecular Heck reaction, with a 5-exo-trig transition state, that undergoes double bond migration to yield the stable aromatic indole **95** where R^1 = H, Me, Ph and R^2 = H, alkyl, Ph.[202]



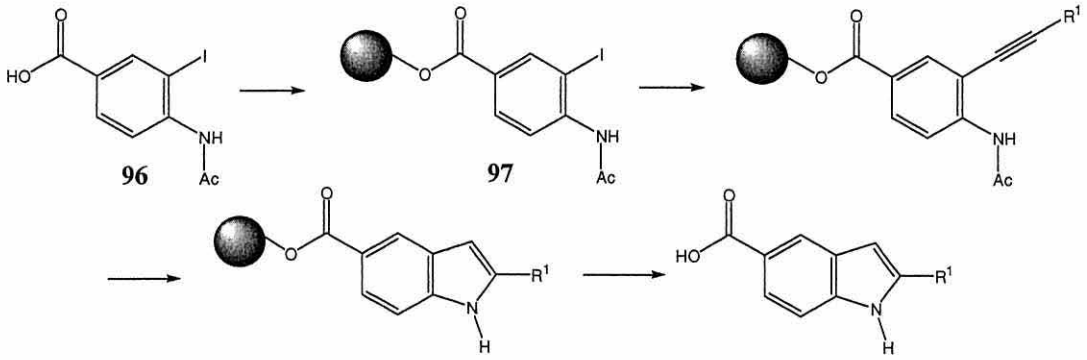
94 **95**

Similar methodologies were utilised by Fancelli *et al.*, who used resin bound *ortho*-hydroxy aryl iodides to produce 2-substituted benzofuran carboxylic acids.[203]

3.3 Discussion

3.3.1 Solid phase synthesis

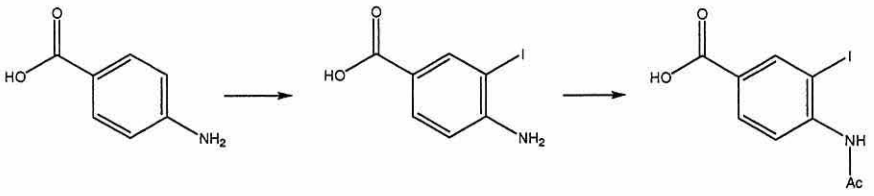
To begin this work, it was attempted to emulate the work of Fagnola *et al.* who developed a resin bound indole synthesis from iodoaniline derivatives, through the coupling of a terminal alkyne, cyclisation to the indole and then cleavage of the product.[204] The scheme of the reaction is shown in **Scheme 3.1**.



Scheme 3.1

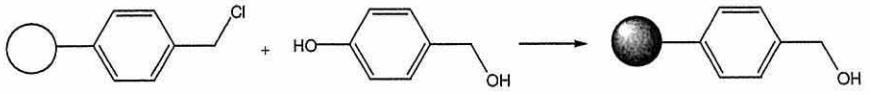
The first step was the synthesis of the substrate to bind to the resin, iodinated 4-acetamidobenzoic acid **(96)** from *p*-aminobenzoic acid **(98)**. This conversion was attempted the selective iodination of **98** with benzyltrimethylammonium iododichloride (BTMA-ICl_2) in acetic acid at room temperature with overnight stirring giving **99**, but in a yield of only 20 %. BTMA-ICl_2 was synthesised from the careful addition of a solution of iodine monochloride to an aqueous solution of benzyltrimethylammonium chloride at room temperature. This gave yellow needles of the iodinating salt after 30 min, identified by elemental analysis and reference to the literature melting point.[205] The crude iodoaniline product **99** was then acylated with acetic anhydride in acetic acid over 24 h at room temperature to give compound **96** which was reproducibly obtained in a low yield. Due to the insolubility in all common deuterated solvents, the methyl ester was made from a small sample of crude **96** by treatment over 1 h with diazomethane in ether. The methylated product would then dissolve in $CDCl_3$ and was identified by its ^1H NMR spectrum. This

provided a perfect spectrum that showed the movement of the amino peak from 4.1 ppm in the starting material to 7.7 ppm in the product, the addition of the acyl singlet at 2.3 ppm and the change in the aromatic pattern from two tented doublets at 6.6 ppm and 7.2 ppm in the *para*-disubstituted **98** to a double doublet at 8.0 ppm (J = 1.8, 8.9 Hz), a doublet at 8.4 ppm (J = 8.5 Hz) and a doublet with a coupling constant of 1.8 Hz at 8.5 ppm for the trisubstituted **96**.



98 **99** **96**

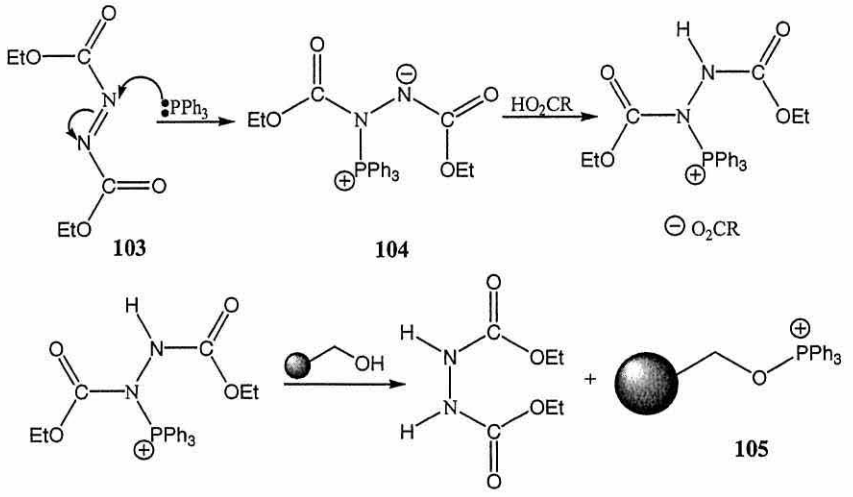
In order to obtain the appropriate resin to couple the acid **96** to, it was necessary to convert the relative cheap Merrifield resin[206] **(100)** into Wang resin[207] **(98)**.



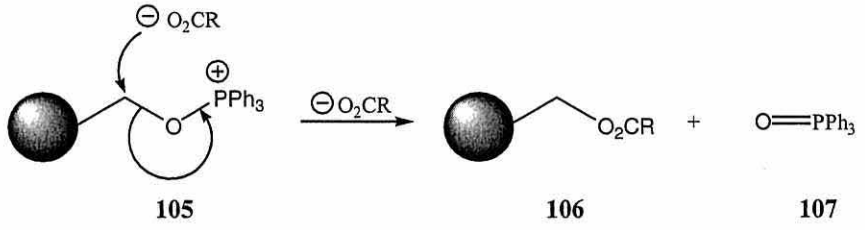
100 **101** **102**

The overnight reaction of **100,** depicted as a chlorotolyl group attached to a polymer bead, with 4-hydroxymethylphenol **(101)** and sodium methoxide at 80 °C, led to the formation of a new carbon-oxygen bond and the elimination of NaCl and methanol. The initial reaction was unsuccessful due to the vigorous stirring of the resin, which caused the polymeric beads to break down. Subsequent reactions were successfully carried out with gentle agitation of the resin to give **102**. The integrity of the resin after the reaction was checked by examination under a microscope, upon which the polymeric beads were visible and appeared undamaged. The fact that the reaction had worked was checked by IR (KBr disc) which showed a large hydroxyl group absorption at 3414 cm^{-1} for the Wang resin that was not previously present in Merrifield resin. The Wang resin product **102** is shown only as the extremity attached to the polymer bead with only the chlorine anion of **100** having been displaced by the reaction.

The coupling of the acid **96** to the resin **102** was carried out under Mitsunobu conditions with DEAD **(103)** and triphenyphosphine that was added with cooling in an ice bath, followed by stirring for 4 h at room temperature. The reaction converted the hydroxyl group of the resin into a potent leaving group through formation of a betaine intermediate **(104)** that deprotonated the acid **96** and bound phosphorus to the alcohol of the resin as a phosphorane **(105)**.



Attack of the nucleophilic acid anion formed the new bond of the product **(106)** by the displacement of the stable triphenyphosphine oxide **(107)**.



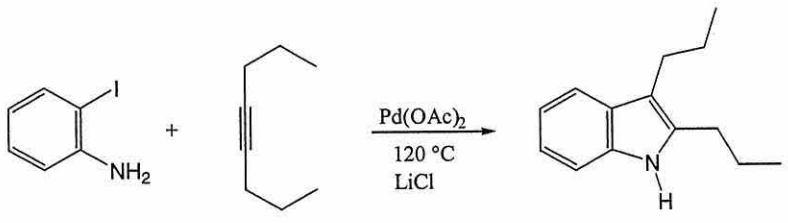
One of the major problems of solid state chemistry is the inability simply to quantitatively view to what extent a reaction has occurred. It is possible to cleave part of the resin and submit the compound for the usual analyses, but this causes the ultimate depletion of the yield of the reaction. In the present case, IR analysis of the resin showed the loss of the hydroxyl absorption and now displayed a carbonyl absorption at 1719 cm^{-1}, whilst elemental analysis showed that the resin contained a nitrogen content of 2.5 % despite Merrifield resin itself having no nitrogen content. This result agrees (within the established machine error of +/- 0.3 %) with the

calculated value for the coupling of 200 mg of compound **96** with 210 mg of Merrifield resin. The nitrogen content of **96** can be calculated as 9.2 mg, thus making the theoretical nitrogen content of the resin 2.24 % for the complete loading. From this analysis that the reaction was considered to have worked.

The coupling of the terminal phenyl acetylene to the resin **97** via a palladium catalysed cycle should have led to the synthesis of 2-phenyl-1H-indole-5-carboxylic acid bound to the resin, as shown previously in **Scheme 3.1**. This was carried out at 90 °C with gentle stirring for 18 h in dioxane with a dichlorobis(triphenylphosphine) palladium(II) catalyst. The reaction product was then analysed after cleavage of 400 mg of the resin with a TFA solution in DCM, a conventional cleaving agent, to give only 23 mg of an oil. Analysis of the NMR spectrum of this oil showed a complex mixture of signals and the reaction was considered not to have worked. A great deal of time was spent repeating Fagnola's reaction,[204] with few positive results. Coupled to the expense of using even the most basic resin, this led to a more conventional indole synthesis being sought.

3.3.2 Solution phase synthesis

For what would be deemed a more conventional Heck reaction it was attempted to couple iodoaniline **(108)** with oct-4-yne **(109)**, which, because of the sp nature of the substrate would be assumed to react into the 2,3-substituted, di-*n*-propyl indole **(110)** in one step.



108 **109** **110**

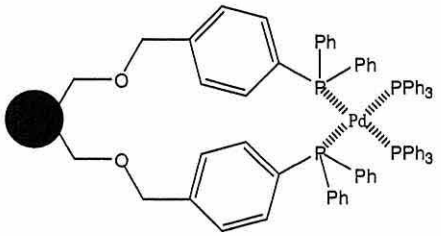
DMF (200 ml) was degassed in a 500 ml three necked flask by bubbling nitrogen gas through the solvent for half an hour. This was due to the instability of palladium catalysts towards oxygen. Three molecular equivalents of **109** were used based on the number of moles of **108** and lithium chloride was added to help stabilise the

palladium (0) complex during the catalytic cycle. The final step was to add 5 % of palladium acetate and the reaction was maintained under stirring at 120 °C with a reflux condenser under a nitrogen atmosphere. After a few days, it became apparent that the catalyst had broken down due to the black palladium metal that had precipitated onto the surface of the flask. The reaction was therefore stopped and the conditions re-examined.

Having tried the reaction under nitrogen, it was repeated under argon. The advantage of this is that as argon is a dense gas, so the air was expelled from the reaction vessel with a greater confidence and it was no longer necessary for the gas having to be blown through the reaction under pressure.

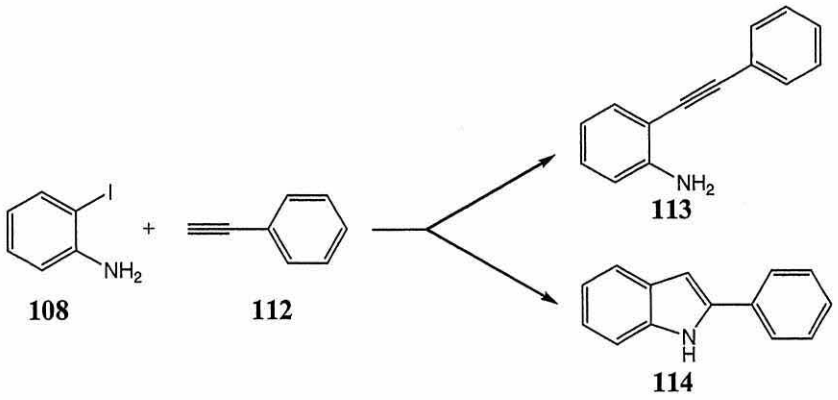
Thus with a number of possible problems eliminated with the change of inert atmosphere, the reaction was repeated with the same reaction conditions employed and monitored by GC analysis. After 40 days this showed that the oct-4-yne had been fully consumed but not iodoaniline. Therefore a further half an equivalent of oct-4-yne was added and the reaction was run for a further four days. After this time a thick brown oil was extracted from the DMF and through treatment with activated charcoal and careful columning, an oil was obtained from a mixture of products which was duly identified as 2,3-di-*n*-propyl indole. This showed an absorption for the N-H bond in the IR spectrum at 3409 cm^{-1}, and two propyl groups in the ^{1}H NMR as three multiplets between 1.1 ppm and 2.8 ppm, derived from the overlap of similar signals of the two propyl groups at the 2 and 3-position of the indole, together with aromatic signals from 7.2 ppm to 7.6 ppm. However, the reaction that took over a month gave a product in only a 2.5 % yield.

In terms of resin chemistry, when reacting two substrates together it is possible to have either attached to the resin. Another possibility was therefore to use a resin bound catalyst. The advantage of having a resin bound catalyst is that it has a greater stability, as described in **Chapter 1.3.4.3.1**, and is easily recoverable at the end of the reaction by filtration. Due to these factors, the catalyst should therefore be reusable. The catalyst **111** is one of a range developed by Menai Organics that is effectively a resin bound tetra-(triphenylphosphine) palladium (II) catalyst.



111

Iodoaniline **(108)** was reacted with one molecular equivalent of the terminal alkyne, phenyl acetylene **(112)** with 5 % of the resin bound palladium catalyst **111,** under the same reaction conditions as previously. This reaction therefore could have given either the *ortho*-coupling of the alkyne **112** to aniline to give 2-phenylethynyl aniline **(113)** or the cyclisation of this alkyne to give 2-phenyl indole **(114)**. After two days at 90 °C, the reaction was deemed to be complete from GC analysis and a solid was extracted. This gave a positive result upon addition of a few drops of Kovacs reagent (dimethylaminobenzaldehyde), a test which turns red in the presence of an indole with an unsubstituted 3-position (see **Appendix 3**). The crude sample was columned to give separate products; the major product was identified as being the intermediate 2-(phenylethynyl)-aniline **(113)**, the minor product being 2-phenylindole **(114)**, in yields of 45 % and 6 % respectively.



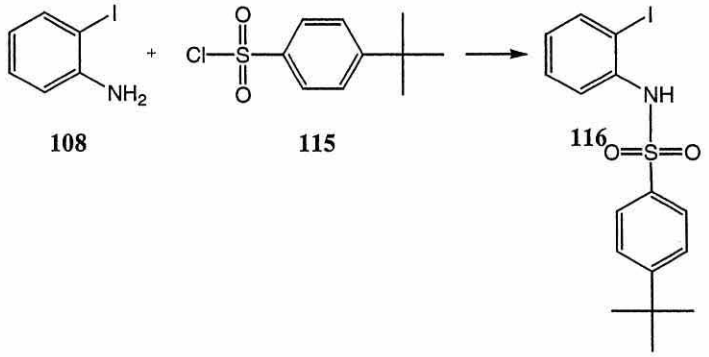
108 **112** **113** **114**

This same reaction was repeated with the resin bound catalyst sample that had been recovered from the previous reaction and washed and dried. One of the great problems with resin chemistry, a problem that is magnified with use of small samples, is that some resin is lost every time it is weighed out, filtered or transferred from one vessel to another. This is due to the electrostatic properties of the resin that

sticks to surfaces to the extent that rinsing with solvent will not remove it and thus leads to a depletion in yield. It is important that the catalyst was recoverable and that it maintained its catalytic properties, in order to be value for money.

The reaction with the used resin **111** was run for two and a half days at 90 °C before an extra half equivalent of phenyl acetylene was added. The reaction was then run for a further day. The sample was columned and gave only the alkyne product **(113)** in a yield of 37 % with recovery of starting material **(108)**, 24 %. This therefore showed a depletion in the catalytic properties of the catalyst.

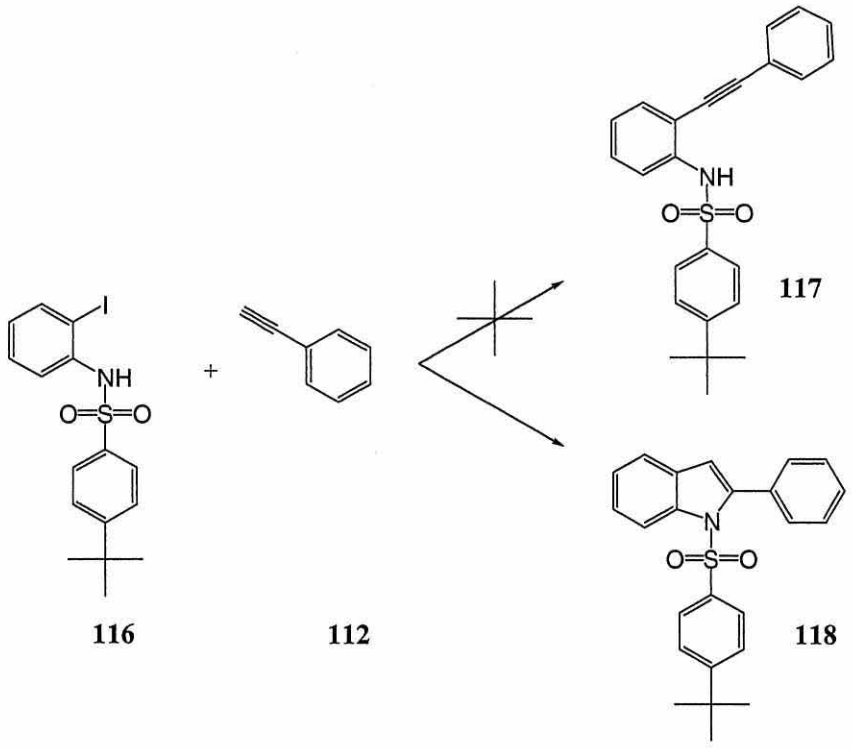
One of the many problems with the previous reaction is that the product was not obtained cleanly, as even after columning the samples could not be recrystallised suitably enough to obtain a clean crystalline product. Therefore it was decided to synthesise an indole that should reasonably be expected to exist with a crystalline structure. To do this, iodoaniline **(108)** was pseudo-tosylated with 4-*tert*-butylbenzenesulfonyl chloride **(115)** in pyridine over 2 h to give **116** as orange crystals in a reasonable yield. These were identified on the basis of the presence of the *tert*-butyl group as a large sharp singlet at 1.3 ppm in the ^{1}H NMR spectrum.



108 **115** **116**

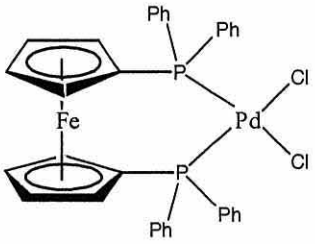
It was hoped that the reaction of **116** with phenyl acetylene would produce a compound with three benzene substituents. Due to the additional planar aromatic ring, compared to the synthesis of **113** and **114** in previous reactions, the perpendicular π-orbitals might overlap with adjacent molecules above and below the ring and so form stable crystal lattices.

The reaction was carried out with equal equivalents of *N-4-tert*-butylbenzenesulfonyl iodoaniline **(116)** and phenyl acetylene **(112)** under standard conditions with 5 % of a palladium acetate catalyst at 90 °C. It was monitored for 40 days, after which time a single product was isolated cleanly through column chromatography as a brown powder that was identified as *N*-4-*tert*-butylbenzenesulfonyl-2-phenyl indole **(118)** in a 37 % yield. The isolated indole gave the correct elemental analysis and in the ^{1}H NMR spectrum, the characteristic indole proton at C2 was observed at 6.6 ppm as well as the expected *tert*-butyl group at 1.2 ppm and the signals for the hydrogens of the benzene rings between 7.3 and 7.5 ppm. The ^{13}C spectrum showed the expected eighteen signals. It was noted that none of the intermediate coupled alkyne **(117)** was obtained; this was apparently due to the electron withdrawing tosyl group on the aniline nitrogen lowering the energy barrier for the cyclisation reaction.



The reaction was repeated with three molecular equivalents of phenyl acetylene under the same reaction conditions as above with 5 % palladium acetate, and monitored by TLC and HPLC. It was deemed to be complete after 22 days, when the product was shown to be the major compound present. Column chromatography and recrystallisation from petrol again gave *N*-4-*tert*-butylbenzene-sulfonyl-2-phenyl indole **(118)**, identified as pure by NMR and with a melting point comparable, albeit

slightly lower than the product of the previous reaction, with an improved yield of 65 %. Using an excess of phenyl acetylene therefore appeared to double the yield.
Palladium acetate is the classical catalyst for the Heck reaction. It is a fine black powder that therefore has a large surface area and so must be stored at all times under an inert atmosphere due to its reactivity in air. As it is used in catalytic amounts, and especially for small scale reactions, it is not known how much of the catalyst is still active and what portion of it has decomposed. Palladacycles such as **119** are reportedly more stable catalysts; as **119** exists as red crystalline needles, its surface area in the solid phase is greatly reduced, this perhaps consequently reduces decomposition of the catalyst.



119

The same reaction with *N*-4-*tert*-butylbenzenesulfonyl iodoaniline **(116)** and phenyl acetylene **(112)** was carried out with the palladacycle **119,** which is effectively dichlorobis(triphenylphosphine)palladium (II) bound to a ferrocene molecule. Equal equivalents of starting material were used with 5 % of the catalyst. The reaction was heated at 110 °C and after 7 days was shown by TLC to consist of a majority of the indole product, with the phenyl acetylene exhausted. The expected product, *N*-4-*tert*-butylbenzenesulfonyl-2-phenyl indole **(118)** was obtained after recrystallisation from petrol as a pale orange powder in a 61 % yield with analysis that agreed with the previous results.

The same reaction was repeated with half the amount of catalyst **119**, i.e. 2.5 % based on the starting materials, under the same reaction conditions as above. The reaction was heated at 110 °C and checked after 24 hours by TLC which showed the reaction to be complete with no starting material remaining. The product was columned to give an oil and precipitated with methanol to give the *N*-4-*tert*-

butylbenzenesulfonyl-2-phenyl indole product in a comparable 56 % yield and that had the same melting point and spectra as in the previous reaction.

Thus the catalyst **119** was found to be a lot more effective for this type of Heck reaction than palladium acetate, with the reaction carried out with only 5 % of **119** having run to completion by the time the reaction was first analysed. The turnover of the reaction gave a reasonable yield with only half the amount of catalyst **119**, and in only 24 hours. This was presumably because of the greater stability of this catalyst compared to conventional palladium catalysts, such as palladium acetate. Even though it did not improve the yield of the reaction when compared to the reactions with a palladium acetate catalyst, it gave these results with equimolar amounts of the aniline and the alkyne, without requiring three equivalents of the latter, therefore providing the greatest efficiency.

3.3.3 Catalyst testing

The coupling reaction with iodoaniline **(108)** and phenylacetylene **(112)** was tried with four rhodium catalysts **208, 209, 210, 211**. The structures given in **Appendix 1**. In no case was a good yield of 2-(phenylethynyl)-aniline **(113)** or of 2-phenyl indole **(114)** obtained.

3.4 Conclusion

In summary, the initial parameters of the study to develop methods for the production of synthetic indole derivatives were quickly altered, with solid phase reactions appearing problematic and ineffectual. Solution phase Heck reactions proved unstable, with many reactions taking far too long, with reaction times taking place over weeks, and gave incomplete conversion of starting materials to a mixture of products. This was with the exception for reactions with an electron withdrawing group on the aniline nitrogen, in which case the sole product obtained was the cyclisation to the corresponding indole.

With very few reactions giving a suitable turnover of products that could easily be obtained in a suitable purity, the Heck reactions were found to be not practical for producing indoles and other methods of synthesis were sought, methods which are discussed in proceeding chapters.

4. Copper mediated indole synthesis

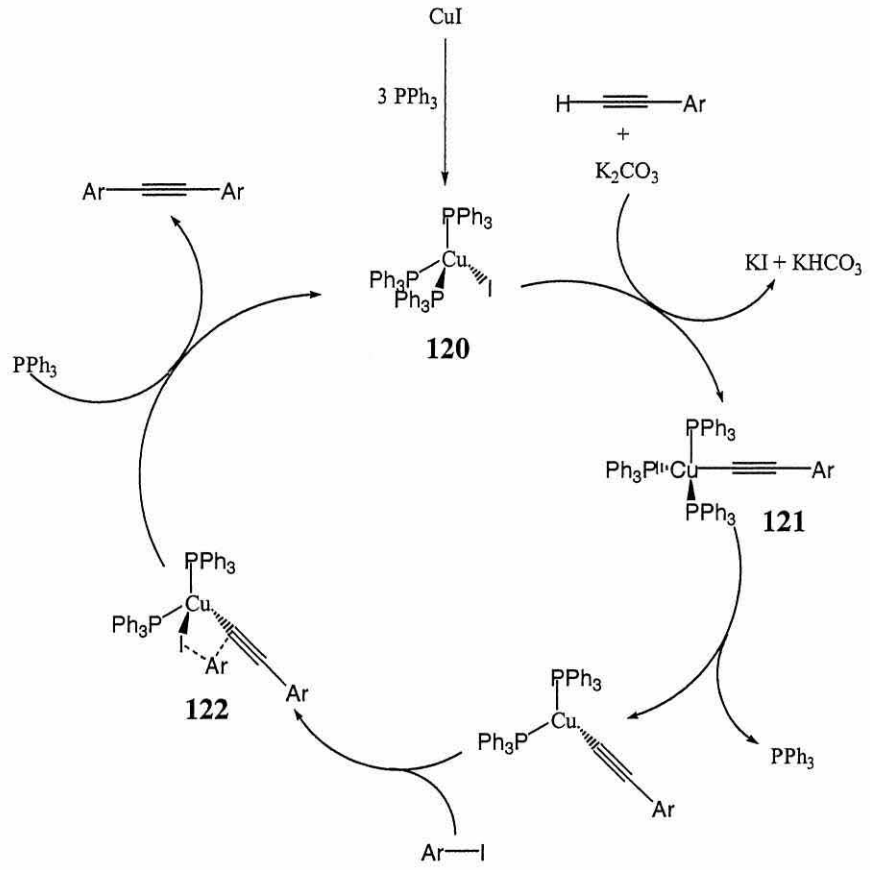
4.1 Indole synthesis via Okuro's modification of the Castro reaction

4.1.1 Introduction

A method for the production of arylacetylene derivatives is the coupling of aryl iodides with cuprous acetylides which in known as the Castro reaction[177, 178] as described in **Chapter 1.3.4.3.2**. This method is undesirable due to the reactive nature of the cuprous acetylides and because they are required in stoichiometric amounts as the reactant.

Okuru *et al.* developed a coupling reaction between aryl or vinyl iodides with terminal alkynes that utilised a catalytic amount of copper iodide with an additional two or three equivalents of triphenylphosphine and potassium carbonate as a base, that was reported to work in high yield.[208, 209] A mechanism for the copper catalysed reaction was postulated in which the *in situ* generated copper acetylides, as found in the Castro reaction, are not formed. This is due to their polymeric nature which makes them almost insoluble in organic solvents and because no precipitation is found during the course of the reaction. It is believed that triphenylphosphine coordinates to the copper species and it is this copper-phosphine complex **(120)** that reacts with the terminal acetylene to give a monomeric copper (I) acetylide **(121)**, a species which is soluble in organic solvents as shown in the catalytic cycle shown in **Scheme 4.1**.

The reaction between the *in situ* generated copper-phosphine complex and the aryl iodide proceeds via a four membered transition state **(122)**, as was proposed for the Castro reaction, which then rearranges to eliminate the coupled product from the complex and regenerate the catalyst.



Scheme 4.1 The proposed mechanism for Okuro's modification of the Castro reaction

4.1.2 Aim

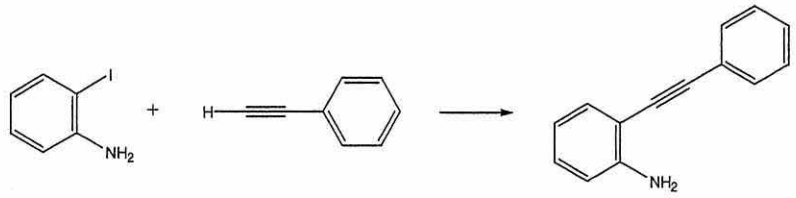
The aim of this part of the project was to investigate Okuro's work as a method for the synthesis of a range of indoles that was superior to the work carried out with solid support resin chemistry and the Heck reaction covered in **Chapter 3**.

4.1.3 Coupling reactions

To begin this work, reactions carried out with the Heck reaction in the previous section were repeated under Okuro's conditions to be able to form a direct comparison between these methods. Therefore the synthesis of 2-phenylindole was repeated with iodoaniline and phenyl acetylene with 5 % copper (I) iodide and three molecular equivalents of triphenylphosphine.

The reaction was heated at 120 °C for 19 hours to give a crude product. Expected results for the reaction ranged from the indole product to a mixture of starting material, indole, and coupled alkyne intermediate. However, after columning, no

indole was obtained as the reaction had proceeded exclusively to the intermediate **113**, with no cyclisation.

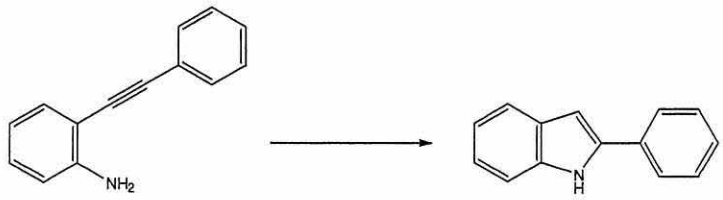


108 **112** **113**

It was duly noted that the 2-(phenylethynyl)-aniline obtained, despite being in a yield of only 38 %, was easier to obtain pure than that obtained as a by-product from the Heck reaction. The product was obtained as yellow needles, identical to previous samples and the literature by NMR and IR values. However it was sometimes necessary for multiple recrystallisations to remove triphenylphosphine contamination from the product.

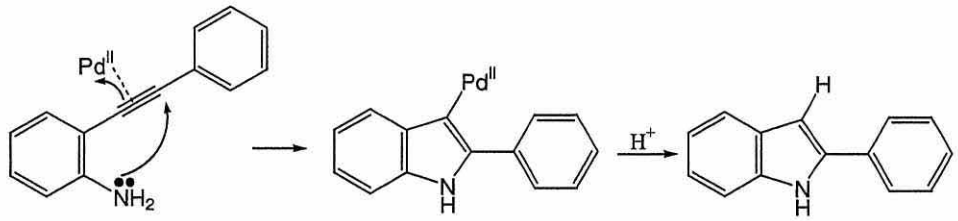
Therefore as the reaction did not proceed with cyclisation, a separate cyclisation step was required. This is detrimental to an efficient reaction scheme as it doubles the number of reactions and therefore purifications required. However, such a reaction has been reported in the cyclisation of 2-alkynylanilines to pyrroles[210] and indoles.[211-213]

In this reaction, the substrate **(113)** was dissolved in a few millilitres of acetonitrile, palladium (II) chloride (1 – 5 %) was added and the solution heated under reflux for a period of one to four hours. This was attempted with 2-(phenylethynyl)-aniline, which was dissolved in acetonitrile and 5 % of palladium (II) chloride added and the solution refluxed for half an hour. After this time, a crude ^{1}H NMR of the reaction mixture showed the complete loss of the NH_2 peak at 4.3 ppm and instead showed signals equivalent to one hydrogen for a broad N-H peak at 8.4 ppm and a sharp singlet signal at 6.9 ppm for the 3-indole proton as well as a large aromatic region ranging from 7.1 ppm – 7.7 ppm. The catalyst was simply removed with the use of a very short column that eluted the product 2-phenylindole **(114)** in a 82 % yield with no impurities.



113 **114**

The reaction is presumed to proceed through a π-complex **(123)** of the acetylenic bond with the palladium (II), which rearranges to a σ-complex **(124)** with an accompanying intramolecular nucleophilic attack of the amine group, which through proton attack and loss of palladium (II) yields the indole.[211]



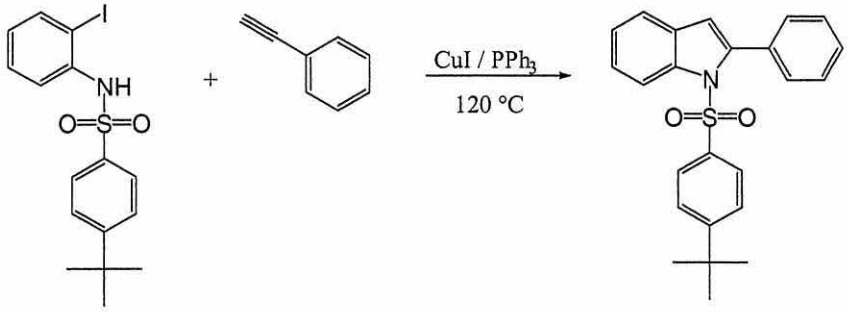
123 **124** **114**

The acetonitrile solvent, and other polar aprotic solvents, favour S_N2 reactions by their tendency to surround metal cations instead of nucleophilic anions and therefore increase the nucleophilicity. Rate increases have been measured, with acetonitrile leading to reactions five thousand times as fast as those in methanol. Despite this, S_N2 reactions in acetonitrile are still forty times slower than nucleophilic reactions in HMPA.[214]

Therefore the reaction was quick, easy and proceeded in an almost quantitative yield to give a cleanly obtained indole product **(114)** that previous Heck reactions had been unable to provide in quantity or quality.

To try to improve the yield of these reactions, the same reaction was repeated with 10 % of copper iodide catalyst and a corresponding amount of triphenylphosphine. This gave problems in the work up as it became very difficult to remove the large quantities of triphenylphosphine from the product which was only purified with repeated columning and washing to give yellow needles of 2-(phenylethynyl)-aniline with no improvement to the yield of 43 %.

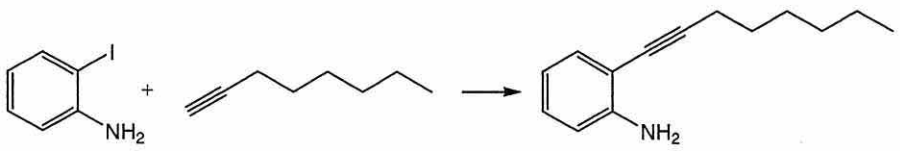
The copper mediated reaction was tried under the same reaction conditions with *N-4-tert*-butylbenzenesulfonyl iodoaniline **(116)**, for which only the indole product had been obtained via the Heck reaction. The reaction was run for 48 hours and the crude product obtained was purified to give exclusively the indole product *N-4-tert*-butylbenzenesulfonyl-2-phenyl indole **(118)** in a 55 % yield.



116 **112** **118**

This unexpected cyclisation reaction apparently happens due to the electron withdrawing pseudo-tosyl group that promotes nucleophilic attack of the *ortho* amine.

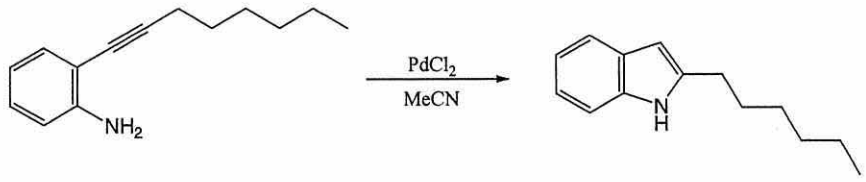
A reaction was carried out to test the diversity of the copper catalysed coupling reaction with a non-aryl containing terminal alkyne. The reaction with iodoaniline **(108)** and oct-1-yne **(125)** was carried out in the same way as above, with three equivalents of triphenylphosphine. The expected uncyclised product, 2-oct-1-ynyl-phenylamine **(126)**, was obtained as an oil, as opposed to crystals, due to the hydrophobic component of the molecule, in a yield of 21 %. The compound was identified by a broad singlet for the NH_2 group at 4.2 ppm in the ^1H NMR spectrum as well as two triplets for positions 3 and 8 of the octyne chain at 2.5 ppm and 1.0 ppm, respectively. The ^{13}C NMR showed 14 signals as expected and an alkyne signal was seen at 2219 cm^{-1} in the IR spectrum.



108 **125** **126**

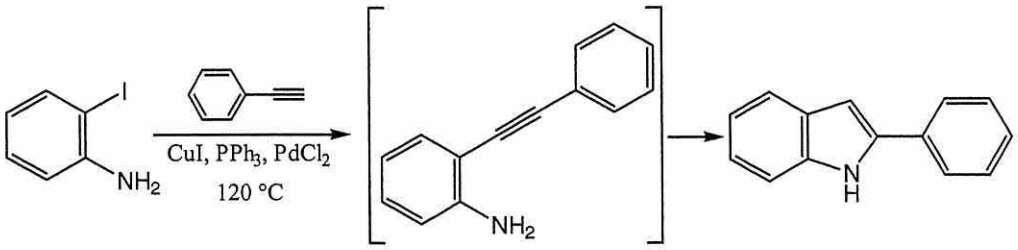
The reaction was repeated under the same conditions but with two equivalents of triphenylphosphine to try and improve the yield, but this returned a similar low yield of 12 %.

The cyclisation of 2-oct-1-ynyl-phenylamine **(126)** was carried out with 5 % palladium (II) chloride in refluxing acetonitrile at 110 °C for 30 minutes. The catalyst was again removed from the crude product by means of a short silica column to once again give exclusively 2-hexyl-indole **(127)**, in a comparable yield to the 2-phenyl indole reaction, 75 %. The ^{1}H NMR spectrum showed the characteristic indole N – H signal at 7.8 ppm and C-3 proton at 6.3 ppm. The two triplets for the terminal CH_2 and the CH_3 of the hexyl group were now observed at 1.0 ppm and 2.8 ppm. This result effectively showed that the copper coupling reaction followed by palladium cyclisation reaction could be extended to alkyl as well as aryl alkynes.



126 **127**

To make the reactions more efficient, saving time and the loss of yield, an attempt was made to combine the two reactions into a one pot method. The choice of indole to synthesise for this reaction was 2-phenylindole because of the availability of starting materials and because the reaction had repeatably been carried out in two steps.



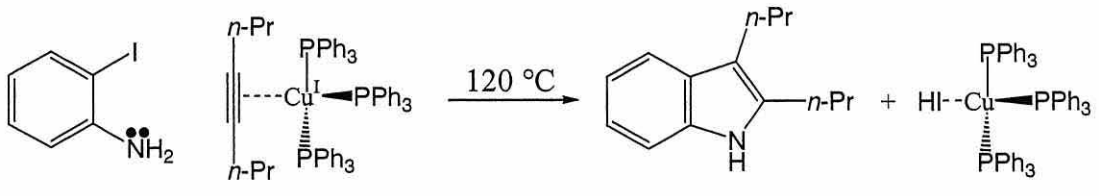
108 **113** **114**

In the first attempt at this one pot synthesis, all reactants for both steps of the reaction

were added together, but this led to the breakdown of the catalyst and the precipitation of palladium metal on the surface of the glass. Therefore the reaction was repeated with the palladium (II) chloride added (with a small amount of acetonitrile) 24 hours after the reaction had been started and the reaction then run overnight. This allowed the second reaction to proceed immediately and not allow the catalyst time to decompose before it has had time to take part in the process. The reaction did not produce just indole but gave 88 % of the alkyne intermediate **113** and a small amount (5 %) of the indole **114** that were identified on the basis of NMR but could not be easily separated.

One possible reason for the incomplete conversion of **113** maybe the different solvent that was used. DMF is a less polar aprotic solvent than acetonitrile, which was used for the previous cyclisation reactions. As such, this is half as favourable to the nucleophilic attack involved with cyclisation.[214] A longer reaction time may have therefore increased the yield, but as the cyclisation reaction with palladium chloride was usually run over half an hour, this hypothesis is doubtful. However, **113,** despite contamination with impurities, was obtained in more than double the yield previously achieved for the same reaction. This fact should be noted and will be commented on later.

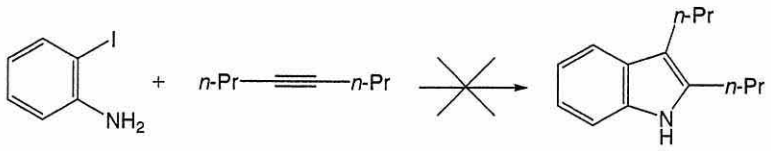
A test of the mechanism of the catalytic cycle proposed by Okuro[209] was carried out with the attempted synthesis of 2,3-dipropylindole **(110),** a product that was obtained via the Heck reaction in a very small yield. The mechanism indicates that the reaction is limited to a terminal alkyne and it is this that binds to the copper-phosphine complex. It was decided to see whether a non-terminal alkyne could be used to generate an indole product via a one step reaction.



108 **110**

Therefore the reaction of iodoaniline **(108)** and oct-4-yne **(109)** was carried out with

5 % copper (I) iodide and three molecular equivalents of triphenylphosphine.



108 **109** **110**

However, the reaction turned purple and yielded a complex mixture of compounds that showed no reaction had occurred. Only starting materials were identified from fractions obtained, together with other compounds that were unidentified but contained none of the expected alkyl signals in the ^{1}H NMR. Therefore the postulated mechanism was upheld and this reaction is therefore limited to the coupling of terminal alkynes. This means that this reaction cannot be used to synthesise 3-substituted indoles and to approach them standard substitution reactions on 3-unsubstituted indoles would be required.

4.1.4 Conclusion

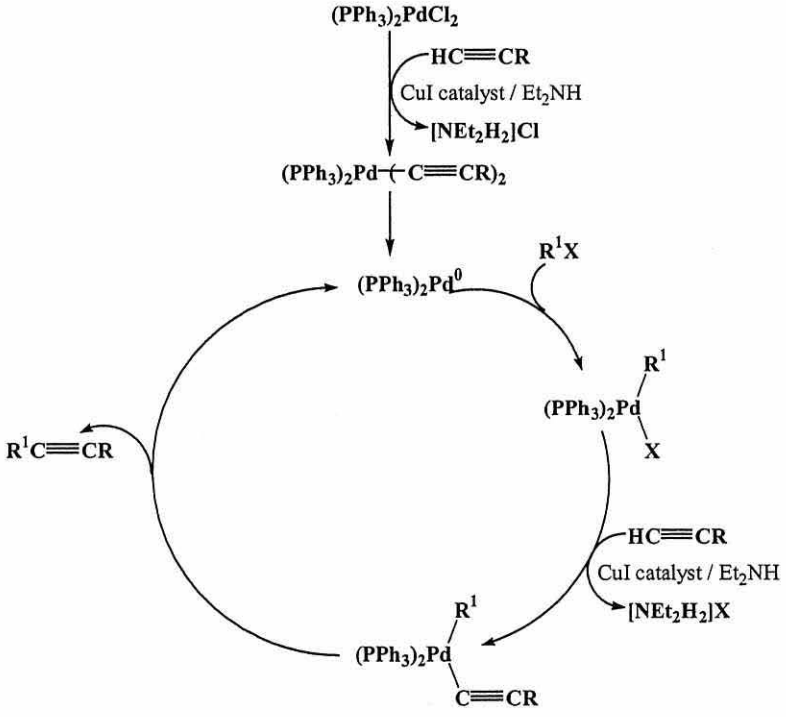
The advantages of Okuro's copper catalysed coupling reaction was found to be the synthesis of cleanly coupled acetylenic intermediates, such as 2-phenylethynyl aniline **(113)**, in reactions that took a few hours, in situations where the Heck reaction took several days to complete. However, the yield was found to be consistently poor and in many of the reactions the co-reactant, triphenylphosphine, was found to be problematic to remove and meant that additional columning of the product was necessary, which was one of the factors that contributed to loss of yield.

4.2 Sonogashira coupling

4.2.1 Introduction

The Sonogashira reaction is similar to both the Heck and Okuro's modification of the Castro reaction in that it utilises palladium and copper co-catalysts to couple terminal alkynes with aromatic or vinyl halides.[215, 216] It is employed under facile conditions and does not use free triphenylphosphine in the reaction.

The mechanism is thought to be similar to that of the Heck reaction with a Pd (0) catalyst generated *in situ*. An oxidative addition reaction inserts the palladium metal into the Ar - X bond to form a Pd (II) complex. After reaction with the alkyne, reductive elimination of the Pd (II) species ejects the coupled product and regenerates the Pd (0) catalyst as postulated by Sonogashira shown in **Scheme 4.2**.[215] The role of the copper catalyst is not known but it is thought that alkyne addition to the palladium catalyst proceeds via a copper acetylide. It is known that it plays an important role, as without it the reaction will not proceed at room temperature and requires forcing conditions.[217, 218] Also reactions with less active aryl halides will not work without this co-catalyst.

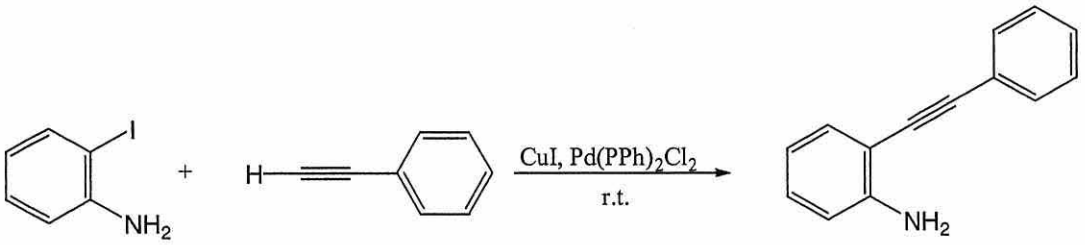


Scheme 4.2 The proposed mechanism for Sonogashira coupling

The typical quantities of catalysts used are 2 % of each of the palladium and the copper catalysts, although the ratios vary between literature reactions.[219] For reactions in this work, the ratio used throughout, unless otherwise stated, was 1 % of bis(triphenylphosphine) palladium (II) chloride and 2 % of copper iodide.

4.2.2 Discussion

To test the Sonogashira reaction the standard coupling of iodoaniline and phenyl acetylene was attempted. The reaction was carried out in diethylamine, one of several basic solvents that works for this system,[220] which also acts as the base for the reaction and immediately introduces advantages over the toxic and mutagenic qualities of DMF which was used in previous reactions, as its lower boiling point allows for ease of removal at the end of the reaction.



108 **112** **113**

The reaction was carried out overnight at room temperature and run under a nitrogen atmosphere. After this time a few ml of a dark brown oil were visible at the bottom of the reaction vessel, the diethylamine salt ($N^{+}Et_2H_2I^{-}$), which was a by-product of the reaction. The salt was precipitated upon addition of ether to the solution and removed by simple filtration. The presence of this salt was used to adjudge whether the reaction had been successful.

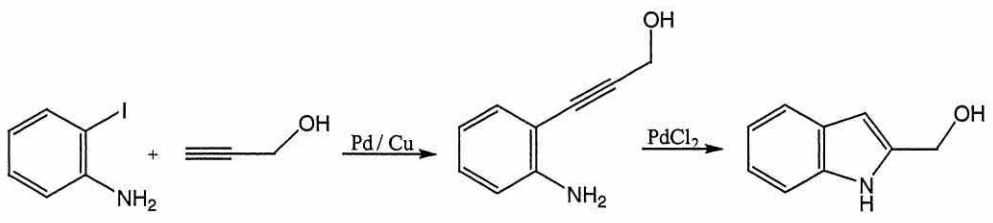
The product of this reaction, one spot by TLC, was put though a short silica gel column to remove the metal catalysts and give 2-(phenylethynyl)-aniline. Without the presence of free triphenylphosphine in the reaction, the product was easily recrystallised from petrol to give a 90 % yield with the expected analysis for the compound.

This yield is far superior to the previously obtained yields of less than 50 % from reactions detailed in **Chapters 3** and **4.1**. Given that **Chapter 4.1** showed that cyclisation of the alkyne to the indole takes place in almost a quantitative yield, the above method should be usable to make indoles in a very high yield.

The same reaction conditions were employed with long alkyl-chain containing terminal acetylenes. Hex-1-yne and oct-1-yne were coupled to iodoaniline **(108)** under the same conditions as above, which after the same work up procedure gave the corresponding coupled products in yields of 85 and 84 %, respectively. These were identified in the case of 2-oct-1-ynyl-phenylamine **(126)** because it gave spectra identical to those previously obtained, whilst for 2-hex-1-ynyl-phenylamine, ^1H NMR showed an aromatic region from 6.7 ppm - 7.3 ppm, a NH_2 singlet at 4.1 ppm and triplets at 1.0 ppm and 2.5 ppm for the methyl group and the CH_2 group at opposite ends of the coupled hexyl chain. This showed that this method could be successfully used for the high yield synthesis of both alkyl and aryl-indole precursors.

To move on and make indoles with a functionalised substituent, reactions therefore were carried out with alkynols, as the alcohol group could be readily modified to give aldehydes, carboxylic acids, alkenes and halides.

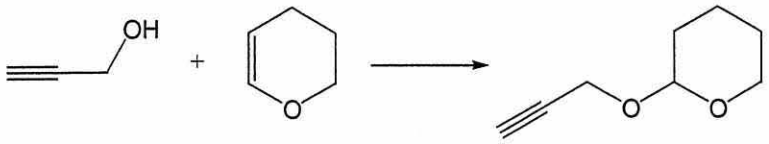
The first attempt to introduce an alcohol group was the synthesis of indole-2-methanol **(129)** from the coupling of propargyl alcohol **(128)** to iodoaniline **(108)** then cyclisation.



108 **128** **129**

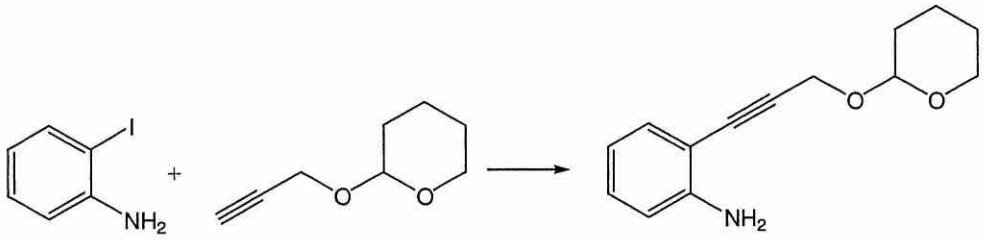
However as the effect of the alcohol group on the reaction was not known, propargyl alcohol **(128)** was protected with 3,4-dihydro-2*H*-pyran **(130)** in a reaction with 0.1 molecular equivalents of pyridinium *p*-toluene sulfonate to give the protected alcohol

131 in a serviceable yield. The product showed an alkyne stretch at 2117 cm^{-1} and no alcohol absorption in the IR, and a large alkyl region in the ^{1}H NMR from 1.5 ppm to 2.4 ppm that corresponded to the THP group.



128 **130** **131**

The protected alcohol **131** was then coupled to iodoaniline **108** under Sonogashira conditions at room temperature overnight to give the alkyne **132.** This was isolated as a low running compound in a low yield after repeated columning. The coupled product showed an alkene stretch at 2221 cm^{-1} and gave the 14 expected signals in the ^{13}C NMR.



108 **131** **132**

The attempted cyclisation of **132** was carried out under the same conditions as previously, with palladium (II) chloride in refluxing acetonitrile, and was expected to cause simple cyclisation in a quantitative yield. However, crude NMR of the reaction showed that the desired reaction had not taken place as there was no C-3 hydrogen singlet present at 6.3 ppm amongst the complex mix of signals.

As the reaction proceeds via the palladium catalyst forming a cation prior to the nucleophilic attack of the amine, it is reasonable to expect that the electron withdrawing acetylated alcoholic oxygen would speed up nucleophilic attack from the amine lone pair, as shown in **Figure 4.1**. A reason why the reaction did not work could be that the lone pairs on the oxygen interact with the palladium and interfere with the catalytic cycle.

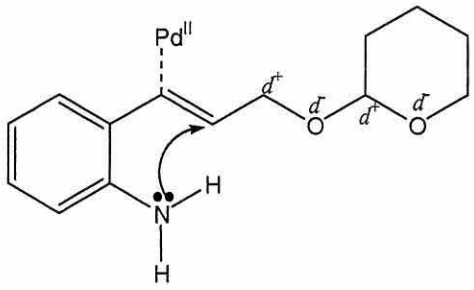
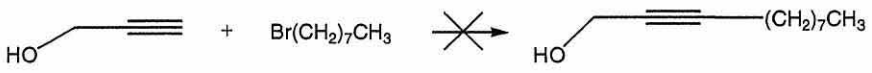


Figure 4.1 The proposed mechanism of cyclisation

Similar reactions were therefore sought with alcohol containing alkyne chains, where there is a greater distance between the oxygen and the sp bond, so the electronegative group would have a negligible effect on the reaction through the σ-framework. Though the coupling of the alkyne **128** was shown not to cyclise to the indole, it was expected that the reaction would work at some point as the length of the chain was increased.

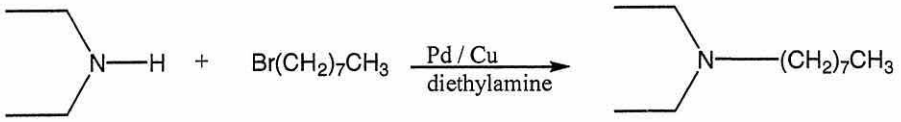
However, terminal alkynes containing an alcohol group are not widely available and even though samples of 3-butyne-1-ol and 4-pentyne-1-ol were located, a method of producing such alkynes of desired chain length was required. Therefore it was attempted to produce undec-2-yne-1-ol from the coupling of propargyl alcohol **(128)** and bromooctane **(133)** under Sonogashira conditions in diethylamine. The coupled product of **134** could then be converted to the desired terminal alkyne.



128 **133** **134**

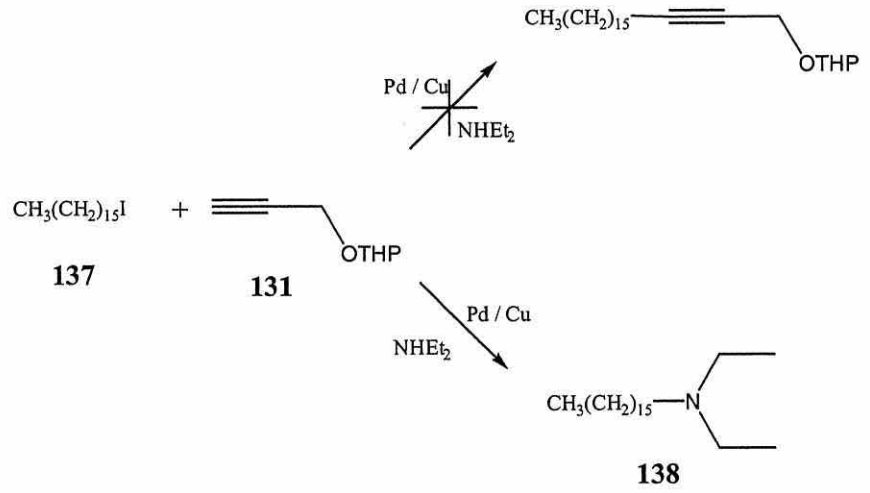
However this reaction failed and only starting materials were recovered. Due to the fact that the substrate being used (bromooctane) was brominated, the conditions for reaction were less favourable for the Sonogashira reaction, than if iodooctane had been used, but nonetheless the reaction was still expected to proceed. The reaction was put back on with some triethylamine, a higher boiling point solvent, and the solution was heated at 80 °C for 48 h. This gave none of the desired product but led to the coupling of the bromooctane **(133)** with the solvent, diethylamine **(135)**, to give a product that had consumed the starting material and was identified as diethyl octylamine **(136)**. The compound was identified with two triplets in the ^{1}H NMR

spectrum at 0.8 ppm (3 H) and 1.0 ppm (6 H) that corresponded to the three terminal CH_3 groups, whilst the ^{13}C NMR showed ten signals.



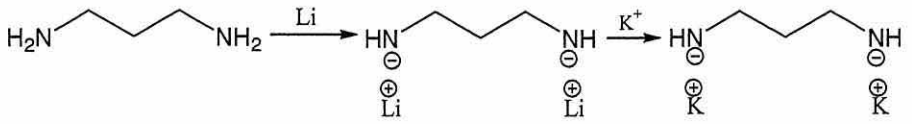
135 **133** **136**

The same type of reaction was therefore carried out at room temperature with 1-iodo hexadecane **(137)** in an attempt to couple it, in this case with the THP-protected propargyl alcohol **(131)**. After overnight stirring starting material was recovered and the only product obtained was that arising from reaction of iodohexadecane with diethylamine **(135)** as per the previous reaction to give a small amount of diethylhexadecylamine **(138)**.



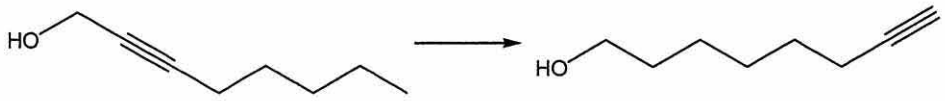
137 **131** **138**

Had these reactions worked it would have been necessary to convert the product to the terminal alkyne by the so called Zipper isomerisation. This reaction was instead carried out on a commercially prepared sample of 2-octyn-1-ol **(120)**. This involved lithium wire, dissolved in a 1,3-diaminopropane **(139)** with a potassium *tert*-butoxide base. This deprotonates the amine groups of **139**, with lithium cations counterbalancing the amine anions, before displacement by the potassium cations to give the active reagent **(140).**



139 **140**

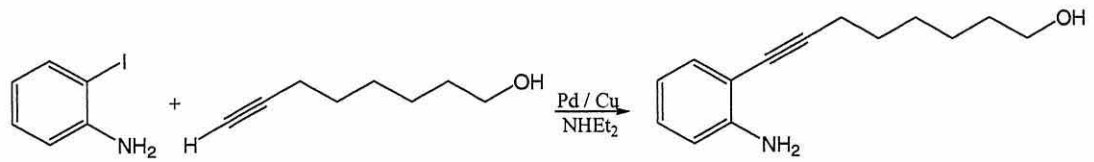
The deprotonated species **140** then acts as a strong base in the transition of alkynes to terminal alkynes. This involves deprotonation adjacent to the alkyne, reprotonation to give a transitory allene intermediates and then formation of a migrated alkyne. The alkyne moves along the chain of the molecule until the reaction ceases when the alkyne becomes terminal and forms the acetylide. This was applied to the transformation from 2-octyn-1-ol **(141)** to 7-octyn-1-ol **(142)** which was obtained in an 76 % yield. The compound was identified with the sp proton observed at 1.9 ppm, split into a triplet with a coupling constant of 2.6 Hz across the triple bond.



141 **142**

The coupling and cyclisation reaction was therefore studied with the two commercial alkynes and with **142**. Should other chain lengths be required the coupling between a commercially available alkynol and a haloalkane could be carried out with lithium in liquid ammonia to give any required alk-2-yn-1-ol, followed by the Zipper process.

7-Octyn-1-ol **(142)** was successfully coupled to iodoaniline **(108)** under Sonogashira conditions to give 5-(2-amino-phenyl)-oct-7-yn-1-ol **(143)** in a 90 % yield.

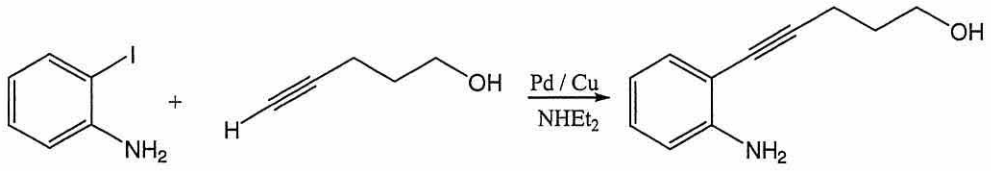


108 **142** **143**

The product showed a large alkyl multiplet in the ^{1}H NMR between 1.3 ppm and 1.7 ppm, as well as triplets at 2.5 ppm and 3.6 ppm for the CH_2 groups at positions 1 and 6 of oct-ynol chain, a large singlet for the NH_2 group at 6.7 ppm. The ^{13}C NMR

showed the expected fourteen signals, whilst IR showed an alcohol absorption at 3466 cm^{-1} and an alkyne stretch at 2221 cm^{-1}.

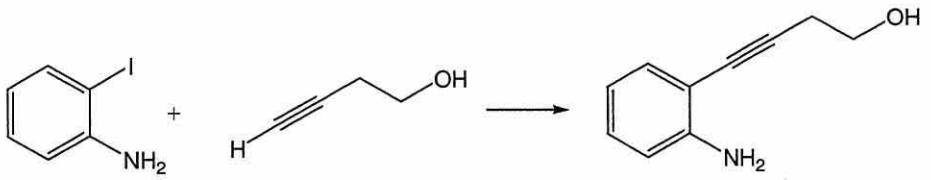
The same coupling reaction was carried out iodoaniline **(108)** and 4-pentyne-1-ol **(144)** to give 5-(2-amino-phenyl)-pent-4-yn-1-ol **(145)** in an equally good yield of 85 %.



108 **144** **145**

Compound **145** gave the correct elemental analysis, a suitable ^{1}H NMR spectrum, eleven signals in the ^{13}C NMR and an alcohol absorption at 3358 cm^{-1} and an alkyne stretch at 2219 cm^{-1} in the infra red.

The same coupling reaction was repeated for 3-butyne-1-ol **(146)** which gave 4-(2-amino-phenyl)-but-3-yn-1-ol **(147)** in an 85 % yield that showed expected spectra similar to **143** and **145** and identical to the literature values.[221]

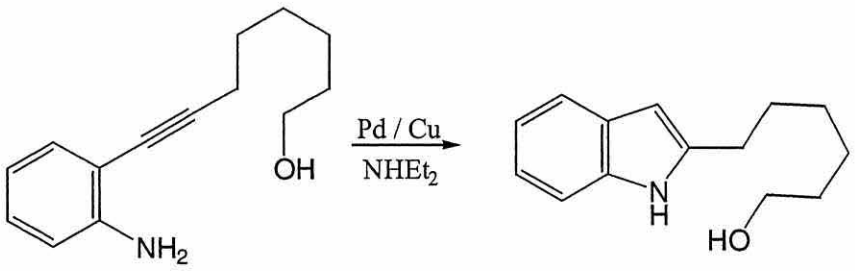


108 **146** **147**

The success of these three coupling reaction was expected under Sonogashira conditions as the reaction had always been successful previously. However, the subsequent cyclisation step of the coupled alkynes to indoles was not a certainty.

The greater length of the chain in the coupled alkynes above, meant that there was an increased distance of the alcohol group from the C2 position of the alkyne bond where nucleophilic attack takes place in the palladium catalysed cyclisation reaction. It was therefore reasonable to expect that if any of the three reactions should work,

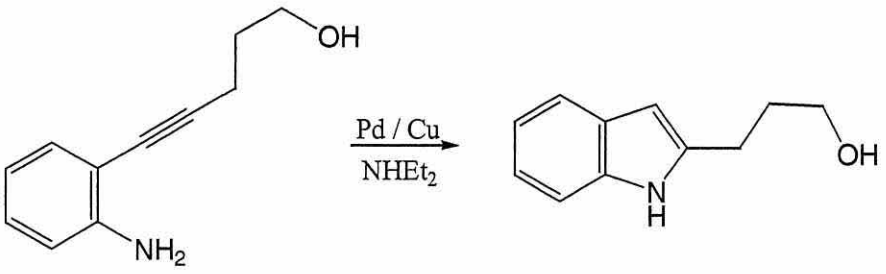
then it should be the cyclisation of the compound with the longest chain, 5-(2-amino-phenyl)-oct-7-yn-1-ol **(143)**. The reaction was carried out under argon and heated at reflux for a period, longer than usual, of an hour. Crude NMR showed that there was complete conversion into 2-indol-2-yl-hexanol **(148)** in a 72 % yield. The ^{1}H NMR spectrum contained the characteristic indole C-3 proton sharp singlet at 6.3 ppm, a broader amine peak at 8.3 ppm as well as four aromatic signals between 7.1 ppm and 7.6 ppm, a large alkyl multiplet between 1.4 ppm and 2.0 ppm and two triplets at 2.7 ppm and 3.7 ppm for the CH_2 groups on the 1 and 6-position of the alkyl chain. ^{13}C NMR showed fourteen signals, whilst IR showed the loss of the alkyne stretch at 2221 cm^{-1} and showed instead the resultant stretch for the double bond at 1458 cm^{-1}.



143 **148**

With the success of this reaction, the reactions with shorter chain alkynols were examined. Thus, it was assumed that the reaction would work for chains of greater length, but with an as yet unestablished critical shorter chain limit, the reaction would stop working. This value at this stage was known to be greater than to one carbon unit.

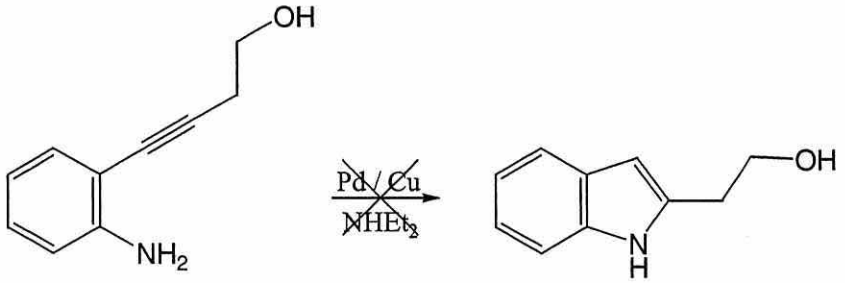
A lot closer to this critical value was 5-(2-amino-phenyl)-pent-4-yn-1-ol **(145)**, with a chain that is three carbons shorter than in **143**. Even though the reaction was carried out on a relatively small scale, under the same conditions as the previous, there was an efficient recovery of 2-indol-2-yl-propanol **(149)** in a 90 % yield.



145 **149**

The ^{1}H NMR showed characteristic signals for a 2-substituted indole with a singlet at 6.3 ppm for the C-3 hydrogen and a broad singlet at 8.5 ppm for the indole N – H. The spectrum also showed three signals for the alkyl chain at 1.9 ppm, 2.8 ppm and at 3.7 ppm, as well as the four aromatic signals between 7.1 ppm and 7.6 ppm. The ^{13}C NMR spectrum showed the expected eleven signals, whilst IR showed signals for the double bond and the alcohol group at 1561 and 3470 cm^{-1}, respectively.

However, the same reaction repeated for 4-(2-amino-phenyl)-but-3-yn-1-ol **(147)** was not successful in cyclisation to 2-indol-2-yl-ethanol **(150)** with the crude NMR showing a mixture of products which on column chromatography gave just one fraction pure which was identified as the starting material.

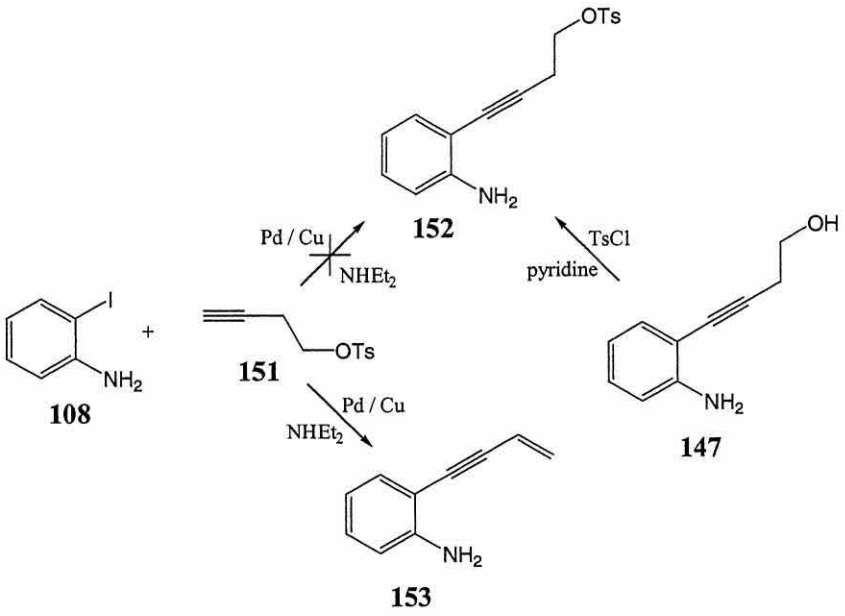


147 **150**

Therefore, this method was successful in the synthesis of indoles with terminal alcohol groups, but only for chain lengths equal to, or greater than, a propyl group between the alcohol group and the alkyne bond.

An attempt was made to circumvent this problem and synthesise 2-indol-2-yl-ethanol **(150)** by substitution of the alcohol group. First the 3-butyne-1-ol **(146)** was tosylated in pyridine to give the toluene-4-sulfonyl but-3-ynyl ester **(151)** in a 96 %

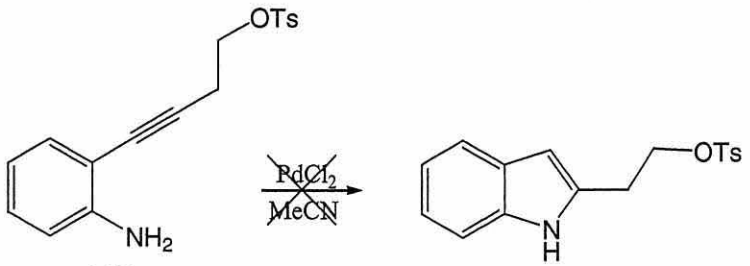
yield before the coupling reaction was attempted with iodoaniline to give the indole precursor **152** at room temperature. However, this product was not obtained, with the crude NMR showing a splitting pattern for a terminal alkene. GC-MS data agreed with this showing that a large proportion of the mixture that went through the GC was the vinyl alkyne **153** showing a mass ion of 143 which could have been formed by the elimination of *p*-toluene sulfonic acid during the reaction.



The alkene **153** is in itself interesting, allowing the possibility of forming vinyl indenes and of further reactions at the double bond.

The desired tosylated alkyne **152** was eventually obtained in a yield of 85 % from the tosylation of 4-(2-amino-phenyl)-but-3-yn-1-ol **(147)** overnight at 0 °C. The product **152** showed the expected tosyl methyl group at 2.4 ppm in the ^{1}H NMR spectrum as well as aromatic protons between 7.0 ppm and 7.8 ppm. The ^{13}C NMR showed the expected fifteen peaks, whilst IR showed the loss of the alcohol absorption at 3358 cm^{-1}.

The resulting tosylate **152** was then reacted with palladium (II) chloride under argon under reflux for an hour. Crude NMR showed that **152** had been consumed, but that the reaction did not give the expected cyclised product **154**.

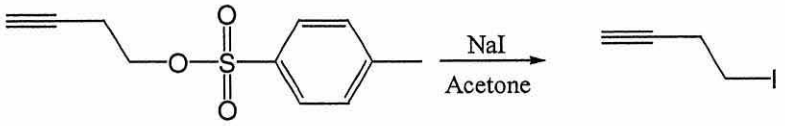


152 **154**

The reaction gave a mixture of compounds that GCMS showed contained one major compound, that appeared to be the starting material. The NMR showed a complex mixture with a sharp singlet at 11.4 ppm and a complex aromatic pattern.

The cyclisation reaction did not work with the tosylate **152** or with the alcohol **147**. The next reaction tried was to try to cyclise the corresponding iodide to try to make a C2 chain substituted indole that could then be converted to different functional groups. The conversion of the tosyl products **151** and **152** to iodides was therefore attempted.

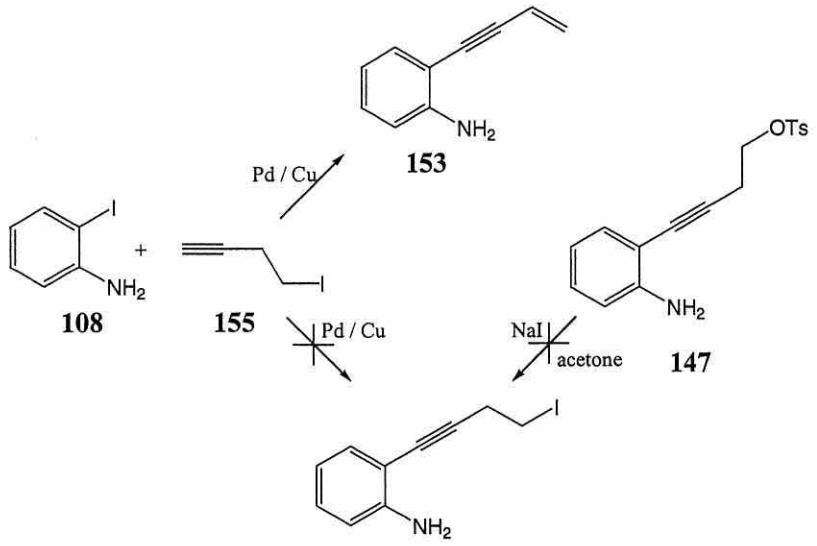
The first step attempt was to generate the iodoalkyne before coupling this to iodoaniline. The iodination of toluene-4-sulfonic acid but-3-ynyl ester **(151)** was carried out in acetone under reflux with the sodium iodide salt for three hours after which time TLC showed the reaction was complete. The reaction works due to the salts solubility in acetone, but columning gave iodobut-3-yne **(155)** in a yield of just 18 %. Analysis showed the loss of the tosyl group in the ^{1}H NMR and just the presence of the CH_2-CH_2 triplets at 2.8 ppm and 3.3 ppm and the alkyne proton as a broad singlet at 2.2 ppm.



151 **155**

Despite the low yield, the reaction was run on a scale that gave enough product **155** to proceed to the next stage, the attempted selective coupling with the aryl iodide. The product of the subsequent coupling reaction of **108** and **155** was shown by crude

^{1}H NMR to be mainly the iodoaniline starting material and a small amount of unisolated coupled product, that had undergone an apparent hydrogen iodide elimination to give the terminal alkene **153.**



This minor product **153** was identified on the basis that there was the characteristic terminal alkene splitting pattern in the ^{1}H NMR spectra with tented doublets at 5.6 ppm and 5.7 ppm and a double doublet at 6.1 ppm.

As the previous reaction had not worked, the iodination of the tosylate **147** was attempted under the same conditions in acetone with sodium iodide. After 4 hours at reflux, TLC showed that the reaction was not working and after 48 h only starting material was recovered. Plans to try to make a C2 chain substituted indole were therefore abandoned.

4.2.3 Conclusion

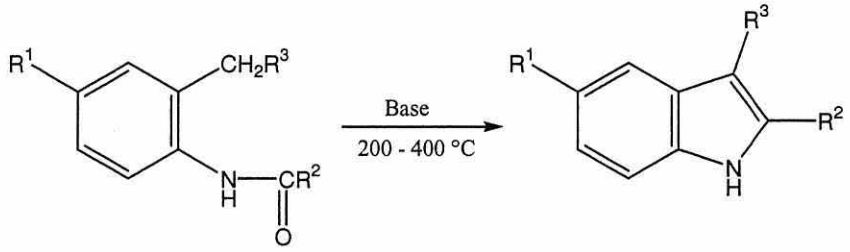
The Sonogashira reaction was proved to be effective for the production of coupled aryl alkynes, in yields consistently approaching 90 %. Through quantitative cyclisation this method presents a successful approach for indole production that has been shown to allow the incorporation of functionalisation and to give products in a quality and yield that far outstrips that produced from palladium or copper catalysed reactions in **Chapters 3** and **4.1**.

It is ironic, therefore, that the Sonogashira reaction required both a palladium and a copper catalyst. But this should not be as surprising as one might think as Sonogashira conditions were encountered prior to **Chapter 4.2** in this thesis. In **Chapter 4.1.3,** the coupling of an alkyne and cyclisation to the indole was attempted in one pot. This reaction used a coupling catalyst of copper iodide and the cyclisation catalyst of palladium (II) chloride. This could this could therefore be considered to be a pseudo-Sonogashira reaction. The product obtained was the alkyne intermediate, although not cleanly, in an 88 % yield. This was double the yield that would have been expected from the copper catalysed coupling reaction alone, but is similar to yields obtained via Sonogashira reactions.

5. Indole synthesis via the modified Madelung reaction

5.1 Introduction

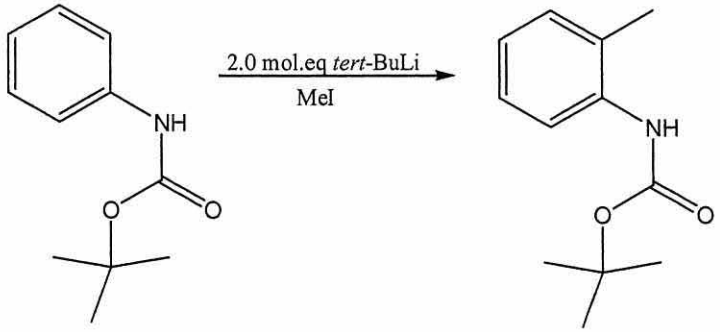
The Madelung indole synthesis, as described in **Chapter 1.3.4.2**, is no longer commonly used due to the harsh conditions involved. The reaction involves the intramolecular cyclisation of an *N*-(2-alkylphenyl)alkanamide with a sodium or potassium alkoxide or amide at temperatures of 200 – 400 °C as shown in **Scheme 5.1**, where R^2 = H, alkyl, aryl.[222, 223] Limitations of the reaction include halogen[224] and alkoxy group[225] substitution and the production of very low yields of indoles with branched alkane chains in the 2-position.[226]



156

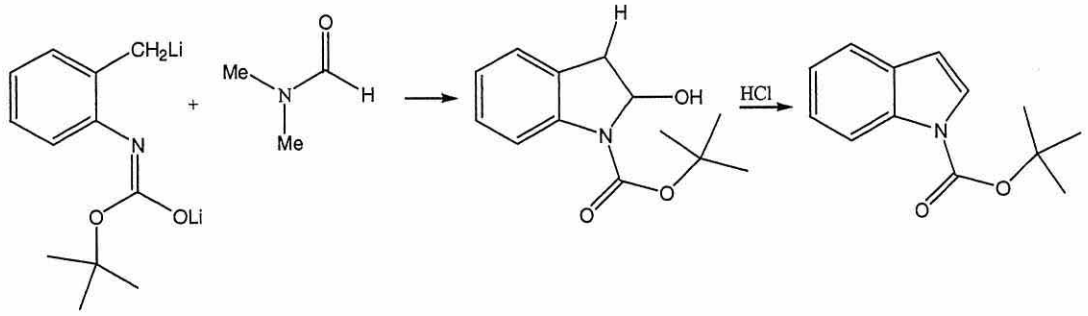
The Houlihan variation of this reaction uses milder conditions with the use of a BuLi or LDA base and a mechanism that proceeds through an organometalic intermediate.[227]

In 1990, Clark *et al.* published the synthesis of BOC protected indoles from 2-alkylanilines.[228] It was shown that BOC protected aniline **(157)** can be *ortho*-lithiated before quenching with electrophiles to give the corresponding 2-alkylanilines[229] **(158)**.



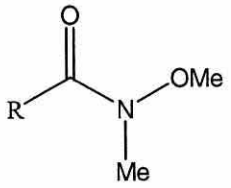
157 **158**

Clark *et al.* then showed that the addition of DMF **(160)** to the dilithiated species **(159)** derived from 2-methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** gave a bicyclic alcohol intermediate **(161)** which could be dehydrated in good yield with HCl to aromatise the system and give the corresponding indole **(162)** without the cleavage of the BOC protecting group. This was performed with a handful of functionalised toluidines.



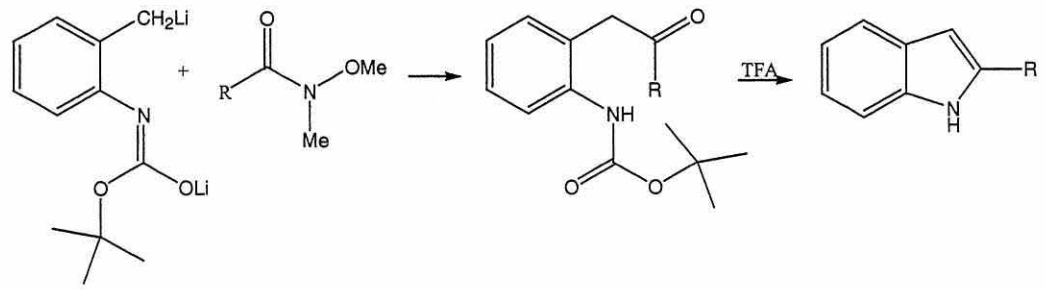
159 **160** **161** **162**

Clark *et al.* then adapted this method to synthesis 2-substituted indoles by changing the quenching agent to a *N*-methoxy-*N*-methyl amide **(163)**, also known as a Weinreb amide,[230] where R is an alkyl or aryl group.



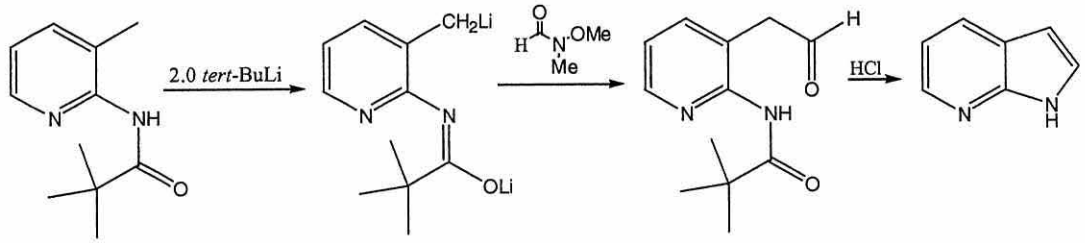
163

This quenching of the reaction with a Weinreb amide gave the corresponding ketone **(164)** which was shown to be cyclised to the unprotected 2-substituted indole **(165)** with TFA which is the common reagent for the removal of BOC protecting groups.[231]



159 **163** **164** **165**

A variation of the Madelung-Houlihan synthesis by Hands *et al.* involves the formation of an intermediate dianion derived from the pyridine intermediate, which when quenched with an amide, gives azaindoles through an aldehyde intermediate that they obtained though addition of DMF.[232]



They report no spectral data for the intermediate which was cyclised with an 8 hour reflux with 5.5 M HCl.

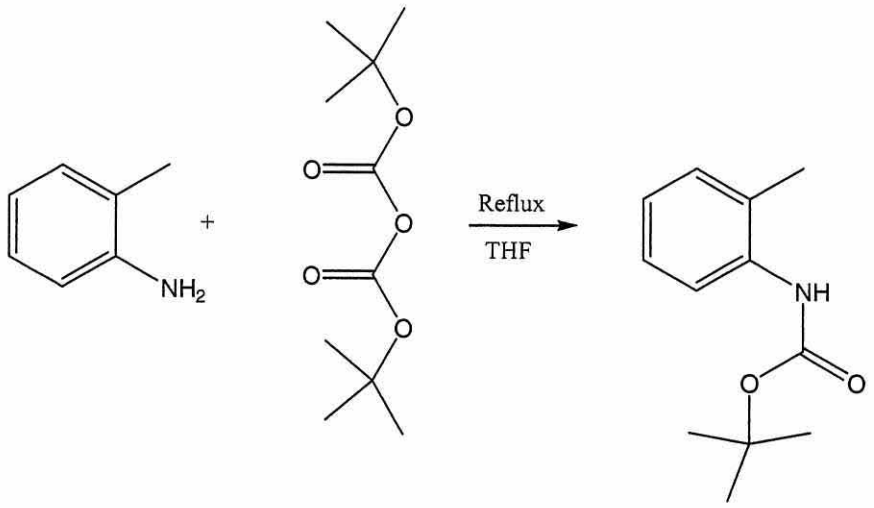
5.2 Aim

Clark's BuLi based synthesis of indoles[233] was investigated to further the scope of indole production, with greater functionalisation of indoles required. This method had the advantage that a range of functionalised anilines are readily available, whereas the iodoanilines used earlier are much more difficult to obtain.

5.3 Discussion

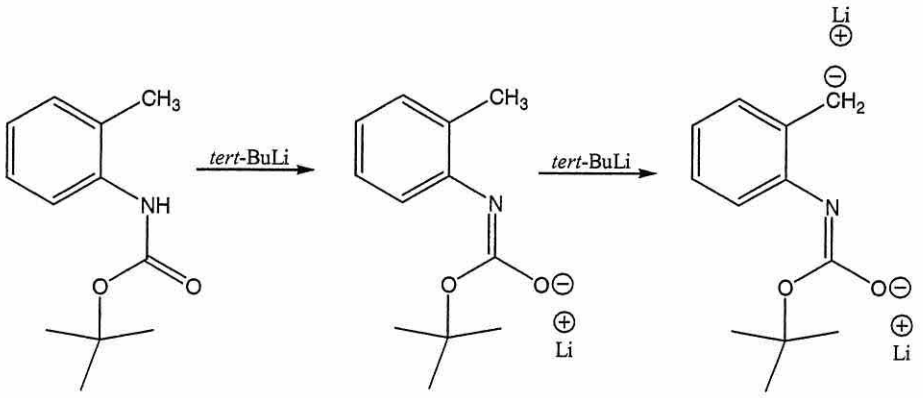
Readily available toluidine **(166)** was protected with a BOC group (*tert*-butoxy carbonyl) in high yield through reaction with BOC_2O **(167)** in refluxing THF for three hours to give the BOC-protected aniline **(158)** as white crystals in good yield. The product showed a large singlet at 1.6 ppm in the ^1H NMR spectrum for the *tert*-butyl ether group as well as ten signals in the ^{13}C NMR and a carbonyl stretch in the

IR at 1676 cm^{-1}. From this product a wide range of indole producing experiments could be carried out.



166 **167** **158**

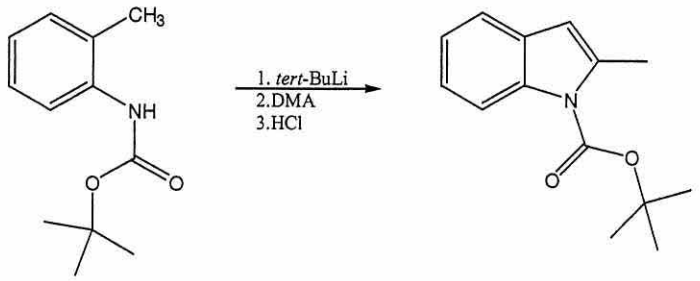
The classical reaction with DMF quenching was carried out with **158** to make the BOC-protected indole. The reactants were cooled to – 40 °C and the reaction was monitored with a digital thermometers to make sure that at no point in the reaction did the internal temperature rise above – 20 °C. The reaction was carried out under an argon atmosphere due to the extreme reactivity of the *tert*-BuLi which combusts spontaneously in air. Due to this reactivity, *tert*-BuLi solutions are very prone to decomposing and the molarity of the solution should normally be checked regularly through a series of reactions. However, it was found that addition of the base to the reaction caused the solution to immediately turn yellow, before disappearance of this colour upon stirring. This colour appeared on the addition of each drop of *tert*-BuLi, presumably due to a coloured intermediate that equilibrated with the more acid amide anion, possibly due to a kinetic versus thermodynamic reaction. It was only after the addition of the first equivalent of *tert*-BuLi was complete and there was stable formation of the dianion **(159)** that the yellow colour became permanent. This colour change could therefore act as an indicator for the completion of the reaction and provide an *in situ* titration of the base, the volume of one equivalent being measured when the solution had turned permanently yellow.



158 **159**

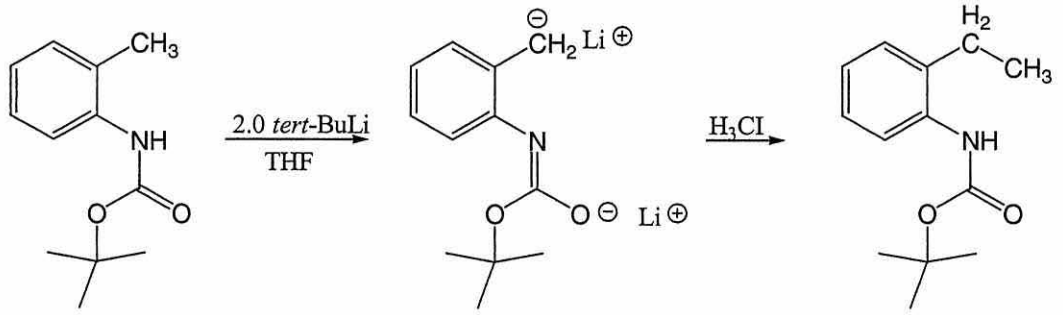
After deprotonation, the solution was quenched with two equivalents of DMF to give a colourless solution which was added to an excess of water, thus easily removing the comparatively small amount of unreacted DMF. The solution was then extracted with ether. Conversion to the indole was easily carried out with exposure of the crude alcohol to 12 M HCl (0.5 ml) over an hour at room temperature in a THF solution. The crude ^{1}H NMR showed the reaction after this time to be complete, giving the clean synthesis of *N*-(*tert*-butoxycarbonyl)indole **(162)** in a reasonable yield. The compound still showed the large singlet at 1.8 ppm in the ^{1}H NMR for the BOC group, showing that treatment with HCl had not led to deprotection of the indole. The NMR also showed the splitting across the double bond with two doublets at 6.7 ppm and 7.7 ppm for the protons at C3 and C2, respectively. The compound gave eleven signals in the ^{13}C NMR and absorptions in the IR at 1607 cm^{-1} for the sp^2 bond and at 1734 cm^{-1} for the carbonyl group.

It seemed reasonable, therefore, that if quenching of dilithiated **158** with DMF would yield *N*-(*tert*-butoxycarbonyl)indole, the same reaction quenched with DMA would yield 2-methyl-*N*-(*tert*-butoxycarbonyl)indole **(168)**. This was found to be the case. When the reaction was carried out under the same conditions as above, the expected product was obtained cleanly in a 41 % yield that showed a ^{1}H NMR spectrum similar to that for indole **162,** apart from a singlet for the C2 methyl at 2.7 ppm and a signal for the proton at C3, no longer split due to the extra substitution, at 6.4 ppm.



158 **168**

It has been reported that the quenching of dilithiated **158** with methyl iodide cleanly affords 2-ethyl-*N*-(*tert*-butoxycarbonyl)aniline **(169)**.[228] No conditions or yield were reported for this reaction. When this reaction was repeated using the standard conditions described above, and quenched with methyl iodide, this result was not reproduced and only a small amount of the ethyl product **167** was formed. The main compound present was starting material.

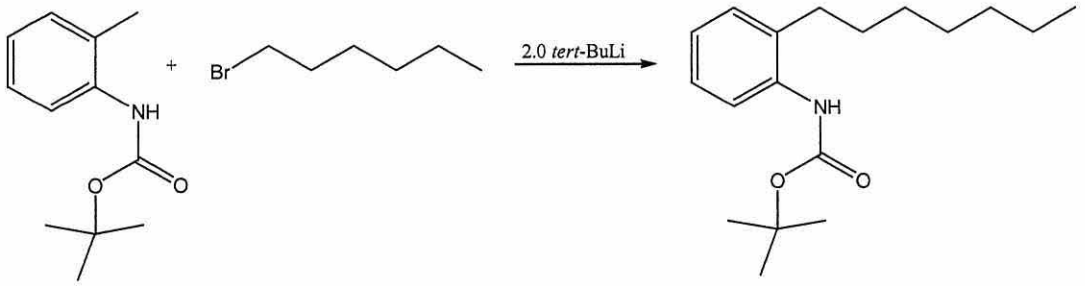


158 **159** **169**

Due to the similar chemical nature of the starting material **158** and the product **169**, the two compounds were not separated by column chromatography. The product was identified by observation of the triplet / quartet splitting pattern for an ethyl group in the ^{1}H NMR at 1.3 ppm and 2.6 ppm, for the CH_3 and CH_2 groups, respectively.

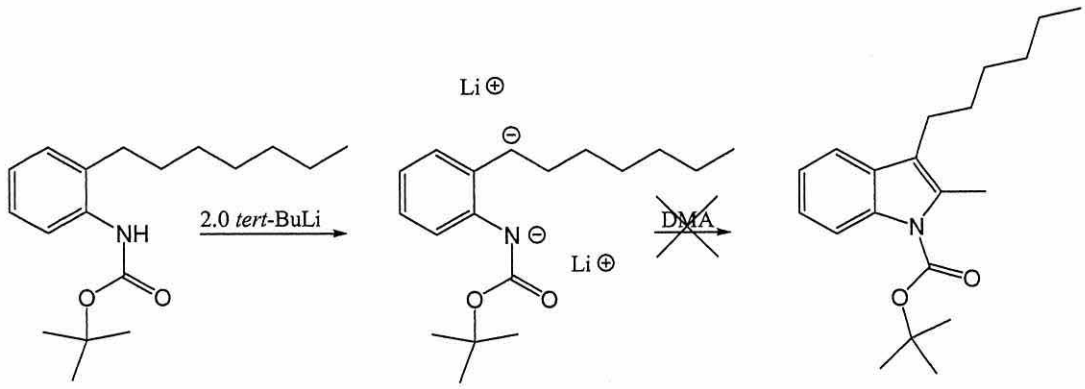
This same type of reaction was therefore repeated with an alkyl halide that would introduce a chemical nature to the product that would be different enough from the starting material that it could be isolated. A solution of 2-methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** in THF was therefore cooled to – 40 °C, deprotonated with two mol. eq. of *tert*-BuLi and quenched with an excess of bromohexane **(170)**. As expected this gave a product of 2-heptyl-*N*-(*tert*-butoxycarbonyl)aniline **(171)**

that was isolated through column chromatography in a 60 % yield as colourless crystals for which elemental analysis was obtained for a product that showed a number of alkyl signals between 0.9 ppm and 1.3 ppm in the ^{1}H NMR, the *tert*-butoxy group singlet at 1.5 ppm, a broad N - H singlet at 6.3 ppm and four aromatic signals between 7.0 ppm and 7.8 ppm, whilst the ^{13}C NMR showed the expected seven alkyl chain signals.



158 **170** **171**

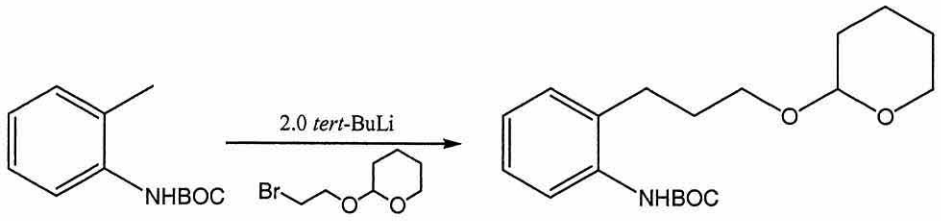
It was therefore attempted to form the indole **(173)** from 2-heptyl-*N*-(*tert*-butoxycarbonyl)aniline **(171)**, using the method that had previously proved successful. The quenching of the dianion **172**, if successful, would lead to a method for the synthesis of 3-substituted indoles. The deprotonation with *tert*-BuLi seemed to occur as usual due to the yellow coloured solution produced. However despite the dissipation of the yellow colour upon quenching, the reaction proved unsuccessful with recovery of the majority of the starting material.



171 **172** **173**

A further attempt was made to produce a 3-substituted indoles via this method through the reaction of a 2-alkyl aniline. For this, bromoethanol was protected with

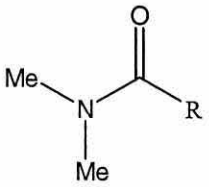
THP with overnight stirring to give 2-(2-bromo-ethoxy)-tetrahydro-pyran in good yield. This was then coupled to 2-methyl-*N*-(*tert*-butoxycarbonyl)aniline to give 2-[3-(tetrahydro-pyran-2-yloxy)-propyl]-*N*-(*tert*-butoxycarbonyl)aniline **(174)** again in good yield. The product gave the correct elemental analysis and the expected seventeen signals were observed in the ^{13}C NMR.



174

However, once again the dilithiation of **174** and quenching with DMF afforded only starting material and the synthesis of a 3-substituted indole was not achieved. One possible explanation for this could be that the alkyl proton is less acidic due to the alkyl chain than a proton on a methyl group.

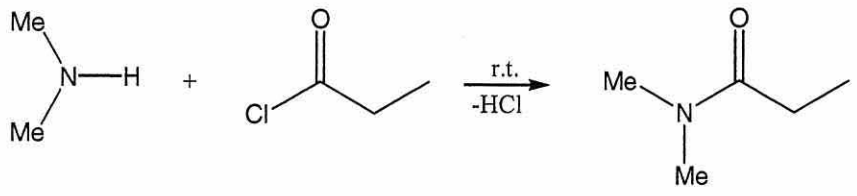
A different approach to extending the range of indoles that could be produced was proposed, due to the quenching reaction with DMA being successful. It was therefore decided next to examine whether it was possible to substitute the R group of the amide quench (**175**, where R = H for DMF and R = Me for DMA) with different groups and therefore selectively to incorporate a range groups onto the indole nucleus.



175

As mentioned previously, literature examples for incorporating a group onto the 2-position of an indole were carried out by quenching of the dianion with Weinreb amides **(175)**. However, these reactions gave a coupled ketone that required a cyclisation reaction with TFA to complete the indole synthesis.

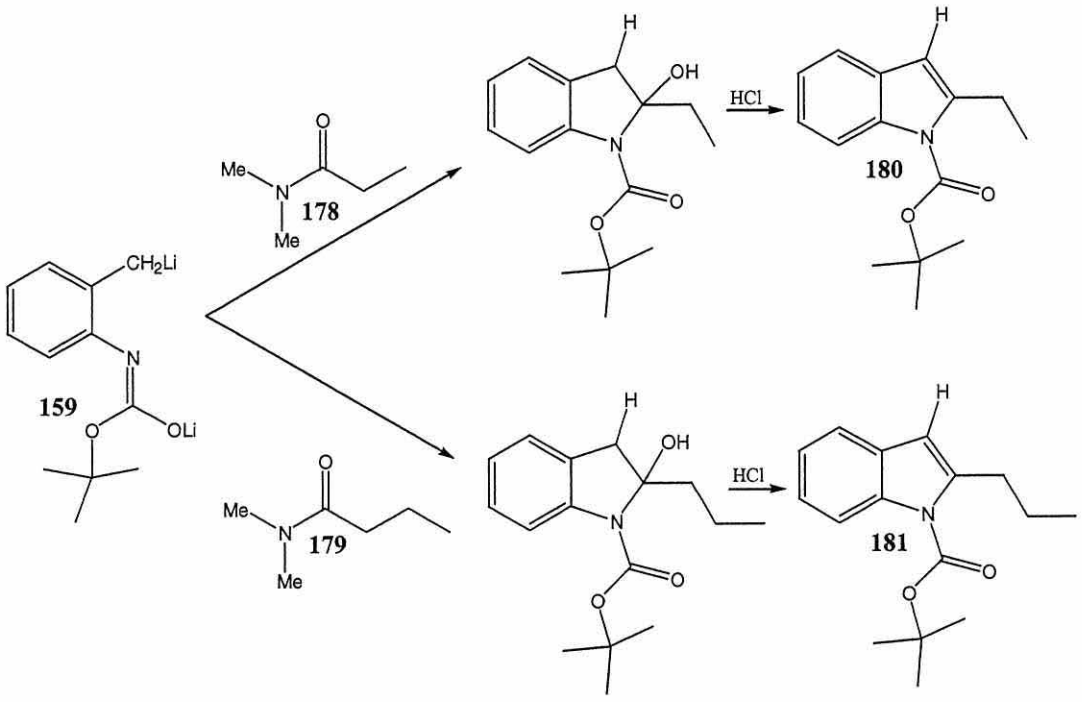
Amides were prepared with the careful exposure of acid chlorides to an aqueous solution of dimethylamine. Dimethylamine **(176)** was therefore reacted with propanoyl chloride **(177)** to give *N,N*-dimethyl-propionamide **(178)**.



176 **177** **178**

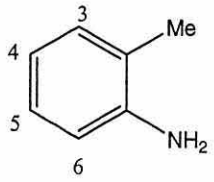
Addition of the chlorides caused the evolution of HCl gas and the internal temperature to rise. After the addition was complete, the reaction was left to stir for an hour, giving good yields of *N,N*-dimethyl-propionamide **(178)** and *N,N*-dimethyl-butyramide **(179)** from the addition of propionyl chloride and butyryl chloride, respectively, to dimethylamine **(176)**. The compounds showed one broad singlet for both the *N*-methyl groups at 3.0 ppm in the ^{1}H NMR due to the nitrogen lone pair being next to the carbonyl group and thus restricting rotation around the C – N bond.

Quenching of the dilithio-species **(159)** with **178** and **179** after deprotonation of 2-methyl-*N*-(*tert*-butoxycarbonyl)aniline under standard conditions followed by treatment with acid gave the corresponding indoles 2-ethyl-*N*-(*tert*-butoxycarbonyl)indole **(180)** and 2-propyl-*N*-(*tert*-butoxycarbonyl)indole **(181),** after the acid work up in equally good yields with ^{1}H NMR spectra that showed the characteristic singlets for the *tert*-butoxy group at 1.7 ppm and for the C-3 proton around 6.4 ppm. Both compounds gave absorptions in the IR at 1732 cm^{-1} for the carbonyl group and gave the expected number of signals in the ^{13}C NMR spectra.



The reactions were found to proceed through the expected alcohol intermediate, as they did with quenching with DMF and DMA, with observation of a single low running spot by TLC after reaction with the amides. Aromatisation to the corresponding indole only required quick treatment with HCl, rather than TFA which was required for the cyclisation reaction when quenching with Weinreb amides. A second advantage of quenching with these reagents is that there is no cleavage of the *tert*-butoxy carbonyl group.

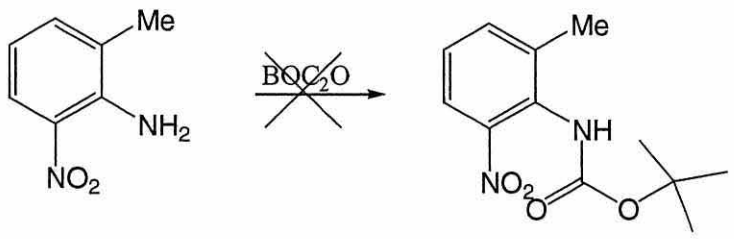
As the aim of this project was to develop a scheme for the synthesis of a range of indoles, substitution on the aromatic ring is an important part in this. As there are many commercially available substituted ortho-toluidines, a selection of these were protected with BOC_2O in the same way that toluidine was. These were then lithiated with *tert*-BuLi and then quenched with either DMF or DMA in an attempt to synthesise functionalised indoles. The results of both stages of these experiments and a comparison of the yields to the initial experiments can be seen below in **Table 5.1**.



Toluidine substitution	BOC substitution yield	**IR carbonyl group / cm^{-1}**	**Quenching agent**	Indole yield	**IR carbonyl** group / cm^{-1}
None	91 %	1676	DMF	56 %	1734
As above	As above	As above	DMA	41 %	1731
6-NO_2	No reaction.	-	-	-	-
6-Me	59 %	1692	DMA	14 %	1737
4,6-Me	48 %	1702	DMA	38 %	1732
3-F	79 %	1690	DMA	23 %	1736
3-NO_2	43 %	1684	DMF	No reaction	-

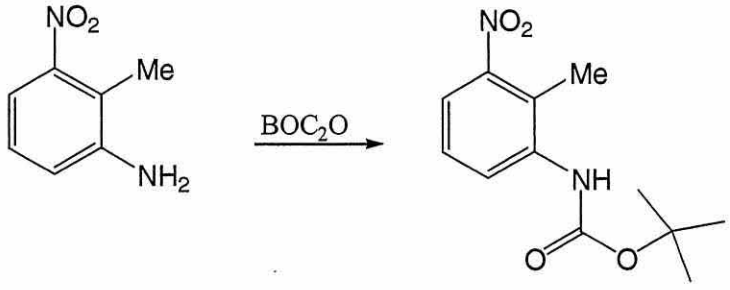
Table 5.1 The BOC protection of substituted toluidines and conversion to indoles

The reaction with 2-methyl-6-nitroaniline **(182)** was found not to work, in the BOC protection stage and starting material was recovered. This could be because of the inductive electron withdrawing properties of the nitro group, making the *ortho*-amine group less reactive or due to steric hindrance.



182

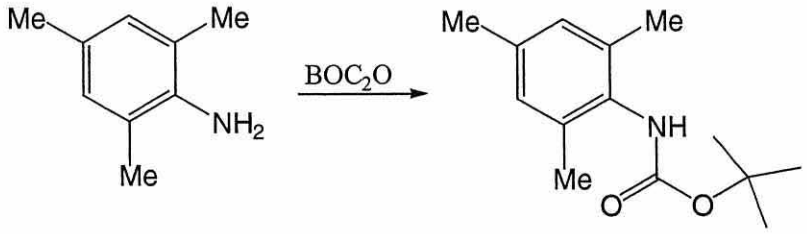
However, with 2-methyl-3-nitroaniline **(183)**, the nitro group is *meta* to the amine group and the electron withdrawing effect on the amine is much less marked and does not prevent the reaction; 2-methyl-3-nitro-*N*-(*tert*-butoxycarbonyl)aniline **(184)** was formed in a reasonable yield.



183 **184**

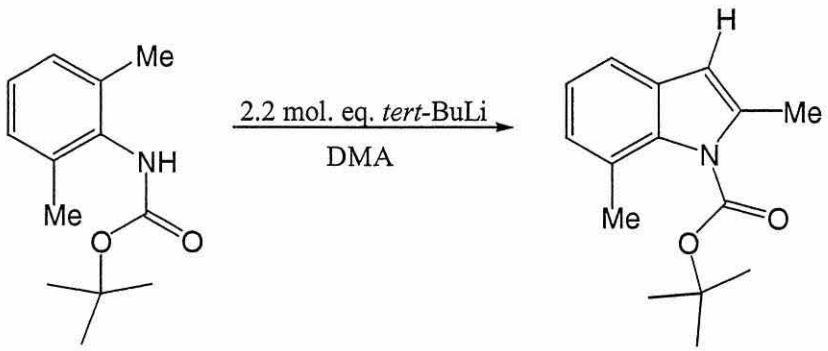
However the indole forming reaction from **184** did not work as addition of the *tert*-BuLi caused the solution to turn a yellow colour immediately before turning a dark brown colour. Quenching with DMF gave no product. The electron withdrawing nitro group is likely to be interfering with the selective deprotonation in this stage of the reaction. Reactions with nitro groups were therefore not continued.

Alkylated toluidines, 2,6-dimethylaniline and 2,4,6-trimethylamine **(185)** were BOC protected in reasonable yields to give 2,6-dimethyl-*N*-(*tert*-butoxycarbonyl)aniline **(187)** and 2,4,6-trimethyl-*N*-(tert-butoxycarbonyl)aniline **(186)**, respectively.



185 **186**

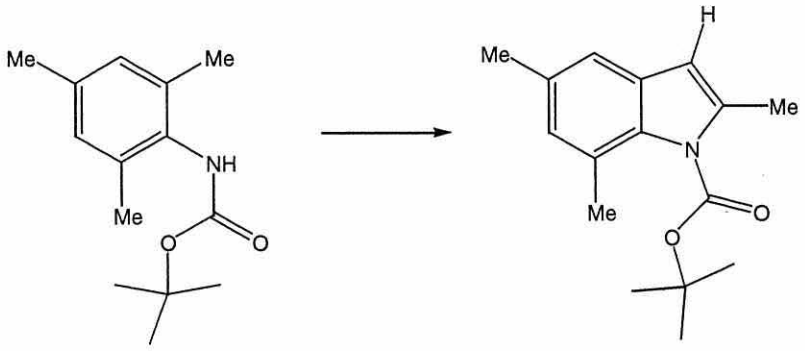
2,6-Dimethyl-*N*-(*tert*-butoxycarbonyl)aniline **(187)** was treated with 2.2 mol. eq. of *tert*-BuLi, with deprotonation of either methyl group leading to the synthesis of 2,7-dimethyl-*N*-(*tert*-butoxycarbonyl)indole **(188)** in a low yield.



187 **188**

The ^{1}H NMR showed signals at 1.7 ppm for the *tert*-butoxy group, at 2.5 for both the methyl groups and three signals between 7.0 ppm and 7.3 ppm for the aromatic protons.

In the synthesis of an indole from 2,4,6-trimethyl-*N*-(tert-butoxycarbonyl)aniline **(186)**, it was possible in theory to deprotonate the *para*-methyl group, so it was as attempted to form the dianion with 3.3 molecular equivalents of *tert*-BuLi. Upon quenching with DMA, this reaction did not work, but when the reaction was repeated with 2.0 molecular equivalents of *tert*-BuLi and quenched with DMA, 2,5,7-trimethyl-*N*-(*tert*-butoxycarbonyl)indole **(189)** was synthesised in a reasonable yield.



186 **189**

This selective deprotonation could be explained due to the electron withdrawing *tert*-butoxycarbonyl-amine group which makes the *ortho*-methyl groups more acidic than the *para*-methyl group, though the coordination of a lithium ion with the *ortho*-related dianion may be a factor.

Indole **189** was found to give an interesting ^{1}H NMR spectrum, for the bulky compound that contains twenty one protons shows no splitting, with seven singlets observed. The characteristic C-3 proton is shown at 6.2 ppm, with the *tert*-butoxy group as the large singlet at 1.7 ppm and the three methyl groups observed between 2.4 ppm and 2.5 ppm. The spectrum is shown in **Figure 5.1**.

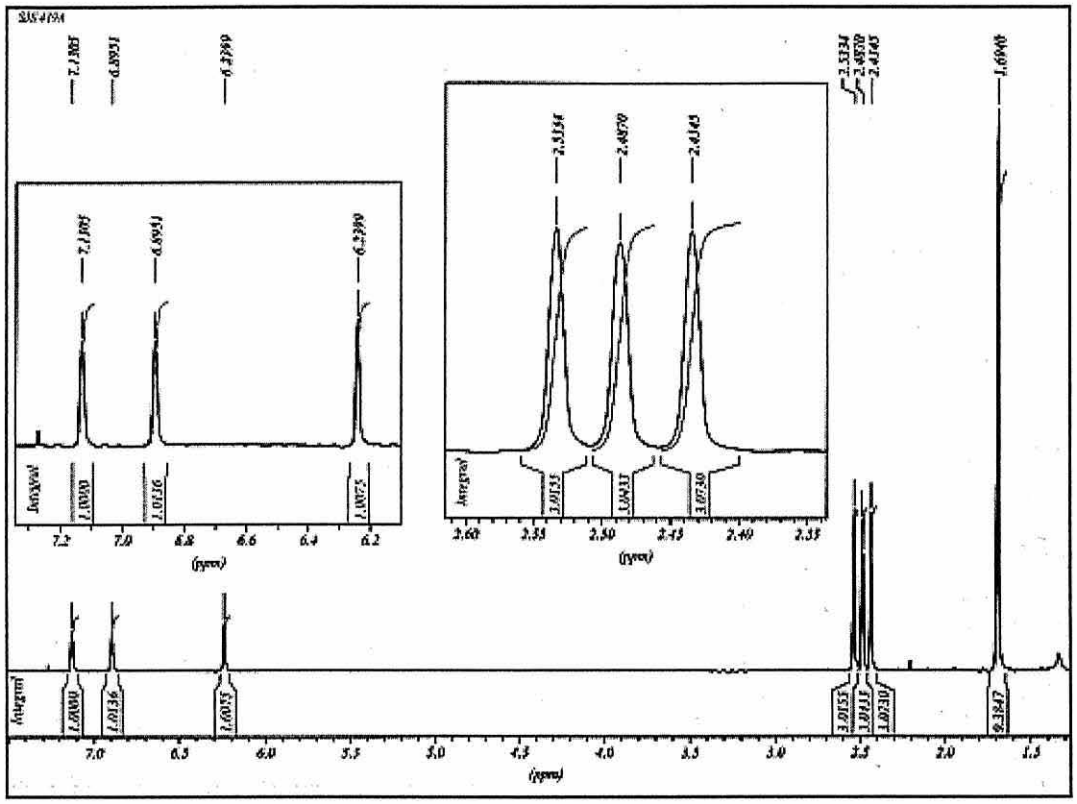
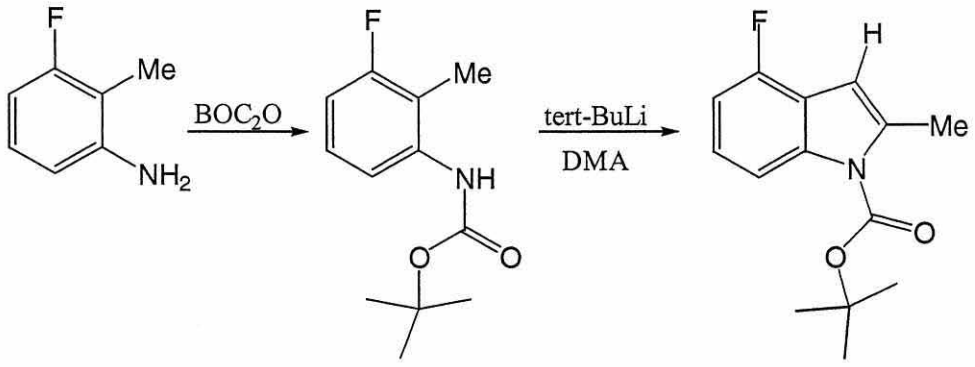


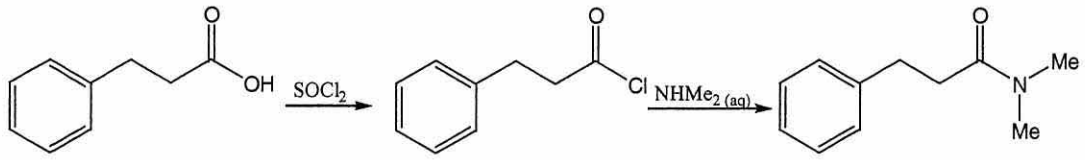
Figure 5.1 The ^{1}H NMR spectrum of 2,5,7-trimethyl-*N*-(*tert*-butoxycarbonyl)indole

Like the previous reactions, the fluorinated toluidine **(190)** was BOC protected in good yield to give **191** that was converted into the 2-methylindole **(192)** with formation of the anion and quenching with DMF.



190 **191** **192**

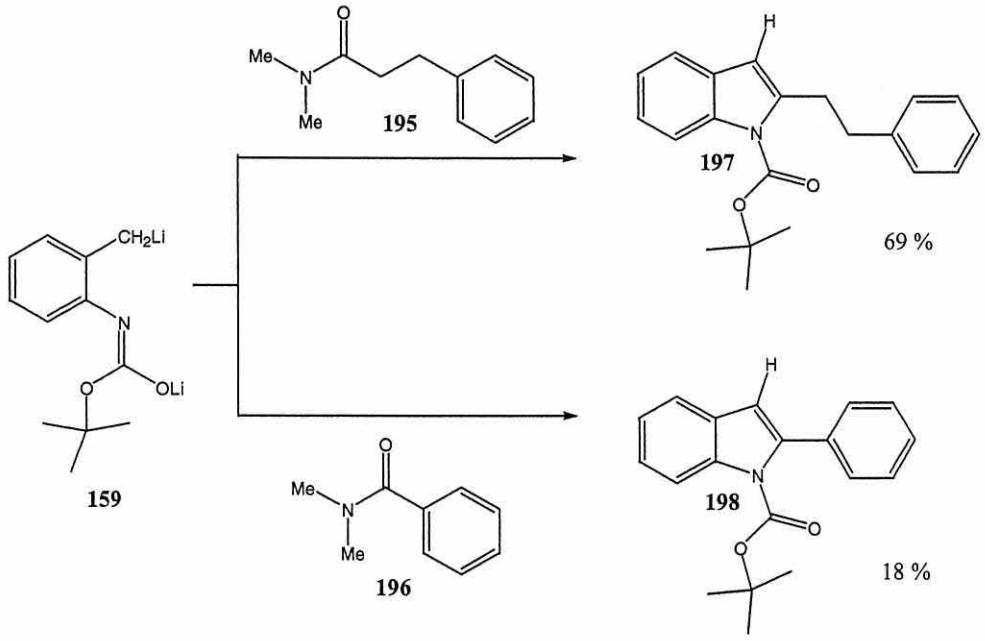
Introducing aromatic groups into the indole with quenching in the same way was therefore examined. 3-Phenylpropionic acid **(193)** was converted into the acid chloride **(194)** in refluxing thionyl chloride for five hours. The excess thionyl chloride was removed and **194** was added to a dimethylamine solution to yield *N,N*-dimethyl-3-phenyl-propionamide **(195)** in good yield.



193 **194** **195**

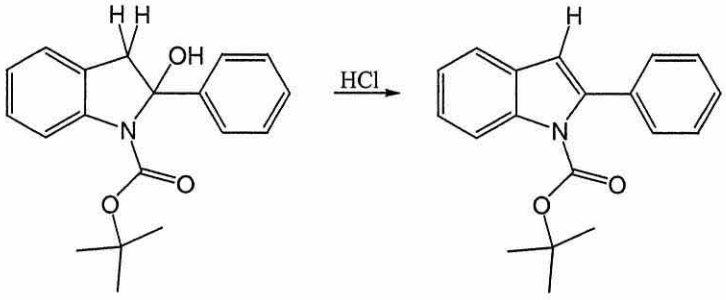
The compound showed two triplets in the ^{1}H NMR for the CH_2-CH_2 group splitting at 2.6 ppm and at 3.0 ppm under the large signal for the methyl groups. The ^{13}C NMR showed the expected nine signals and the IR showed the carbonyl absorption at 1632 cm^{-1}. The reaction was repeated with treatment of benzoyl chloride with a dimethylamine solution, as above, to give the corresponding *N,N*-dimethyl-benzamide **(196)** in good yield.

These amides **195** and **196** were therefore used in reactions with **159** to try to insert aromatic groups onto the 2-position of the indole skeleton, and duly gave the corresponding indoles **197** and **198**.



The *N*-(*tert*-butoxycarbonyl)-2-phenylethynyl indole **(197)** was obtained in a good yield with characteristic signals in the ^{1}H NMR at 1.7 ppm for the *tert*-butoxy group, at 3.1 ppm and 3.4 ppm for the two triplets of the CH_2-CH_2 group and at 6.4 ppm for the C-3 proton, whilst the ^{13}C NMR showed the expected seventeen signals.

However the quenching of **159** with **196** was not as successful, with the alcohol intermediate **199** only being obtained in a 22 % yield. The alcohol **199** was isolated and an elemental analysis obtained. This intermediate was treated with HCl to give *N*-(*tert*-butoxycarbonyl)-2-phenylindole **(200)** in good yield. The overall yield for both steps being 18 %. Compound **200** showed the characteristic C-2 proton in the ^{1}H NMR at 6.6 ppm.

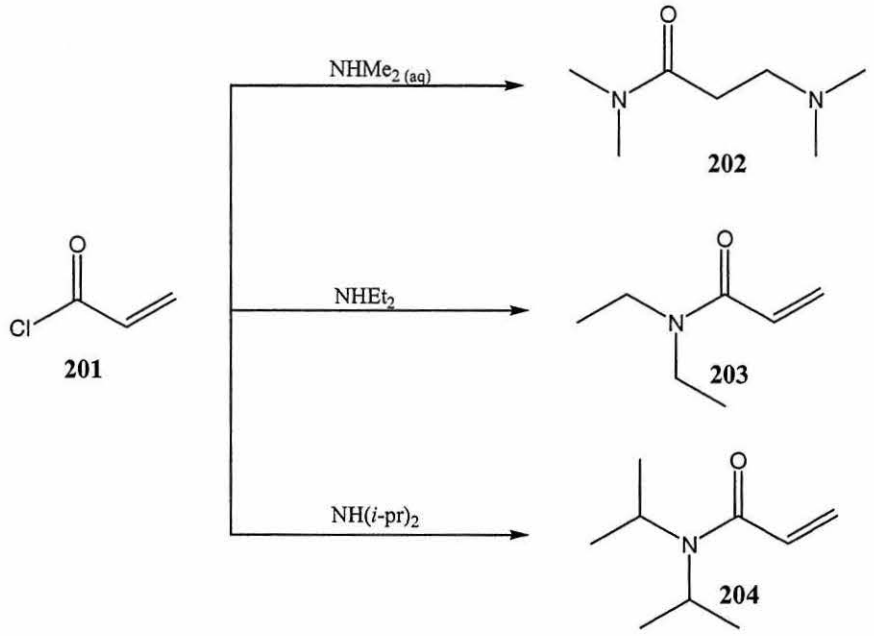


199 **200**

Thus it could be surmised that a range of aromatics could be introduced in this way.

Further functionalisation was sought with the inclusion of an alkene onto the indole structure. To do this, it was attempted to synthesise *N,N*-dimethylacrylamide through the reaction of acryloyl chloride **(201)** with dimethylamine. The only readily available source of dimethylamine was an aqueous solution, therefore this reaction was tried. However, 3-dimethylamino-*N,N*-dimethyl-propionamide **(202)** was isolated in low yield through addition of the dimethylamine across the double bond. This was identified with a singlet in the ^{1}H NMR at 2.2 ppm for the dimethyl group and two separate singlets at 2.9 ppm and 3.0 ppm for the methyl groups adjacent to the carbonyl group. The mass ion was found to be 144. This reaction was repeated with a small amount of hydroquinone, to try and prevent the saturation of the *N,N*-dimethylacrylamide product. However this gave the same product of **202**.

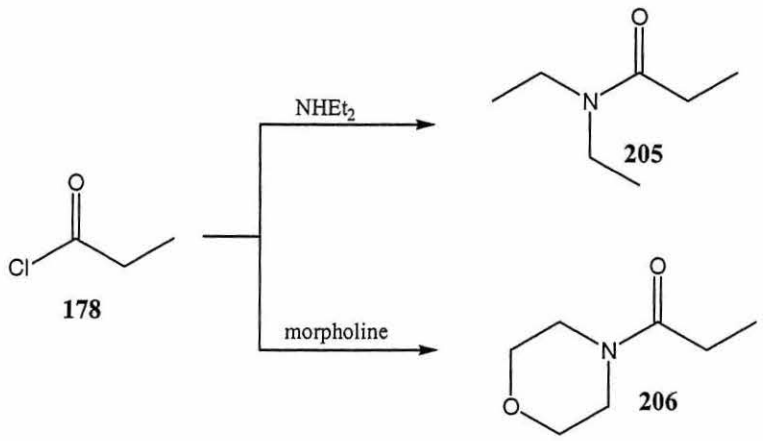
Other amines were then used, under anhydrous conditions, to see if the product of these could be used to quench the reaction. Diethylamine and *N,N*-di-*iso*-propylamine were used to form the corresponding acrylamides, *N,N*-diethylacrylamide **(203)** and *N,N*-di-*iso*-propylacrylamide **(204)** in good yields.



The acrylamides **203** and **204** were then used quench the dianion **159** with the aim of producing 2-vinyl-*N*-(*tert*-butoxycarbonyl)indole. However, after quenching under standard conditions employed for previous reactions, both reactions failed to work and starting material was recovered.

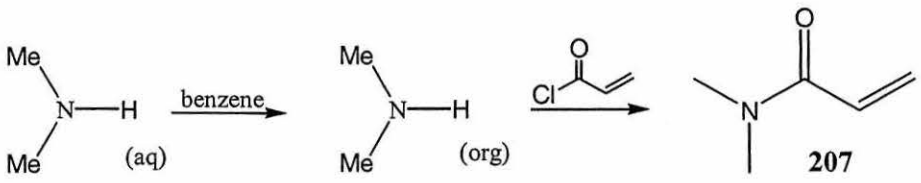
It was not known whether the failure of the reaction could be attributed to the vinyl group or to the nitrogen alkyl groups, as previous reactions had used quenching reagents with dimethylamine groups. It is known that **178** will react with the dianion **159** to give 2-ethyl-*N*-(*tert*-butoxycarbonyl)indole **(180)**. Therefore **178** was replaced with amides with other groups on the nitrogen.

Propionyl chloride **(178)** was reacted with diethylamine and morpholine to give *N,N*-diethyl-propionamide **(205)** and 4-propionyl-morpholine **(206)** in yields of 67 % and 17 %, respectively.



Both these reagents **205** and **206** were used in quenching reactions, the expected product being 2-ethyl-*N*-(*tert*-butoxycarbonyl)indole **(180)**. However, like the previous reactions no product was obtained and starting material was recovered.

Given that these reactions did not work, the conclusion could be drawn that the quenching requires methyl groups on the amine. Dimethylamine aqueous solution was extracted with benzene and the same reaction as above carried out under non-aqueous conditions. This reaction gave the acrylamide **207**.



A quenching reaction was then carried out with **207**, but as in the previous reactions attempting to synthesise 2-vinyl-*N*-(*tert*-butoxycarbonyl)indole, the reaction did not work and only starting material was recovered. The reactions to synthesise this product were therefore abandoned.

5.4 Conclusion

The modified Madelung reaction was found to provide an effective route to a range of indoles cleanly, in serviceable yields. The scope of the reaction can be increased by the combination of the customisable quenching agents that have been found to work to introduce alkyl and aromatic substituents to the indole. When this is coupled with a wide range of commercially available toluidines that were found to work in

differing yields, this method can be used to produce a wide range of indoles. However, all attempts to introduce substitution on the 3-position proved unsuccessful via this method.

6. Indole synthesis summary

This work set out to examine the use of catalytic methods to synthesise indoles.

The Heck reaction was found to synthesise 2-substituted and 2,3-disubstituted indoles in low yield after lengthy reaction times with harsh conditions. The use of unstable palladium (II) catalysts led to the breakdown of the catalytic cycle in some cases, a problem which was magnified by the required length of the reaction. The reactions, when coupling terminal alkynes to iodoaniline, did not commonly provide clean synthesis of the indole. More commonly they gave the coupled uncyclised compound as the major product. The exception to this was with the coupling of terminal alkynes with *N*-substituted iodoaniline, where the indole product was exclusively obtained. Palladacycles were found to be more stable catalysts, and gave higher yields than with conventional palladium catalysts.

Castro type copper (I) iodide catalytic coupling was found to give similar results to the Heck reactions. No indole was obtained, with coupled alkyne the exclusive product. The reactions were carried out at high temperatures over a short reaction time to give clean crystalline products in low yields that commonly required purification to remove the triphenylphosphine used in the reaction. A subsequent short palladium (II) chloride coupling reaction was required to cyclise the alkynes in high yield to 2-phenyl and 2-alkyl-indoles.

Sonogashira coupling was used to synthesis the same products from the previous reactions in diethylamine at room temperature to give alkyne products in high yield that did not require removal of triphenylphosphine. Cyclisation with palladium (II) chloride gave a high yield of indole product. Indoles obtained were 2-phenyl, 2-alkyl and alcohol containing chains in the 2-position where the chain length between the indole and the alcohol group was greater than an ethyl group.

The modified Madelung reaction was used to synthesise indoles with a range of functionalised alkyl and halo-toluidines in good yields through deprotonation with *tert*-BuLi. Through development of a range of quenching reagents, a series of aromatic and alkyl substituents were incorporated onto the 2-position of the indole, with all attempts to produce 2-vinyl and 3-substituted indoles being unsuccessful.

7. Experimental

7.1 General Experimental

Organic solutions were dried using anhydrous magnesium sulfate and solvents were removed at 14mm Hg. Petrol used was of the boiling point range of 40 – 60 °C. Dry diethyl ether and THF were distilled over sodium wire.

The purity of compounds was checked by gas chromatography (GC) using a Perkin-Elmer model F_{17} F.I.D. on a capillary column (30m x 0.32 mm id phase, DB5) with nitrogen carrier gas, and also checked by thin layer chromatography (TLC) which were run using glass silica gel plates coated with silica Kieselgel 60 F254 (Art. 5554; Merck).

Separation of compounds was achieved with column chromatography using Merck 7736 silica gel (Kieselgel 230 – 400 mesh). Columns were base treated by elution of the solvent with a few drops of triethylamine before the compound was put on the column.

NMR spectra were recorded using a Brucker AC250 at 250 MHz for proton spectra and 62.5 MHz for carbon spectra. The spectra were calibrated using tetramethylsilane (TMS) as an internal reference.

Infra Red spectra were obtained as either liquid nujol films on NaCl plates or KBr discs on a Perkin-Elmer 1600 FT-IR spectrometer.

Mass spectras were measured on Hewlett Packard 5970 series mass spectrometer with a mass selective detector.

Methyl lithium was added as a solution in dry ether and its molarity was calculated by regular titration. The amount used is therefore given in molecular equivalents.

7.2 Chapter 2 Experimental

The preparation of 3-chloromethyl-3-methyl-1,2-dichlorocyclopropene (62)

MeLi (1.3 mol. eq.) was added slowly to a cooled solution of 3-chloromethyl-3-methyl-1,1,2,2-tetrachlorocyclopropane **(68)** (2.0 g, 8.3 mmol) in dry ether (20 ml) under an argon atmosphere. After the MeLi addition, the ice bath was removed and the solution allowed to warm to room temperature. The reaction was stirred overnight and then worked up with water (10 ml). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed under vacuum to give *3-chloromethyl-3-methyl-1,2-dichlorocyclopropene* **(62)** (1.4 g, 8.2 mmol, 99.6 %) which showed δ_H 1.6 (3 H, s), 3.9 (2 H, s) which was in agreement with that quoted in the literature.[99]

The preparation of 1,2,4-trichloro-3-methyl-1-(2-propoxy)-buta-1,3-diene (64)

MeLi (1.3 mol. eq.) was added slowly to a cooled solution of 3-chloromethyl-3-methyl-1,1,2,2-tetrachlorocyclopropene **(68)** (2.0 g, 11.7 mmol) in dry ether (20 ml) under an argon atmosphere. When the addition was complete, the ice bath was removed and the solution allowed to warm to room temperature and stirred overnight. Water (10 ml) was added and the organic layer removed, dried ($MgSO_4$) and filtered. The solvent was removed under vacuum and the mixture was treated with acetone (3.0 mol. eq.). The excess acetone removed under vacuum to give an oil that was columned (petrol / ether, 100 : 1), to give a fraction identified as *1,2,4-trichloro-3-methyl-1-(2-propoxy)-buta-1,3-diene* **(64)** (0.9 g, 4.1 mmol, 35 %) which showed δ_H 1.3 (6 H, d, J = 10.4 Hz), 1.9 (3 H, d, J = 1.5 Hz), 4.5 (1 H, septet, J = 6.2 Hz), 6.0 (1 H, q, J = 1.5 Hz); δ_C 19.8, 21.7, 75.6, 113.4, 118.1, 133.7, 141.4 which was in agreement with that quoted in the literature.[234]

The attempted preparation of 1,2,4-trichloro-3-methyl-1-(2-pentoxy)-buta-1,3-diene (64, R = Me, R^1 = n-Pr)

MeLi (1.3 mol. eq.) was added slowly to a cooled solution of 3-chloromethyl-3-methyl-1,1,2,2-tetrachlorocyclopropene **(68)** (2.0 g, 11.7 mmol) in dry ether (20 ml) under an argon atmosphere. When the addition was complete, the ice bath was removed and the solution allowed to warm to room temperature with stirring

overnight. Water (10 ml) was added and the organic layer removed, dried ($MgSO_4$) and filtered. The solvent was removed under vacuum and the mixture worked up with pentan-2-one (2.3 g, 3.0 mol. eq.) at room temperature overnight, after which TLC and GC both showed a number of products. Excess pentan-2-one was evaporated under vacuum to give an oil (1.3 g) that crude ^1H NMR showed a large alkyl region (0.7 – 2.5 ppm) but did not contain the characteristic signals of a multiplet for the proton adjacent to the oxygen in a successful reaction around 4.5 ppm, nor a singlet for the alkene proton at 6.0 ppm.

The attempted preparation of 1,2,4-trichloro-3-methyl-1-(2-pentoxy)-buta-1,3-diene (64, R = H, R^1 = Ph)

MeLi (1.3 mol. eq.) was added slowly to a cooled solution of 3-chloromethyl-3-methyl-1,1,2,2-tetrachlorocyclopropene **(68)** (2.0 g, 11.7 mmol) in dry ether (20 ml) under an argon atmosphere. When the addition was complete, the ice bath was removed and the solution allowed to warm to room temperature overnight with stirring. Water (10 ml) was added and the organic layer removed, dried ($MgSO_4$) and filtered. The solvent was removed under vacuum and the mixture was treated with freshly distilled benzaldehyde (3.0 mol. eq.) at room temperature. After a day, ^1H NMR showed a spectrum of unreacted benzaldehyde with no characteristic proton signals for the trapped product at 4.5 ppm and 6.0 ppm, as above.

The preparation of 1,1,3-trichloro-2-methyl-1-propene (67)

Thionyl chloride (300 ml) was added slowly with stirring to a cooled mixture of 1,1,1-trichloro-2-methyl-2-propanol (177 g, 1.0 mol) and tetrabutylammonium bromide (1.9 g, 5.9 mmol). The mixture was stirred at 0 °C for 20 min then potassium iodide (2.5 g, 15.1 mmol) was added and the mixture was refluxed for 72 h after which time ^1H NMR showed that no starting material was left. The excess thionyl chloride was removed by distillation and the residue was distilled at 95 °C to give *1,1,3-trichloro-2-methyl-1-propene* **(67)** (150 g, 0.94 mmol, 94 %) which showed δ_H 2.1 (3 H, s), 4.4 (2 H, s) which was in agreement with that quoted in the literature.[235]

The preparation of 3-chloromethyl-3-methyl-1,1,2,2-tetrachlorocyclopropane (68)

Sodium hydroxide (250 g) in water (250 ml) was added slowly to a solution of 1,1,3-trichloro-2-methyl-1-propene **(67)** (100.0 g, 0.63 mol) and cetrimide (5.0 g, 13.7 mmol) in chloroform (450 ml). The mixture was cooled to room temperature and stirred rapidly for 5 days after which time G.C. showed that there was no starting material. The mixture was worked up with brine solution (250 ml) and extracted with dichloromethane (300 ml). The organic layer was vigorously stirred with petrol (400 ml), dried ($MgSO_4$), filtered and the solvent removed under vacuum to give *3-chloromethyl-3-methyl-1,1,2,2-tetrachlorocyclopropane* **(68)** (41.0 g, 0.17 mol, 27 %) which showed δ_H 1.6 (3 H, s), 3.7 (2 H, s), in agreement with that quoted in the literature.[99]

The attempted preparation of 1,2,4-trichloro-3-methyl-1-(2-propoxy)-5,6-tetracyano-cyclohex-2-ene (70)

MeLi (1.3 mol. eq.) was added slowly to a cooled solution of 3-chloromethyl-3-methyl-1,1,2,2-tetrachlorocyclopropane (2.0 g, 11.7 mmol) in dry ether (20 ml) under an argon atmosphere. When the addition was complete, the ice bath was removed and the solution allowed to warm to room temperature with stirring for 15 min. Water (10 ml) was added and the organic layer removed, dried ($MgSO_4$) and filtered. Acetone (1.44 g, 24.8 mmol) and TCNE (0.55 g, 4.3 mmol) were added and the solution stirred overnight. The solvent was evaporated to give a brown solid (1.8 g); ^1H NMR showed a complex mix of signals and TLC a number of spots that did not appear to contain either the uncyclised or cyclised product through lack of characteristic peaks. The solid was columned (petrol / ether) to give a large number of fractions that ^1H NMR signals not present in the crude NMR that indicated that the sample had decomposed during purification attempts.

The preparation of 2-methyl-1,7-dichloro-1,2-indene (74) and 3-methyl-1,2-dichloro-1,2-indene (76)

3-Phenyl-3-methyl-1,1,2,2-tetrachlorocyclopropane **(85)** (0.5 g, 1.85 mmol) was dissolved in dry ether (4 ml) under an argon atmosphere and MeLi (1.2 mol. eq.) was added whilst cooling the flask in an ice bath. Once addition was complete the ice bath was removed and the solution allowed to warm to room temperature. After

stirring for 3 h, the reaction was quenched with water and the product extracted with ether. The organic phase was dried ($MgSO_4$), filtered and the solvent removed under vacuum. The crude liquid product (0.16 g, 0.80 mmol, 43 %) was shown by NMR to contain two products in the ratio 10 : 1. Flash chromatography (petrol) gave a major product characterised as *2-methyl-1,7-dichloro-1,2-indene* **(74)**. Required for $C_{10}H_8Cl_2$: C, 60.5 ; H, 4.3, found: C, 60.6 ; H, 4.1, that showed δ_H 2.1 (3 H, s), 5.2 (1 H, s), 7.3 (4 H, m); δ_C 10.6, 60.4, 119.3, 124.1, 126.7, 129.1, 132.9, 137.4, 141.6 142.0; ν_{max} 3070, 1624, 1458, 1380, 782 cm^{-1}. A minor product that was not isolated but was characterised on the basis of ^1H NMR as *3-methyl-1,2-dichloro-1,2-indene* **(76)**; δ_H 1.4 (3 H, d, J = 7.2 Hz), 3.55 (1 H, q, J = 7.2 Hz), 7.3 (4 H, m).

The preparation of 1,1-dichloro-2-phenylpropene (79, X = H)

Triphenylphosphine (2 mol. eq.) was added to a stirring and refluxing mixture of acetophenone (30 g, 0.25 mol), dissolved in CCl_4 (300 ml). The mixture was stirred under reflux for 24 h and was worked up by vigorous stirring with petrol. The organic phase was concentrated under vacuum to give a pale yellow oil. Flash chromatography removed the residue of acetophenone to leave the residue of the distillation, which was characterised as *1,1-dichloro-2-phenylpropene* **(79, X = H)** (20.1 g, 0.11 mol, 43 %) as an oil which showed δ_H 2.2 (3 H, s), 7.3 (5 H, m); δ_C 23.1, 112.7, 117.1, 127.8, 128.4, 135.8, 140.1; ν_{max} 3058, 3023, 2919, 1492, 1443, 1013, 898 cm^{-1}; m/z 188, 186, 184, 116, which was in agreement with that quoted in the literature.[236]

The preparation of 1,1-dichloro-2-(4-methoxyphenyl)propene (79, X = OMe)

Triphenylphosphine (2 mol. eq.) was added to a refluxing mixture of *p*-methoxyacetophenone (5 g, 33 mmol) dissolved in CCl_4 (100 ml) and was stirred under reflux for 24 h. The reaction was allowed to cool and was worked up by vigorous stirring with petrol. The solvent was removed under vacuum to give a thick oil that was identified as *1,1-dichloro-2-(4-methoxyphenyl)propene* **(79, X = OMe)** (6.6 g, 30.45 mmol, 92 %). Required for $C_{10}H_{10}OCl_2$: C, 55.3; H, 4.6; found C, 55.4; H, 4.6 which showed δ_H 2.2 (3 H, s), 3.8 (3 H, s), 6.9 (2 H, d, J = 10.7 Hz), 7.2 (2 H, d, J = 10.7 Hz); δ_C 23.1, 55.2, 113.6, 128.6, 129.1, 135.3, 159.0; ν_{max} 1897, 1606, 1509, 1299, 1023, 900 cm^{-1}; m/z 217.

The preparation of 1,1-dichloro-2-(4-nitrophenyl)propene (79, X = NO_2)

Triphenylphosphine (2 mol. eq.) and 4-nitroacetophenone (5 g, 30 mmol), dissolved in CCl_4 (300 ml) were stirred under reflux for 24 h. The solution was cooled and rapidly stirred with petrol. The solvent was removed under vacuum and flash chromatography gave an oil identified as *1,1-dichloro-2-(4-nitrophenyl)propene* **(79, X = NO_2)** (4.51 g, 20 mmol, 65 %). Required for $C_9H_7NO_2Cl_2$: C, 46.6; H, 3.0; N, 6.0; found C, 46.8; H, 2.9; N, 6.0 which showed δ_H 2.2 (3 H, s), 7.4 (2 H, d, J = 7.1 Hz), 8.2 (2 H, d, J = 7.1 Hz); δ_C 20.0, 118.0, 124.0, 128.0, 134.0, 146.0, 147.0; ν_{max} 1597, 1518, 1348, 785, 754 cm^{-1}.

The preparation of 3-(4-nitrophenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane (80, X = NO_2)

3-Phenyl-3-methyl-1,1,2,2-tetrachlorocyclopropane **(85)** (97 mg; 2.2 mmol) was dissolved in CCl_4 (25 ml) whilst cooling the flask in an ice bath. A portion of nitration mixture (0.5 ml) prepared from the dropwise addition of conc. sulfuric acid (12 ml) to ice cooled conc. nitric acid (10 ml). The mixture was stirred overnight and the solvent allowed to evaporate. Water (20 ml) was added and the solution extracted with ether (2 x 20 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent removed under vacuum. The white powder obtained was washed with ether and petrol (1 : 1) to give a pale yellow powder that was characterised as *3-(4-nitrophenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane* **(80, X = NO_2)** (67 mg, 59 %), mp 117 - 122 °C (Found: C, 38.2; H, 2.2; N, 4.2. Required for $C_{10}H_7Cl_4NO_2$: C, 38.1; H, 2.4; N, 4.4) which showed δ_H 1.8 (3 H, s), 7.6 (2 H, d, J = 17.1 Hz), 8.3 (2 H, d, J = 7.1 Hz); δ_C 25.7, 68.9, 123.7, 130.6, 135.7, 156.4, 169.0; m/z 314; ν_{max} 858, 1351, 1522 cm^{-1}. This reaction was carried out by Silvia Benedetti.[197]

The attempted preparation of 2-methyl-1,7-dichloro-5-nitro-1,2-indene (80, X = NO_2)

3-(4-Nitrophenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(80, X = NO_2)** (0.24 g; 0.76 mmol) was dissolved in dry ether (4 ml) under an argon atmosphere. MeLi (1.2 mol. eq.) was added whilst cooling the flask on an ice bath. The mixture was stirred for 3 h at room temperature after which time the solution was a dark brown colour. The reaction was quenched with water and the product extracted with ether. The organic phase was dried ($MgSO_4$), filtered and the solvent removed under vacuum.

Crude ^{1}H NMR of the brown oil showed a complex spectra that no longer contained the aromatic signals of the starting material at 7.7 and 8.4 ppm but more importantly did not contain the visible signal that the expected cyclisation had occurred with a singlet at 5.2 ppm.

The preparation of 3-(4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane (81)

Cetrimide (3.4 g) was added to a solution of 1,1-dichloro-2-(4-methoxyphenyl)propene **(79, X = OMe)** (6.6 g, 24 mmol) in chloroform (150 ml). Whilst cooling the flask in an ice bath, a solution of sodium hydroxide (49 g in 49 ml water) was added slowly. The mixture was stirred vigorously and refluxed over 3 days then worked up with chloroform and sat. aq. sodium chloride. The solution was extracted with ether, the organic layer dried ($MgSO_4$), filtered and the solvent removed under vacuum. The mixture was treated with chloroform (150 ml), cetrimide (3.4 g) and a solution of sodium hydroxide (49 g in 49 ml water) as above, and stirred under reflux for 4 days. The solid isolated was columned (petrol / ether, 5 : 0.1) to give a major product that was identified as *3-(4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane* **(81)** (1.1 g, 16 %), mp 88 - 91 °C (Found: C, 44.3; H, 3.4. Required for $C_{11}H_{10}C1_4O$: C, 44.0; H, 3.4) which showed δ_H 1.7 (3 H, s), 3.8 (3 H, s), 6.9 (2 H, d, J = 7.2 Hz), 7.3 (2 H, d, J = 7.2 Hz); δ_C 26.2, 44.6, 55.3, 113.8, 129.5, 130.5, 158.9; ν_{max} 903, 1035, 1295, 1514, 1608, 2048, 2834, 2934 cm^{-1}. This reaction was carried out by Silvia Benedetti.[197]

The preparation of 3-(3-bromo-4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane (82)

One molecular equivalent of bromine (0.09 ml, 1.75 mmol) was added to a stirred mixture of 3-(4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(81)** (0.5 g, 1.67 mmol) with an iron filing catalyst (0.2 g, 3.58 mmol) in CCl_4 (2.2 ml) at 50 °C. After 30 min the heating was removed and the mixture stirred for 48 h. Ether (10 ml) was then added and the products were treated with sat. aq. sodium bisulfite (20 ml) and aqueous sodium hydroxide (20 ml, 2 M) and extracted with ether. The organic layer was dried ($MgSO_4$) and the solvent removed under vacuum. Flash chromatography (petrol / ether, 9 : 1) gave a major solid product identified as *3-(3-bromo-4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane* **(82)** (0.17 g,

0.45 mmol, 27 %), m.p. 139 - 141 °C. Required for $C_{11}H_9Cl_4OBr$: C, 34.9; H, 2.4; found: C, 35.0; H, 2.4, which showed δ_H as 1.7 (3 H, s), 3.9 (3 H, s), 6.9 (1 H, d, J = 8.6 Hz), 7.3 (1 H, dd, J = 2.4, 8.7 Hz), 7.6 (1 H, d, J = 2.2 Hz); δ_C 26.0, 56.3, 111.6, 129.6, 134.2; ν_{max} 1050, 1288 cm^{-1}.

The preparation of 3-(3,5-dibromo-4-hydroxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane (84)

Two molecular equivalents of bromine (0.18ml, 3.5 mmol) were added to a stirred mixture of 3-(4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(81)** (0.5g, 1.7 mmol) with an iron filing catalyst (0.2 g, 3.6 mmol) in CCl_4 (2.2 ml) at 50 °C. After 30 min the heating was removed and the mixture stirred for 48 h. Ether (10 ml) was then added and the products were treated with sat. aq. sodium bisulfite (20 ml) and aq. sodium hydroxide (20 ml, 2 M) and extracted with ether. The organic layer was dried ($MgSO_4$), filtered and the solvent removed under vacuum to give a solid identified as *3-(3,5-dibromo-4-hydroxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane* **(84)** (0.43 g, 0.97 mmol, 58 %), m.p. 130 - 132 °C. Required for $C_{10}H_6Cl_4OBr_2$: C, 27.1; H, 1.4; found: C, 27.0; H, 1.4, which showed δ_H 1.8 (3H, s), 6.0 (1H, s), 7.5 (2H, s); δ_C 25.9, 43.6, 71.3, 109.6, 131.5, 133.0, 149.1; ν_{max} 3483 cm^{-1}.

The preparation of 3-phenyl-3-methyl-1,1,2,2-tetrachlorocyclopropane (85)

Cetrimide (3 g) was added to a solution of 1,1-dichloro-2-phenyl-propene **(79, X = H)** (20 g, 0.11 mol) in chloroform (130 ml). Whilst cooling the flask in an ice bath, a solution of sodium hydroxide (50 g in 50 ml water) was added slowly. The mixture was stirred vigorously and refluxed for 12 h, then worked up with dichloromethane and sat. aq. sodium chloride. To remove the remaining cetrimide, the mixture was washed with ether. A solid was obtained, which was treated again with chloroform (75 ml), cetrimide (2.0 g) and sodium hydroxide (30 g in 30 ml water) as above. After 84 h the mixture was worked up as above, and treated again with chloroform (75 ml), cetrimide (2 g) and sodium hydroxide (30 g in 30 ml water). After 12 h, the mixture was worked up. The organic layer was dried ($MgSO_4$), filtered and the solvent removed under vacuum. Brown crystals were obtained, which were recrystallised from methanol. The yellow powder obtained was characterised as *3-*

phenyl-3-melhyl-1,1,2,2-tetrachlorocyclopropane **(85)** (44.6 mmol, 42 %), m.p. 45 - 47 °C, (Found: C, 44.5; H, 3.2. Required for $C_{10}H_8C1_4$: C, 44.5; H, 3.0) which showed δ_H 1.7 (3 H, s), 7.2 (5 H, m); δ_C 26.3, 45.1, 71.8, 127.6, 128.4, 129.4, 137.4; m/z 233; ν_{max} 700, 759, 853 cm^{-1}. This reaction was carried out by Silvia Benedetti.[197]

The attempted preparation of 2-methyl-1,7-dichloro-7-carboxylic acid-indene (89)

3-Phenyl-3-methyl-1,1,2,2-tetrachlorocyclopropane **(85)** (0.5 g, 1.85 mmol) was dissolved in dry ether (20 ml) under an argon atmosphere. MeLi (2 mol. eq.) was added whilst cooling the flask in an ice bath and the mixture was stirred for 6 h at room temperature. The reaction was quenched with an excess of solid carbon dioxide (10 g, 230 mmol) whilst being cooled in a water bath. The reaction was left stirring until the carbon dioxide had all evaporated and aqueous sodium bicarbonate was added until the aqueous layer was neutral to pH paper, to transfer the product to the aqueous layer. The organic phase was removed, dried ($MgSO_4$), filtered and the solvent removed under vacuum to give 300 mg of oil. Concentrated HCl was added to acidify the aqueous layer and ether was added (20ml) to transfer the product back into the organic layer. The second organic phase was removed, dried ($MgSO_4$), filtered and the solvent removed under vacuum to give 23 mg of oil. This analysis of both oils showed complex ^1H NMR's that did not show the expected acid, nor the simple indene.

The preparation of 2-methyl-1,7-dichloro-5-methoxy-1,2-indene (90)

3-(4-Methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(80, X = Me)** (1.05 g; 3.48 mmol) was dissolved in dry ether (5 ml) under an argon atmosphere. MeLi (1.2 mol. eq.) was added while cooling the flask in an ice bath. The mixture was stirred at room temperature for 3 h. The reaction was quenched with water and the product extracted with ether. The organic phase was dried ($MgSO_4$) and the solvent removed under vacuum. NMR on the crude reaction product (0.74 g, 93 %) showed the presence of two indene isomers in the ratio 1.0 : 2.6. Flash chromatography failed to separate the isomers completely, with the minor isomer not isolated, but identified with a quartet partially concealed under the methoxy singlet at 3.8 ppm for the major isomer. This was identified as *1,7-dichloro-2-methyl-5-methoxy-1,2-indene* **(90)**,

obtained pure by recrystallisation, mp 101 - 102 °C, (Required for $C_{10}H_{10}Cl_2O$: C, 47.7; H, 4.4; found C, 47.8; H, 4.4), which showed δ_H 2.1 (3 H, s), 3.8 (3 H, s), 5.1 (1 H, s), 6.8 (1 H, d, J = 7.2 Hz), 7.1 (1 H, d, J = 7.2 Hz), 7.3 (1 H, s); δ_C 10.5, 55.4, 60.1, 11.1, 113.5, 119.6, 134.5, 136.9, 143.1, 156.1, 159.0; ν_{max} 3017, 2944, 2841, 1618, 1477, 1294, 1237, 1021, 821 cm^{-1}.

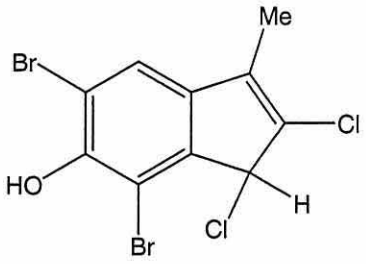
The preparation of 2-methyl-1,7-dichloro-4-bromo-5-methoxy-1,2-indene (92) and 2-methyl-1,7-dichloro-6-bromo-5-methoxy-1,2-indene (93)

3-(3-Bromo-4-methoxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(82)** (0.6 g, 1.58 mmol) was dissolved in dry ether (20 ml) under an argon atmosphere. MeLi (1.3 mol. eq.) was added whilst cooling the flask on an ice bath and the mixture was stirred at room temperature for 3 h. The reaction was quenched with water and the product extracted with ether. The organic phase was dried ($MgSO_4$), filtered and the solvent removed under vacuum to give yellow crystals of two indene isomers that on repeated recrystallisation gave only enriched samples of both isomers that were identified on the basis of ^1H NMR as *2-methyl-1,7-dichloro-4-bromo-5-methoxy-1,2-indene* **(92)** δ_H 2.08 (3 H, s), 3.94 (3 H, s), 5.09 (1 H, s), 7.1 (1 H, s), 7.4 (1 H, s) and *2-methyl-1,7-dichloro-6-bromo-5-methoxy-1,2-indene* **(93)** δ_H 2.07 (3 H, s), 3.90 (3 H, s), 5.14 (1 H, s), 6.8 (1 H, d, J = 8.2 Hz), 7.1 (1 H, d, J = 8.0 Hz) (0.4 g, 1.3 mmol, 82 %) in a ratio of 55 : 45 %, (Required for $C_{11}H_9BrCl_2O$: C, 42.9; H, 3.0; found C, 42.6; H, 2.9), which showed m.p. 116 – 118 °C; ν_{max} 1038, 1259 cm^{-1}.

The attempted preparation of 2-methyl-1,7-dichloro-4,6-dibromo-5-hydroxy-1,2-indene (92a)

3-(3,5-Dibromo-4-hydroxyphenyl)-3-methyl-1,1,2,2-tetrachlorocyclopropane **(84)** (0.26 g, 0.59 mmol) was dissolved in dry ether (8 ml) under an argon atmosphere. MeLi (3 mol. eq.) was added whilst cooling the flask on an ice bath and then the mixture was stirred at room temperature for 3 h, during which time the solution changed from a red / orange colour to dark brown. The reaction was quenched with water and the organic layer removed, dried ($MgSO_4$), filtered and the solvent evaporated to give 11 mg of an orange oil. As it was apparent that the vast majority of organic material had not been extracted by the organic layer, concentrated hydrochloric acid was added until the aqueous layer was acid to pH paper to remove any salt of the product. The aqueous layer was then extracted with ether and dried

($MgSO_4$), filtered and concentrated to give 68 mg of a brown oil. Analysis of both organic layers by ^1H NMR showed the starting material to have reacted to a number of compounds with no indole product present in the mixture based on the absence of a singlet for the C3 proton at 5.2 ppm.



92a

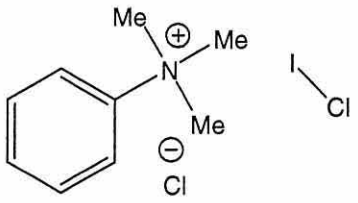
7.3 Chapter 3 Experimental

The preparation of 3-iodo-4-acetamidobenzoic acid (96)

BTMA-ICl_2 (2.6 g, 7.5 mmol) was added to a solution of *p*-aminobenzoic acid **(98)** (1.0 g, 7.3 mmol) in acetic acid (100 ml) and the reaction stirred overnight. The solid was collected by filtration, washed with DCM and dried in a desiccator to give a brown solid which was the iodo derivative **(99)** (0.38 g, 1.45 mmol, 20 %). The crude product (0.32 g) was then dissolved in acetic acid (6 ml) and acetic anhydride (0.23 ml) added and the reaction stirred at room temperature overnight. TLC after this time showed that the reaction had stopped, so extra acetic anhydride (0.05 ml) was added and 2 h later the reaction was shown to be complete. The solution was concentrated *in vacuo* and a white powder collected by filtration, dried in a vacuum desiccator overnight to remove traces of acetic acid and identified as *3-iodo-4-acetamidobenzoic acid* **(96)** (0.27 g, 0.9 mmol, 12 %), m.p. 250 - 251 °C (lit.,[237] 230 °C). This compound was found to be particularly insoluble in conventional NMR deuterated solvents, so a small amount was methylated with diazomethane to give *3-iodo-4-acetamidobenzoic acid methyl ester* which showed δ_H 2.3 (3 H, s), 3.9 (3 H, s), 7.6 (1 H, br. s), 8.0 (1 H, dd, J = 1.8, 8.9 Hz), 8.4 (1 H, d, J = 8.5 Hz), 8.5 (1 H, d, J = 1.8 Hz) which was in agreement with that quoted in the literature.[204]

The preparation of benzyltrimethylammonium iodine dichloride (96a)

A solution of iodine monochloride (8.1 g, 0.05 mol) in dichloromethane (100 ml) was added dropwise to a solution of benzyltrimethylammonium chloride (9.3 g, 0.05 mol) in water (50 ml). The mixture was stirred at room temperature for 30 min. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The brilliant yellow needles were then collected by filtration and dried in a desiccator over for a couple of days and were identified as *benzyltrimethylammonium iodine dichloride* **(96a)** (12.5 g, 72 %) m.p. 121 -123 °C, (lit.,[205] 125 - 126 °C). Required for $C_{10}H_{16}NCl_2I$: C, 34.5; H, 4.6; N, 4.0; found C, 34.5; H, 4.7; N, 4.3 which showed ν_{max} 1406 cm^{-1} which was in agreement with that quoted in the literature.[205]



99a

The loading of Wang resin with a Mitsunobu coupling (97)

3-Iodo-4-acetamidobenzoic acid **(96)** (1.0 g, 3.3 mmol, 5 mol. eq.) was dissolved in THF (10 ml) under an argon atmosphere and Wang resin **(102)** (0.21 g, 3.2 $mmolg^{-1}$) was added. Triphenylphosphine (1.7 g, 6.7 mmol, 10 mol. eq.) was then added and a 2 M solution of DEAD **(103)** (1.1 g, 6.7 mmol, 10 mol. eq.) in THF (3.3 ml) was added dropwise to the mixture on an ice bath. The mixture was stirred at room temperature for 4 h, filtered on a sinter and washed with portions (10 ml) of THF, methanol and ether. The resin was dried in a desiccator and identified as loaded *Wang resin* **(97)** with C, 71.5; H, 6.1; N, 2.5 that showed ν_{max} 1719, 3382 cm^{-1}.

The attempted Heck coupling of the loaded resin 97

Ten molecular equivalents of TMG (0.84 ml, 6.7 mmol) was added to dioxane (25 ml) along with copper iodide (0.64 g, 3.4 mmol) and dichlorobis(triphenylphosphine) palladium (II) (0.1 g, 0.13 mmol). A portion of loaded resin **(97)** (0.40 g, 3.2 $mmolg^{-1}$) and six molecular equivalents of phenylacetylene (0.41 g, 4.0 mmol) were added and the reaction mixture was heated at 90 °C with gentle stirring for 18 h. The resin was filtered on a sinter and washed with portions of dioxane, ether, methanol and THF before drying to give a brown solid (0.37 g). Cleavage of the resin bound indole was attempted with TFA in DCM (50 ml, 30 %) with stirring for 2 h. This yielded an oil (23 mg) that analysis of the cleaved product with ^1H NMR showed a complex aromatic and alkyl regions, with no characteristic indole proton signal of a sharp singlet at around 6.9 ppm.

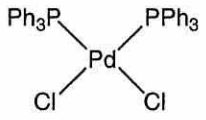
The conversion of Merrifield resin to Wang resin (102)

Merrifield resin **(100)** (1 g, 3.2 $mmolg^{-1}$) was added to DMA (30 ml) and three molecular equivalents of 4-hydroxymethylphenol (1.2 g, 9.6 mmol) and sodium methoxide (0.52 g, 9.6 mmol) were added and the mixture was stirred at 80 °C overnight. The resin was then filtered on a sinter and washed with portions (10 ml) of

methanol, DCM, water and methanol again and then dried in a desiccator to yield resin that was identified as *Wang resin* **(102)** (1.17 g), found C, 84.2; H, 7.0, which showed ν_{max} 3414 cm^{-1} that was in agreement with that quoted in the literature.[238]

The preparation of bis(triphenylphosphine)palladium(II) dichloride (106a)

Palladium (II) chloride (1 g, 5.6 mmol) was added to acetonitrile (25ml) and the mixture was stirred overnight. The orange precipitate of the crude intermediate *dichlorobis(acetronitrile)palladium(II)* (1.3 g, 85 %) was collected by filtration and dried in a desiccator. A portion of this (0.8 g, 3.1 mmol) was suspended in benzene under a nitrogen atmosphere. Triphenylphosphine (1.6 g, 2 mol. eq.) was added and the mixture was stirred at room temperature overnight. The yellow solid was collected by filtration, washed with ether and dried under vacuum. The catalyst was identified as *bis(triphenylphosphine)palladium(II) dichloride* **(106a)** (2.0 g, 2.9 mmol, 92 %) which showed δ_H 7.4 (18 H, m), 7.7 (12 H, m); δ_P 23.9; ν_{max} 1464 cm^{-1}, that was in agreement with that quoted in the literature.[239, 240]



106a

The attempted preparation of 2,3-dipropylindole (110)

DMF was degassed with argon for 15 min in a round bottom flask with a condenser sealed with quick fit septum. Oct-4-yne **(109)** (0.83 g, 0.58 ml, 7.5 mmol), iodoaniline **(108)** (0.55 g, 2.5 mmol), LiCl (0.11 g, 2.5 mmol), KOAc (0.25 g, 2.5 mmol) and 5% palladium acetate catalyst (30 mg, 0.13 mmol) were added and the solution maintained at 120 °C whilst under an argon atmosphere for 3 days. The precipitation of palladium metal onto the glass surface showed that the catalyst had been destroyed and that the reaction had not worked.

The preparation of 2,3-dipropylindole (110)

DMF (250 ml) was degassed with nitrogen gas for 30 min. Iodoaniline **(108)** (5.0 g, 23 mmol) was added along with oct-4-yne **(109)** (5.3 ml, 64 mmol), LiCl (1.0 g, 24 mmol) and K_2CO_3 (15.8 g, 115 mmol) which was ground to a fine powder first.

Palladacycle **(97)** (5 %, 0.77 g, 1.2 mmol) was added and the solution stirred and maintained at 90 - 100 °C under a nitrogen atmosphere for 40 days. After this time, GC analysis showed that the oct-4-yne had been consumed, so a further amount (0.84 ml, 11 mmol) was added and the reaction continued. The reaction was stopped 4 days later and the solution diluted with ether and washed with saturated ammonium chloride and water. The organic layer was dried (Na_2SO_4) and concentrated under vacuum to give a thick brown oil. The oil was boiled in methanol with activated charcoal oil and columned (ethyl acetate / hexane, 1 : 1) to give an oil identified as *2,3-dipropylindole* **(110)** (0.11 g, 0.6 mmol, 3 %) that showed δ_H 1.1 (6 H, m), 1.8 (4 H, m), 2.8 (4 H, m), 7.2 - 7.4 (3 H, m), 7.6 (1 H, m), 7.8 (1 H, s); δ_C 14.1, 14.3, 23.2, 24.2, 26.4, 28.2, 110.3, 112.1, 118.4, 118.9, 120.8, 128.9, 135.3, 135.4; ν_{max} 3409 cm^{-1} that was in agreement with that quoted in the literature.[241]

The preparation of 2-phenylindole (114) and 2-phenylethynyl aniline (113)

DMF (250 ml) was degassed with nitrogen gas for 30 min. Phenylacetylene **(112)** (1.7 g, 16.4 mmol) was added with iodoaniline **(108)** (3.6 g, 16.4 mmol), LiCl (0.7 g, 16.4 mmol) and K_2CO_3 (11.33 g, 82.0 mmol) which was ground to a fine powder just before addition. A resin bound palladium catalyst **(111)** with a 0.39 $mmolg^{-1}$ loading (5 %, 2.1 g, 0.8 mmol) was added and the mixture gently stirred to maintain agitation of the resin under a nitrogen atmosphere and maintained at 90 °C for 2 days. The solution was diluted with ether (100 ml) and washed with sat. aq. ammonium chloride (2 x 50 ml) and water (2 x 50 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated under vacuum to give a brown crude solid which gave a positive result to Kovacs reagent for indoles with unsubstituted 3-position. The different products of the reaction were obtained with columning (DCM) to give impure samples that were identified by ^1H NMR as being mainly of *2-phenylethynyl aniline* **(113)** (1.4 g, 7.4 mmol, 45 %), m.p. 68 – 70 °C (lit.,[242] 88 – 89 °C) which showed δ_H 4.0 (2 H, br. s), 6.5 – 7.7 (9 H, m) and a minor product of *2-phenylindole* **(114)** (0.2 g, 1.0 mmol, 6 %), m.p. 129 – 131 °C (lit.,[243] 188 – 189 °C) that showed δ_H 6.9 (1 H, s), 7.1 - 7.7 (9 H, m), 8.4 (1 H, br. s). The products could not be obtained pure despite attempted recrystallisation, but the analysis was in agreement with that quoted in the literature.[244]

The preparation of *N*-4-*tert*-butylbenzenesulfonyl iodoaniline (116)

Iodoaniline **(108)** (1.69 g, 7.7 mmol) and 4-*tert*-butylbenzenesulfonyl chloride **(115)** (1.80 g, 7.7 mmol) were dissolved in pyridine (50 ml) and stirred for 2 h. An excess of water (100 ml) was added to the reaction to precipitate orange crystals that were collected by filtration, dried in an oven and identified as *N-4-tert-butylbenzenesulfonyl iodoaniline* **(116)** (2.0 g, 4.9 mol, 64 %), m.p. 151 - 153 °C (Required for $C_{16}H_{18}NSO_2I$: C, 46.3; H, 4.4; N, 3.4; found: C, 46.3; H, 4.5; N, 3.5), which showed δ_H 1.3 (9 H, s), 6.8 - 6.9 (2 H, m), 7.3-7.4 (1 H, m), 7.4 - 7.5 (2 H, m), 7.6 - 7.7 (4 H, m); δ_C 31.0, 35.1, 122.5, 126.1, 126.8, 127.2, 129.5, 135.8, 137.5, 139.1, 156.3, 157.3; ν_{max} 1467, 1379, 1171 cm^{-1}.

The preparation of *N*-4-*tert*-butylbenzenesulfonyl-2-phenylindole (118)

DMF (250 ml) was degassed with nitrogen gas for 30 min. Phenylacetylene **(112)** (0.37 g, 0.4 ml, 3.6 mmol) was added along with *N*-4-*tert*-butylbenzenesulfonyl iodoaniline **(116)** (1.5 g, 3.6 mmol), LiCl (0.15 g, 3.6 mmol) and K_2CO_3 (2.5 g, 18.0 mmol) which was ground to a fine powder just before addition. Palladium acetate (5 %, 40 mg, 0.2 mmol) was added and the solution was maintained at 90 - 100 °C with stirring for 40 days. After this time the solution was diluted with ether (250 ml) and washed with sat. aq. ammonium chloride (2 x 100 ml) and water (2 x 100 ml). The organic layer was concentrated under vacuum and columned (DCM) to give a brown solid that was identified as *N-4-tert-butylbenzenesulfonyl-2-phenylindole* **(118)** (0.49 g, 1.3 mmol, 37 %), m.p. 113 – 116 °C, (Required for $C_{22}H_{23}NSO_2$: C, 73.7; H, 5.7; N, 3.5, found: C, 74.0; H, 6.0; N, 3.6), that showed δ_H 1.2 (9 H, s), 6.6 (1 H, s), 7.3 - 7.5 (12 H, m), 8.3 (1 H, d, J = 8.6 Hz); δ_C 30.9, 35.1, 113.4, 116.5, 120.7, 124.2, 124.8, 125.7, 126.7, 127.5, 128.7, 130.4, 130.5, 132.4, 134.9, 138.2, 142.0, 157.4; ν_{max} 1594, 1460, 1377, 1180, 828 cm^{-1}.

The same reaction was carried out with N-*4-tert*-butylbenzenesulfonyl iodoaniline **(116)** (1.5 g, 3.6 mmol), with 3 mol. eq. of phenylacetylene **(112)** (1.11 g, 10.8 mmol), LiCl (0.15 g, 3.6 mmol) and K_2CO_3 (2.5 g, 18.0 mmol), which was ground to a fine powder just before addition. The same reaction conditions were employed as above with palladium acetate catalyst (5 %, 40 mg, 0.2 mmol) added under a nitrogen atmosphere and the solution was maintained at 90 - 100 °C with stirring.

The reaction was monitored with TLC and HPLC for 22 days when the product was the majority of the reaction mixture and the reaction was stopped. The solution was diluted with ether (250 ml), washed with sat. aq. ammonium chloride (2 x 100 ml) and water (2 x 100 ml); and the organic layer was removed and further extractions were taken from the water layer with ethyl acetate (2 x 50 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under vacuum to give a crude product that was columned (DCM) and recrystallised from petrol to give a brown powder identified as *N-4-tert-butylbenzenesulfonyl-2-phenylindole* **(118)** (0.91 g, 2.3 mmol, 65 %), m.p. 106 – 109 °C, which was identical by ^{1}H and ^{13}C and IR to the sample above.

The preparation of *N*-4-*tert*-butylbenzenesulfonyl-2-phenylindole (118) with a ferrocene - palladium catalyst

DMF (250 ml) was degassed with nitrogen gas for 30 min. Phenylacetylene **(112)** (0.32 g, 3.1 mmol) was added along with *N*-4-*tert*-butylbenzenesulfonyl iodoaniline **(116)** (1.3 g, 3.1 mmol), LiCl (0.13 g, 3.1 mmol), K_2CO_3 (2.2 g, 15.5 mmol) and **119** (5 %, 0.12 g, 0.16 mmol). The reaction was heated at 110 °C and monitored by TLC after 7 days, which showed the majority of product. The solution was then diluted with ether (250 ml), washed with sat. aq. ammonium chloride (2 x 100 ml) and water (2 x 100 ml). The organic layer was removed and further extractions of the aqueous layer were made with ethyl acetate (2 x 50 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under vacuum to give a crude solid that was columned (DCM) and recrystallised from petrol to give a pale orange powder which was identified as *N-4-tert-butylbenzenesulfonyl-2-phenylindole* **(118)** (0.74 g, 1.9 mmol, 61 %), m.p. 110 – 112 °C, which was identical by ^{1}H and ^{13}C and IR to the sample above.

The same reaction was repeated with phenylacetylene **(112)** (0.32 g, 3.1 mmol), *N*-4-*tert*-butylbenzenesulfonyl iodoaniline **(116)** (1.3 g, 3.1 mmol), LiCl (0.13 g, 3.1 mmol), K_2CO_3 (2.2 g, 15.5 mmol) but with half the amount of catalyst **119** (0.06 g, 2.5 %, 0.08 mmol). The reaction was heated at 110 °C for 24 h after which time TLC showed no starting material remaining. The solution was added to an excess of water (250 ml) and extracted with ethyl acetate (3 x 100 ml) and washed with water (2 x 100 ml). The organic layer was dried ($MgSO_4$), concentrated under vacuum and

columned (DCM) to give a brown oil. Methanol was added to precipitate a pale yellow powder that was identified as *N-4-tert-butylbenzenesulfonyl-2-phenylindole* **(118)** (0.69 g, 1.8 mmol, 56 %), m.p. 110 – 113 °C, which was identical by ^{1}H and ^{13}C and IR to the sample above.

7.4 Chapter 4 Experimental

The attempted preparation of 2,3-dipropylindole (110)

DMF (50 ml) was degassed with nitrogen gas for 30 min in the apparatus shown in Appendix 2. Copper iodide (0.10 g, 0.5 mmol) was added with triphenylphosphine (0.39 g, 1.5 mmol) and K_2CO_3 (2.1 g, 15 mmol) which was ground to a fine powder. Iodoaniline **(108)** (2.2 g, 10 mmol) and oct-4-yne **(109)** (1.1 g, 0.83 ml, 10 mmol) were added and the solution was heated at 100 °C overnight with stirring. After this time the solution had turned purple and was poured into an excess of water and extracted with ether (3 x 50 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated under vacuum to give a purple oil the ^1H NMR spectrum of which showed no signals in the alkyl regions.

The preparation of 2-(phenylethynyl)-aniline (113)

DMF (20 ml) was degassed with nitrogen gas for 30 min in the apparatus shown in Appendix 2. Copper iodide (0.10 g, 0.5 mmol) was added along with triphenylphosphine (0.39 g, 1.5 mmol) and K_2CO_3 (2.1 g, 15 mmol) which was ground to a fine powder. Iodoaniline **(108)** (2.2 g, 10 mmol) and phenylacetylene **(112)** (1.0 g, 1.1 ml, 10 mmol) were added and the solution was heated at 120 °C for 19 h with stirring and agitation from nitrogen gas which was slowly bubbled through the solution. The mixture was poured into water, extracted with ether, dried ($MgSO_4$), filtered and concentrated under vacuum to give a brown solid that was purified by column chromatography (DCM) to give pale yellow crystals of *2-(phenylethynyl)-aniline* **(113)** (0.73 g, 3.8 mmol, 38 %), m.p. 74 – 77 °C (lit.,[243] mp 88 – 89 °C) that showed δ_H 4.3 (2 H, s), 6.8 (2 H, m), 7.2 (1 H, m), 7.4 - 7.5 (4 H, m), 7.6 (2 H, m); δ_C 86.0, 94.8, 114.4, 118.0, 123.4, 128.3, 128.4, 128.5, 129.8, 131.5, 132.2, 147.9; ν_{max} 2206, 3364, 3458 cm^{-1}, which was in agreement with that quoted in the literature.[244]

The attempted one pot preparation of 2-phenylindole (113)

DMF (20 ml) was degassed with nitrogen gas for 30 min in the apparatus shown in Appendix 2. Copper iodide (0.05 g, 0.3 mmol) was added along with triphenylphosphine (0.20 g, 0.8 mmol) and K_2CO_3 (1.0 g, 7.5 mmol) which was

ground to a fine powder. Iodoaniline **(108)** (1.1 g, 5.0 mmol) and phenylacetylene **(112)** (0.5 g, 0.6 ml, 5.0 mmol) were added and the solution heated at 120 °C for 24 h with stirring and agitation from nitrogen gas which was bubbled through the solution. After this time, palladium (II) chloride (0.04 g, 0.3 mmol) was added to the reaction and washed down the reaction vessels glass walls with a few millilitres of acetonitrile. The reaction was then left to run overnight. The mixture was poured into an excess of water, extracted with ether (3 x 50 ml), dried ($MgSO_4$), filtered and concentrated under vacuum to give a brown solid that was columned (DCM) to give fractions that were identified on the basis of ^1H NMR as impure samples of *2-(phenylethynyl)-aniline* **(113)** (0.85 g, 4.4 mmol, 88 %) and *2-phenylindole* **(114)** (49 mg, 0.25 mmol, 5 %), which were identical by ^1H NMR to the previous samples above.

The preparation of 2-(phenylethynyl)-aniline (113) with 10 % of catalyst

The same reaction was repeated with double the amount of catalyst. DMF (20 ml) was degassed with nitrogen gas for 30 min in the apparatus shown in Appendix 2. Copper iodide (0.19 g, 1.0 mmol) was added along with triphenylphosphine (0.79 g, 3.0 mmol) and K_2CO_3 (2.1 g, 15 mmol) which was ground to a fine powder prior to addition. Iodoaniline **(108)** (2.2 g, 10 mmol) and phenylacetylene **(112)** (1.0 g, 1.1 ml, 10 mmol) were added and the solution heated at 120 °C for 24 h with stirring and agitation with nitrogen gas bubbled through the solution. The solution was poured into an excess of water to precipitate a brown solid that was filtered, dried and columned (DCM) to give a product contaminated with triphenylphosphine. The product was recolumned (DCM) and washed (petrol / ether, 5 : 2) to give yellow needles that were identified as *2-(phenylethynyl)-aniline* **(113)** (0.84 g, 4.3 mmol, 43 %), m.p. 76 – 79 °C, (lit.,[243] mp 88 – 89 °C), which was identical by ^1H and ^{13}C and IR to the sample above.

The preparation of 2-(phenylethynyl)-aniline (113) under Sonogashira conditions

Iodoaniline **(108)** (1.1 g, 5 mmol) was dissolved in diethylamine **(135)** (30 ml) in a Shlenk tube and phenylacetylene **(112)** (0.51 g, 0.55 ml, 5 mmol) was added along with co-catalysts of copper iodide (21 mg, 0.11 mmol) and bis(triphenylphosphine)palladium (II) chloride (36 mg, 0.05 mmol). The solution

was stirred overnight under nitrogen at room temperature, after which time a dense brown liquid had precipitated in the solution. Ether (35 ml) was added to precipitate a brown solid which was removed by filtration, the solution concentrated *in vacuo* and left overnight in a desiccator to remove traces of diethylamine. The catalysts were removed with a short silica gel column (DCM) and the product was recrystallised from petrol to give orange crystals that were identified as *2-(phenylethynyl)-aniline* **(113)** (0.87 g, 4.5 mmol, 90 %), which was identical by ^{1}H and ^{13}C and IR to the sample above.

The preparation of 2-phenylindole (114)

A sample of 2-(phenylethynyl)-aniline **(113)** (0.1 g, 0.52 mmol) was dissolved in acetonitrile (10 ml) and palladium (II) chloride (5 %, 4.6 mg, 0.03 mmol) was added and the solution refluxed for 30 min. The solvent was evaporated under vacuum to give a crude product was purified on a short silica gel column (DCM) to give a product that was identified as *2-phenylindole* **(114)** (82 mg, 0.42 mmol, 82 %), m.p. 186 - 188 °C, (lit.,[242] mp 188 – 189 °C) that showed δ_H 6.9 (1 H, s), 7.1 - 7.5 (6 H, m), 7.7 (3 H, m), 8.3 (1 H, br. s), δ_C 100.0, 110.9, 120.3, 120.7, 122.4, 125.2, 127.7, 129.0, 129.3, 132.4, 136.8, 137.9; ν_{max} 1604, 3445 cm^{-1}, which was in agreement with that quoted in the literature.[244]

The preparation of *N*-4-*tert*-butylbenzenesulfonyl-2-phenylindole (118)

DMF (20 ml) was degassed with nitrogen gas for 20 min in the apparatus shown in Appendix 2. Copper iodide (0.03 g, 0.16 mmol) was added along with triphenylphosphine (0.12 g, 0.47 mmol) and K_2CO_3 (0.65 g, 4.7 mmol) which was ground to a fine powder. *N*-4-*tert*-Butylbenzenesulfonyl iodoaniline **(116)** (1.3 g, 3.2 mmol) and phenylacetylene **(112)** (0.32 g, 0.35 ml, 3.2 mmol) were added and the solution was heated at 120 °C for 3 days with stirring and agitation from nitrogen gas bubbled through the solution. The solution was poured into an excess of water and extracted with ether (2 x 50 ml) and ethyl acetate (2 x 50 ml). These extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a brown oil that was columned (DCM) and recrystallised from DCM and methanol to give a yellow solid that was identified as *N-4-tert-butylbenzenesulfonyl-2-phenylindole* **(118)** (0.68

g, 1.8 mmol, 55 %), m.p. 106 - 109 °C, which was identical by ^{1}H and ^{13}C and IR to the sample above.

The preparation of 2-oct-1-ynyl-phenyl amine (126)

DMF (20 ml) was degassed with nitrogen gas for 30 min in the apparatus shown in Appendix 2. Copper iodide (0.05 g, 0.25 mmol) was added with triphenylphosphine (0.20 g, 0.75 mmol) and K_2CO_3 (1.04 g, 7.5 mmol) which was ground to a fine powder. Iodoaniline **(108)** (1.09 g, 5.0 mmol) and oct-1-yne **(125)** (0.55 g, 0.74 ml, 5.0 mmol) were added and the solution was heated at 100 °C overnight with stirring and agitation from nitrogen gas bubbled through the solution. The mixture was poured into an excess of water and extracted with ether. The organic layer was dried ($MgSO_4$), filtered and concentrated under vacuum to give a brown solid that columned (DCM) to give a yellow oil identified as *2-oct-1-ynyl-phenyl amine* **(126)** (0.21 g, 1.0 mmol, 21 %) that showed δ_H 1.0 (3 H, t, J = 6.7 Hz), 1.3 - 1.7 (8 H, m), 2.5 (2 H, t, J = 6.8 Hz), 4.2 (2 H, br. s), 6.7 (2 H, m), 7.1 (1 H, dt, J = 1.5, 8.4 Hz), 7.3 (1 H, dd, J = 1.4, 7.9 Hz); δ_C 14.1, 19.7, 22.6, 28.7, 29.0, 31.4, 77.1, 95.8, 109.0, 114.1, 117.8, 128.8, 132.0, 147.7; ν_{max} 2219, 3376, 3471 cm^{-1}, which was in agreement with that quoted in the literature.[245]

The preparation of 2-oct-1-ynyl-phenylamine (126) with less PPh_3

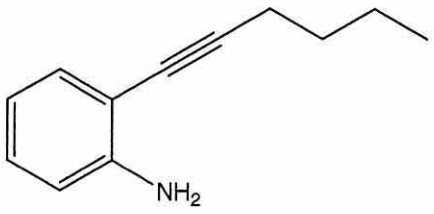
DMF (20 ml) was degassed with nitrogen gas for 30 min in the apparatus shown in Appendix 2. Copper iodide (0.05 g, 0.25 mmol) was added with triphenylphosphine (0.13 g, 0.5 mmol) and K_2CO_3 (1.04 g, 7.5 mmol) which was ground to a fine powder. Iodoaniline **(108)** (1.09 g, 5.0 mmol) and oct-1-yne **(125)** (0.55 g, 0.74 ml, 5.0 mmol) were added and the solution heated at 100 °C for 24 h with stirring and agitation from nitrogen gas bubbled through the solution. The mixture was poured into an excess of water, extracted with ether (3 x 50 ml), dried ($MgSO_4$), filtered and concentrated under vacuum to give a brown oil that was columned (DCM) to give a yellow oil that was identified as *2-oct-1-ynyl-phenylamine* **(126)** (0.12 g, 0.6 mmol, 12 %), which was identical by ^{1}H and ^{13}C and IR to the sample above.

The preparation of 2-oct-1-ynyl-phenylamine (126) under Sonogashira conditions

Iodoaniline **(108)** (1.1 g, 5 mmol) was added to diethylamine **(135)** (30 ml) along with 1-octyne **(125)** (0.55 g, 0.74 ml, 5 mmol) and co-catalysts copper iodide (21 mg, 0.11 mmol) and bis(triphenylphosphine) palladium (II) chloride (36 mg, 0.05 mmol). The solution was stirred under a nitrogen atmosphere overnight at room temperature, after which time a dense brown liquid had precipitated in the solution. Ether (35 ml) was added to precipitate a brown solid which was removed by filtration and the solution was concentrated *in vacuo* to give a crude oil that was left overnight in a desiccator to remove traces of diethylamine. The catalysts were removed with a short silica gel column (DCM) and the compound boiled in methanol with activated charcoal for 30 min. The solution was filtered and concentrated *in vacuo* to give an orange brown oil that was identified as *2-oct-1-ynyl-phenylamine* **(126)** (0.84 g, 4.8 mmol, 84 %), which was identical by ^{1}H and ^{13}C and IR to the sample above.

The preparation of 2-hex-1-ynyl-phenylamine (126a) under Sonogashira conditions

Iodoaniline **(108)** (1.1 g, 5 mmol) was dissolved in diethylamine **(135)** (50 ml) and hex-1-yne (0.41 g, 0.57 ml, 5 mmol) was added with co-catalysts copper iodide (21 mg, 0.11 mmol) and bis(triphenylphosphine)palladium (II) chloride (36 mg, 0.05 mmol). The solution was stirred under a nitrogen atmosphere overnight at room temperature, after which time a dense brown liquid had precipitated. Ether (35 ml) was added to precipitate a brown solid which was removed by filtration and the solution was concentrated *in vacuo* to give a brown oil that was boiled in methanol with activated charcoal for 30 min and put through a short silica column (petrol / ether, 5 : 1) to give an orange oil that was identified as *2-hex-1-ynyl-phenylamine* **(126a)** (0.74 g, 4.3 mmol, 85 %) that showed δ_H 1.0 (3 H, t, J = 7.0 Hz), 1.4 – 1.7 (4 H, m), 2.5 (2 H, t, J = 6.9 Hz), 4.1 (2 H, br. s), 6.7 (2 H, m), 7.2 (1 H, m), 7.3 (1 H, m); δ_C 13.7, 22.4, 27.8, 31.2, 76.9, 95.6, 114.1, 117.8, 122.4, 128.6, 139.8, 147.7; ν_{max} 2239 cm^{-1}, that was in agreement with literature values.[246]



126a

The preparation of 2-hexyl-indole (127)

2-Oct-1-ynyl-phenyl amine **(126)** (100 mg, 0.50 mmol) was dissolved in a few millilitres of acetonitrile. Palladium (II) chloride (4.4 mg, 0.02 mmol) was added and the solution heated at reflux for 30 min. The solvent was evaporated under vacuum and the crude product columned (DCM) to give an oil of *2-hexyl-indole* **(127)** (75 mg, 0.37 mmol, 75 %) that showed δ_H 1.0 (3 H, m), 1.4 - 1.5 (6 H, m), 1.8 (2 H, m), 2.8 (2 H, t, J = 7.6 Hz), 6.3 (1 H, s), 7.1 - 7.2 (2 H, m), 7.3 (1 H, d, J = 7.3 Hz), 7.6 (1 H, d, J = 6.7 Hz), 7.8 (1 H, s); δ_C 14.1, 22.6, 28.3, 29.1, 29.2, 31.7, 99.4, 110.3, 119.6, 119.8, 120.9, 128.9, 135.9, 140.1; ν_{max} 1287, 1458, 3055, 3405 cm^{-1}, which was in agreement with that quoted in the literature.[247]

The preparation of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (131)

Propargyl alcohol **(128)** (2.0 g, 35.7 mmol) was dissolved in dry dichloromethane (100 ml) and 3,4-dihydro-2H-pyran **(130)** (6.0 g, 71.3 mmol) was added along with pyridinium *p*-toluene sulfonate (0.9 g, 3.6 mmol). The reaction was stirred overnight, after which time TLC showed it had run to completion. Sodium hydrogen carbonate solution was added and the organic layer separated, dried ($MgSO_4$), filtered and the solvent evaporated to give a crude product that was columned (petrol / ether, 5 : 1) to give a colourless oil identified as *tetrahydro-2-(2-propynyloxy)-2H-pyran* **(131)** (2.9 g, 14.7 mmol, 41 %) that showed δ_H 1.5 - 1.9 (6 H, m), 2.4 (1 H, t, J = 2.3 Hz), 3.5 (1 H, m), 3.8 (1 H, m), 4.2 (2 H, dd, J = 2.5, 15.9 Hz), 4.8 (1 H, s); δ_C 18.9, 25.3, 30.1, 53.9, 61.8, 73.9, 79.7, 96.7; ν_{max} 2117, 3292 cm^{-1}, that was in agreement with literature values.[248]

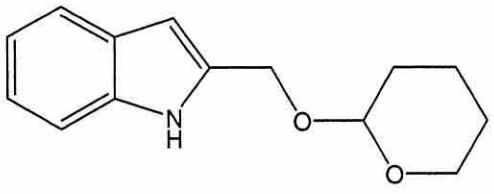
The preparation of 2-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-phenylamine (132)

Iodoaniline **(108)** (2.2 g, 10 mmol) was dissolved in diethylamine **(135)** (60 ml) and tetrahydro-2-(2-propynyloxy)-2H-pyran **(131)** (1.4 g, 10 mmol) was added with co-

catalysts of copper iodide (42 mg, 0.22 mmol) and bis(triphenylphosphine) palladium (II) chloride (72 mg, 0.1 mmol). The solution was stirred overnight at room temperature under a nitrogen atmosphere, after which time a dense brown liquid had precipitated. Ether (50 ml) was added to precipitate a brown solid which was removed by filtration and the solution was concentrated *in vacuo* to give a brown oil and a small amount of a green precipitate. The precipitate was removed with a short column (DCM) to give a brown oil which by NMR contained the product. The oil was columned (petrol / ether, 5 : 2) to remove impurities and then the column was flushed with methanol to elute the more polar product as a brown oil which was recolumned (petrol / ether, 1 : 1) to give an orange oil identified as *2-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-phenylamine* **(132)** (0.70 g, 3.0 mmol, 30 %) that showed δ_H 1.6 – 1.9 (6 H, m), 3.6 (1 H, m), 3.9 (1 H, m), 4.2 (2 H, br. s), 4.6 (2 H, s), 4.9 (1 H, s), 6.7 (2 H, m), 7.1 (1 H, t, J = 7.8 Hz), 7.3 (1 H, d, J = 7.6 Hz); δ_C 19.1, 25.4, 30.3, 55.0, 62.1, 82.5, 90.5, 97.0, 107.2, 114.2, 117.7, 129.8, 132.4, 148.3; ν_{max} 2221 cm^{-1}, that was in agreement with literature values.[249]

The attempted cyclisation of 2-(tetrahydro-pyran-2-yloxymethyl)-indole (132a)

2-[3-(Tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-phenylamine **(132)** (51 mg, 0.2 mmol) was dissolved in acetonitrile (10 ml) and palladium (II) chloride (1.9 mg, 0.01 mmol) was added and the solution was heated at reflux for 30 min, after which time TLC showed that all the starting material had reacted. The solution was concentrated *in vacuo* and the metal catalysts removed with a short silica gel column (DCM) to give a crude yellow solid that ^{1}H NMR analysis showed to be a complex mixture with no indication of the presence of the desired product with the expected singlet for the C-3 proton at 6.3 ppm.



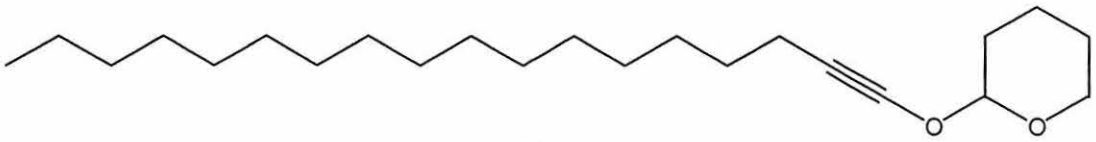
132a

The attempted preparation of 2-undec-2-yne-1-ol (134)

Propargyl alcohol **(128)** (1.74 g, 1.81 ml, 30 mmol) was dissolved in diethylamine **(135)** (40 ml) in a Shlenk tube and 1-bromooctane **(133)** (5.90 g, 30 mmol) was added with copper iodide (130 mg, 0.7 mmol) and bis(triphenylphosphine) palladium (II) chloride (230 mg, 0.3 mmol). The solution was stirred overnight at room temperature under nitrogen after which time a dense brown liquid had precipitated. Ether (60 ml) was added to precipitate a brown solid which was removed by filtration to give a solution that was shown by TLC (petrol / ether, 2 : 1) and GC to be mostly starting material. The solution was returned to the Shlenk tube with triethylamine solvent (30 ml). This was then heated at 80 °C for 48 h under nitrogen, after which time the Shlenk tube had boiled dry to leave a brown oil. Ether (50 ml) was added to give a yellow solution and a brown solid. Analysis of the solution by GC showed a loss of starting material. The solid was removed with filtration and the solution concentrated *in vacuo* to precipitate a small amount crude solid that was removed by filtration and washed with petrol to give an oil that was identified as *diethyl octylamine* **(136)** (4.3 g, 23.3 mmol, 78 %) that showed δ_H 0.8 (3 H, t, J = 6.4 Hz), 1.0 (6 H, t, J = 7.0 Hz), 1.2 (10 H, s), 1.4 (2 H, m), 2.3 (2 H, dd, J = 7.3, 7.9 Hz), 2.4 (4 H, q, J = 7.0 Hz); δ_C 11.5, 14.0, 22.5, 26.9, 27.6, 29.2, 29.5, 31.8, 46.8, 52.9; ν_{max} 1070 cm^{-1}, that was in agreement with the literature values.[250]

The attempted preparation of tetrahydro-2-(2-hexadecynyloxy)-2*H*-pyran (138a)

Tetrahydro-2-(2-propynyloxy)-2H-pyran **(131)** (1.20 g, 8.6 mmol) and iodohexadecane **(137)** (3.0 g, 8.6 mmol) were added to diethylamine **(135)** (40 ml) in a Shlenk tube with copper iodide (34 mg, 0.19 mmol) and bis(triphenylphosphine) palladium (II) chloride (70 mg, 0.09 mmol). The solution was stirred at room temperature overnight under a nitrogen atmosphere after which time a dense brown liquid was observed. Ether (35 ml) was added to precipitate a brown solid which was removed by filtration to give a yellow solution that gave several spots by TLC (petrol / ether, 2 : 1). The solution was concentrated *in vacuo* and columned (petrol / ether, 2 : 1) to give the majority of the iodohexadecane starting material (2.5 g, 7.2 mmol).



138a

The preparation of oct-7-yn-1-ol (142) by Zipper isomerisation

Lithium wire (1.7 g, 0.24 mol) was added in freshly cut 1 cm portions over 20 min to 1,3-diaminopropane **(139)** (120 ml) under an argon atmosphere. Gentle heating was applied until the lithium started to dissolve and the solution turned blue. Stirring was continued for 30 min. The solution was heated at 70 °C for 90 min, after which time the blue colour had been discharged. The resulting suspension was cooled to 25 °C and potassium *tert*-butoxide (18.0 g, 0.16 mol) was added, and the solution stirred at room temperature for a further 20 min. Oct-2-yn-1-ol **(141)** (5.0 g, 0.04 mol) was added dropwise over 10 min and the mixture was left to stir for 1 h. The mixture was then poured onto ice (250 g) and the aqueous solution was extracted with ether (4 x 50 ml). The organic extracts were combined, dried ($MgSO_4$), filtered and the solution concentrated *in vacuo* to give a crude oil. The by-product of *tert*-butanol was removed with gentle heating under high vacuum and the crude oil remaining was purified on a short column (petrol / ether, 1 : 1) to give a pale yellow oil that was identified as *oct-7-yn-1-ol* **(142)** (4.0 g, 0.03 mol, 76 %); δ_H 1.3 - 1.5 (8 H, m), 1.9 (1 H, t, J = 2.6 Hz), 2.1 (2 H, dt, J = 2.4, 7.0 Hz), 3.1 (1 H, br. s), 3.5 (2 H, t, J = 6.5 Hz); δ_C 18.2, 25.2, 28.3, 28.4, 32.4, 62.3, 68.2, 84.5; ν_{max} 2116, 3310 cm^{-1}, that was in agreement with literature values.[251]

The preparation of 5-(2-amino-phenyl)-oct-7-yn-1-ol (143)

Iodoaniline **(108)** (1.7 g, 7.9 mmol) was dissolved in diethylamine **(135)** (50 ml) and oct-7-yne-1-ol **(142)** (1.0 g, 7.9 mmol) was added along with copper iodide (30 mg, 0.16 mmol) and bis(triphenylphosphine) palladium (II) chloride (57 mg, 0.08 mmol). The solution was stirred overnight at room temperature under a nitrogen atmosphere, after which time a dense brown liquid layer had precipitated. Ether (50 ml) was added to precipitate a brown solid which was removed by filtration and the solution was concentrated *in vacuo* and columned (ethyl acetate) to give a light brown oil identified as *5-(2-amino-phenyl)-oct-7-yn-1-ol* **(143)** (1.5 g, 7.1 mmol, 90 %), (required for $C_{14}H_{19}NO$: C, 77.3; H, 8.8; N, 6.5; found C, 76.8; H, 8.7; N, 6.1), that

showed δ_H 1.3 - 1.7 (8 H, m), 2.5 (2 H, t, J = 6.8 Hz), 3.6 (2 H, t, J = 6.4 Hz), 6.7 (2 H, m), 7.1 (1 H, dt, J = 1.5, 7.8 Hz), 7.2 (1 H, dd, J = 1.5, 7.9 Hz); δ_C 19.6, 25.3, 28.7, 28.8, 32.6, 62.6, 77.1, 95.7, 109.0, 114.2, 118.0, 128.9, 132.0, 147.6; ν_{max} 2221, 3373, 3466 cm^{-1}.

The preparation of 5-(2-amino-phenyl)-pent-4-yn-1-ol (145)

Iodoaniline **(108)** (1.1 g, 5 mmol) was dissolved in diethylamine **(135)** (30 ml) and 4-pentyne-1-ol **(144)** (0.42 g, 5 mmol) was added along with copper iodide (21 mg, 0.11 mmol) and bis(triphenylphosphine) palladium (II) chloride (36 mg, 0.05 mmol). The solution was stirred overnight at room temperature under nitrogen, after which time a dense brown liquid layer was observed. Ether (50 ml) was added to precipitate a brown solid that was removed by filtration. The solution was concentrated *in vacuo* and columned (ethyl acetate) to give a brown oil that was identified as *5-(2-amino-phenyl)-pent-4-yn-1-ol* **(145)** (0.75 g, 4.3 mmol, 85 %), (Required for $C_{11}H_{13}NO$: C, 75.4; H, 7.5; N, 8.0; found C, 75.1; H, 7.7; N, 8.0), which showed δ_H 1.8 (2 H, m), 2.6 (2 H, t, J = 6.8 Hz), 3.8 (2 H, t, J = 6.1 Hz), 4.2 (2 H, br. s), 6.7 (2 H, m), 7.1 (1 H, dt, J = 1.5, 7.6 Hz), 7.2 (1 H, dd, J = 1.5, 8.0 Hz); δ_C 16.2, 31.5, 61.5, 77.5, 94.9, 108.7, 114.3, 118.0, 129.0, 132.0, 147.7; ν_{max} 2219, 3358 cm^{-1}.

The preparation of 4-(2-amino-phenyl)-but-3-yn-1-ol (147)

Iodoaniline **(108)** (1.1 g, 5 mmol) was dissolved in diethylamine **(135)** (30 ml) and 3-butyne-1-ol **(146)** (0.35 g, 0.38 ml, 5 mmol) was added along with copper iodide (21 mg, 0.11 mmol) and bis(triphenylphosphine) palladium (II) chloride (36 mg, 0.05 mmol). The solution was stirred overnight at room temperature (15 °C at this time) under nitrogen, after which time the expected dense brown liquid was absent, though a dark brown smear was seen on the Shlenk tube walls. The reaction was heated at 32 °C for 24 h, after which time the dense brown liquid was present and TLC showed one spot. Ether (35 ml) was added to precipitate a brown solid which was removed by filtration and the solution was concentrated *in vacuo* and left overnight in a desiccator to remove any remaining diethylamine. The crude oil was columned (petrol / ether, 2 : 1) to remove a small amount of starting material and the product was eluted (ethyl acetate) as a low running dark spot that was concentrated *in vacuo* to give a yellow - brown oil identified as *4-(2-amino-phenyl)-but-3-yn-1-ol* **(147)** (0.7 g, 4.2 mmol, 85 %) that showed δ_H 2.7 (2 H, t, J = 6.4 Hz), 3.8 (2 H, t, J = 6.4

Hz), 4.2 (br. s), 6.7 (2 H, m), 7.1 (1 H, dt, J = 1.2, 7.9 Hz), 7.3 (1 H, dd, J = 1.5, 9.2 Hz); δ_C 23.9, 61.1, 78.7, 92.3, 108.4, 114.5, 118.0, 129.2, 132.0, 147.8; ν_{max} 3358, 2224 cm^{-1}, that was in agreement with literature values.[221]

The preparation of 2-indol-2-yl-hexanol (148)

5-(2-Amino-phenyl)-oct-7-yn-1-ol **(143)** (200 mg, 0.92 mmol) was dissolved in acetonitrile (10 ml), palladium (II) chloride (8.1 mg, 0.05 mmol) was added and the solution was refluxed for 1 h under argon. The solution was concentrated *in vacuo* and crude NMR showed the complete conversion to the indole product. The crude product was columned (ether) to give a pale yellow brown solid that was identified as *2-indol-2-yl-hexanol* **(148)** (143 mg, 0.66 mmol, 72 %), m.p. 60 - 62 °C, (required for $C_{14}H_{19}NO$: C, 77.4; H, 8.8; N, 6.4; found C, 77.1; H, 8.9; N, 6.5), that showed δ_H 1.4 - 2.0 (8 H, m), 2.7 (2 H, t, J = 7.5 Hz), 3.7 (2 H, t, 6.2 Hz), 6.3 (1 H, s), 7.1 - 7.2 (2 H, m), 7.3 (1 H, d, 7.3 Hz), 7.6 (1 H, d, 7.3 Hz), 8.3 (1 H, br. s); δ_C 25.5, 28.1, 28.9, 29.1, 32.6, 62.9, 99.4, 110.3, 119.5, 119.7, 120.9, 128.8, 135.8, 139.9; ν_{max} 1458, 3388 cm^{-1}.

The preparation of 2-indol-2-yl-propanol (149)

5-(2-Amino-phenyl)-pent-4-yn-1-ol **(145)** (119 mg, 0.69 mmol) was dissolved in acetonitrile (10 ml) and palladium (II) chloride (6.0 mg, 0.03 mmol) was added and the solution was refluxed for 1 h under argon. The solvent was concentrated *in vacuo* and the crude product columned on a triethylamine washed column (ether) to give a pale yellow-brown oil that was identified as *2-indol-2-yl-propanol* **(149)** (107 mg, 0.62 mmol, 90 %) that showed δ_H 1.9 - 2.0 (2 H, m), 2.8 (2 H, t, J = 7.3 Hz), 3.7 (2 H, t, 6.2 Hz), 6.3 (1 H, s), 7.1 - 7.2 (2 H, m), 7.3 (1 H, d, 7.3 Hz), 7.6 (1 H, d, 6.7 Hz), 8.5 (1 H, br. s); δ_C 24.6, 31.8, 61.9, 99.3, 110.6, 119.5, 119.7, 121.0, 128.8, 136.0, 139.4; ν_{max} 1561, 3470 cm^{-1}, that was in agreement with literature values.[252]

The attempted preparation of 2-indol-2-yl-ethanol (150)

4-(2-Amino-phenyl)-but-3-yn-1-ol **(147)** (0.13 g, 0.78 mmol) was dissolved in acetonitrile (20 ml) and palladium (II) chloride (6.8 mg, 0.04 mmol) was added and the solution was heated at reflux for 30 min. The solution was concentrated *in vacuo* and the crude product columned (ethyl acetate) to give a yellow oil; the NMR spectrum showed a complex mixture of products, but did not contain the

characteristic CH_2-CH_2 triplets at 2.9 ppm and 3.8 ppm for 2-indol-2-yl-ethanol that was given in the literature.[253, 254]

The preparation of toluene-4-sulfonyl but-3-ynyl ester (151)

But-3-yn-1-ol (3.0 g, 42.8 mmol) was dissolved in pyridine (50 ml) and *p*-toluenesulfonyl chloride (12.3 g, 64 mmol) was added in small portions over 30 min with stirring at 0 °C. The reaction was stirred at this temperature for 2 h and then left in the fridge for 48 h. Ice water (50 ml) was added over 5 min and the solution was added to water (200 ml) and extracted with DCM (3 x 75 ml). The organic extracts were combined, cooled on an ice bath and treated with hydrochloric acid (2 M, 300 ml) over half an hour until the water layer was acidic to litmus paper. The layers were separated, the aqueous layer extracted with DCM (50 ml) and the organic layers combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil identified as *toluene-4-sulfonic acid but-3-ynyl ester* **(151)** (9.2 g, 41.0 mmol, 96 %) that showed δ_H 2.0 (1 H, t, J = 2.6 Hz), 2.4 (3 H, s), 2.5 (2 H, dt, J = 2.6, 7.0 Hz), 4.0 (2 H, t, J = 7.0 Hz), 7.4 (2 H, d, J = 8.0), 7.8 (2 H, d, J = 8.3 Hz); δ_C 19.4, 21.6, 67.5, 70.8, 78.4,127.9, 129.9, 132.7, 145.1; ν_{max} 2122 cm^{-1}, that was in agreement with literature values.[255]

The attempted preparation of toluene-4-sulfonyl-[4-(2-amino-phenyl)-but-3-ynyl] ester (152)

Toluene-4-sulfonic acid but-3-ynyl ester **(151)** (1.12 g, 5 mmol) was dissolved in diethylamine **(135)** (50 ml) and iodoaniline **(108)** (1.10 g, 5 mmol) was added along with copper iodide (21 mg, 0.11 mmol) and bis(triphenylphosphine) palladium (II) chloride (36 mg, 0.05 mmol). The solution was stirred overnight at room temperature under nitrogen, after which there was a large amount of yellow precipitate. Ether (50 ml) was added and the precipitate removed by filtration. The solution was concentrated *in vacuo* and columned (ether) to give a light brown oil that was shown to be a mixture of starting material and a small amount of alkene product that was not be isolated, but identified as *2-but-3-ene-1-ynyl-phenylamine* **(153)** on the basis of a terminal alkene splitting pattern that showed δ_H 5.6 (1 H, dd, J = 1.5, 11.0 Hz), 5.8 (1 H, dd, J = 1.2, 17.4 Hz), 6.1 (1 H, dd, J = 11.2, 17.4 Hz) and m/z M^+ 143.

The preparation of toluene-4-sulfonyl-[4-(2-amino-phenyl)-but-3-ynyl] ester (152)

(2-Amino-phenyl)-but-3-yn-1-ol **(147)** (1.5 g, 9.2 mmol) was dissolved in pyridine (50 ml) and *p*-toluene sulfonyl chloride (2.6 g, 13.9 mmol) was added in small portions over 30 min whilst the reaction was cooled to 0 °C. The reaction was maintained at this temperature for 4 h with stirring and stored in a fridge overnight. Ice water (50 ml) was added over 5 min to the solution which was then poured into water (200 ml) and extracted with DCM (3 x 75 ml). The organic extracts were combined, cooled on an ice bath and hydrochloric acid (2 M, 300 ml) was added over half an hour until the water layer was acidic to litmus paper. The layers were separated, the aqueous layer extracted with DCM (50 ml) and the organic layers combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange powder that was identified as *toluene-4-sulfonic acid-[4-(2-amino-phenyl)-but-3-ynyl] ester* **(152)** (2.5 g, 7.8 mmol, 85 %), m.p. 84 - 85 °C, (required for $C_{17}H_{17}NSO_3$: C, 64.7; H, 5.4; N, 4.4; found C, 65.0; H, 5.4; N, 4.3), that showed δ_H 2.4 (3 H, s), 2.7 (2 H, t, J = 6.1 Hz), 3.9 (2 H, t, J = 6.1 Hz), 7.0 (1 H, m), 7.2 (5 H, m), 7.5 – 7.8 (4 H, m); δ_C 21.5, 23.5, 60.7, 94.8, 114.5, 119.4, 124.1, 127.2, 129.0, 129.5, 131.4, 136.2, 138.2, 143.9, 156.3; ν_{max} 1462, 1159, 2238, 2926 cm^{-1}.

The attempted preparation of 2-(2-tosyloxyethyl)indole (154)

Toluene-4-sulfonic acid-[4-(2-amino-phenyl)-but-3-ynyl] ether (104 mg, 0.33 mmol) was dissolved in acetonitrile (20 ml) and palladium (II) chloride (2.9 mg, 0.02 mmol) was added and the solution refluxed with stirring for 1 h under argon. The solvent was concentrated *in vacuo* and columned (ether) to give a white solid that was shown to be the starting material.

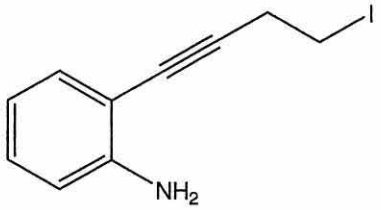
The preparation of iodobut-3-yne (155)

Sodium iodide (25.7 g, 172 mmol) was dissolved in acetone (125 ml) and stirred at room temperature for 10 min. Toluene-4-sulfonyl but-3-ynyl ester **(151)** (7.7 g, 34.3 mmol) was added with sodium hydrogen carbonate (2.9 g, 34.3 mmol) and the solution was heated at reflux for 3 h, after which time TLC showed the reaction to be complete. After cooling, the acetone was evaporated and DCM (50 ml) was added and the solution washed with water (2 x 25 ml). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an oil that was columned

(DCM) to give a yellow oil that was identified as *iodobut-3-yne* **(155)** (1.1 g, 6.2 mmol, 18 %) that showed δ_H 2.2 (1 H, br. s), 2.8 (2 H, t, J = 7.1 Hz), 3.3 (2 H, t, J = 7.2 Hz); δ_C 1.0, 23.7, 70.2, 77.0; ν_{max} 630, 2119, 3293 cm^{-1}, that was in agreement with literature values.[256]

The attempted preparation of 4-(2-amino-phenyl)-but-3-yn-1-iodide (155a)

Iodoaniline **(108)** (0.61 g, 2.8 mmol) and iodobut-3-yne **(155)** (0.5 g, 2.8 mmol) was dissolved in diethylamine **(135)** (50 ml) with copper iodide (11 mg, 0.06 mmol) and bis(triphenylphosphine) palladium (II) chloride (20 mg, 0.03 mmol). The solution was stirred for 36 h at room temperature under nitrogen, then ether (50 ml) was added to precipitate a solid that was removed by filtration. The solution was concentrated *in vacuo* and columned (DCM) to give an oil that was shown by ^1H NMR to be iodoaniline.



155a

The attempted preparation of 4-(2-amino-phenyl)-but-3-yn-1-iodide (155a)

Sodium iodide (1.1 g, 7.1 mmol) was dissolved in acetone (20 ml) and stirred at room temperature for 10 min. Toluene-4-sulfonyl-[4-(2-amino-phenyl)-but-3-ynyl] ester **(147)** (0.44 g, 1.4 mmol) was added with sodium hydrogen carbonate (0.12 g, 1.4 mmol) and the solution was heated at reflux for 4 h, after which time TLC showed that no reaction had taken place. The reaction was stirred for 48 h when there was still no reaction. The acetone was evaporated, DCM (50 ml) added and washed with water (2 x 25 ml). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give white crystals that were identified as starting materials.

7.5 Chapter 5 Experimental

The preparation of 2-methyl-*N*-(*tert*-butoxycarbonyl)aniline (158)

o-Toluidine **(166)** (2.7 ml, 25 mmol) was dissolved in THF (25 ml) and BOC_2O **(167)** (6.0 g, 27.5 ml) added and the solution heated at reflux for 3 h. The reaction was allowed to cool and the solvent evaporated. Ethyl acetate was added and the solution was washed with 1M citric acid and brine solution. The organic layer was dried ($MgSO_4$), filtered and evaporated to give a yellow solid that was recrystallised from *n*-hexane to give white crystals that were identified as *2-methyl-N-(tert-butoxycarbonyl)aniline* **(158)** (4.7 g, 22.8 mmol, 91 %) m.p. 73 - 74 °C (lit.,[229] 82 - 83 °C) that showed δ_H 1.6 (9 H, s), 2.3 (3 H, s), 6.3 (1 H, br.s), 7.0 (1 H, dt, J = 0.5, 3.8 Hz), 7.2 (1 H, d, J = 3.6 Hz), 7.2 (1 H, t, J = 3.8 Hz), 7.8 (1 H, br.d, J = 3.3 Hz); δ_C 17.7, 28.3, 80.4, 120.8, 123.6, 126.7, 130.3, 136.3, 153.0, 185.3; ν_{max} 1676 cm^{-1}, that was in agreement with literature values.[229]

The preparation of *N*-(*tert*-butoxycarbonyl)indole (162)

BOC protected *o*-toluidine **(158)** (0.5 g, 2.4 mmol) was dissolved in dry THF (25 ml) cooled to – 40 °C and *t*-BuLi (2.2 mol. eq.) was added dropwise so that the internal temperature did not rise above – 20 °C and the solution turned bright yellow. The reaction mixture was cooled to – 40 °C for 5 min and DMF **(160)** (0.35 g, 4.8 mmol) was added to give a colourless solution. The solution was added to water (50 ml) and extracted with ether. The crude alcohol **(161)** was concentrated and dissolved in THF (50 ml). Hydrochloric acid (0.5 ml, 12 M) was added and the mixture was stirred at room temperature for an hour after which time TLC showed full conversion of alcohol. Ether (50 ml) was added and the solution washed with water and saturated $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), filtered and columned (petrol / ether, 25 : 1) on a column washed with triethylamine solution to give a clear oil identified as *N-(tert-butoxycarbonyl)indole* **(162)** (0.30 g, 1.4 mmol, 56 %) that showed δ_H 1.8 (9 H, s), 6.7 (1 H, d, J = 3.7 Hz), 7.3 (1 H, dt, J = 0.9, 7.3 Hz), 7.4 (1 H, dt, J = 0.9, 7.0 Hz), 7.7 (1 H, d, J = 7.3 Hz), 7.7 (1 H, d, J = 3.7 Hz), 8.3 (1 H, br.d, J = 8.2 Hz); δ_C 28.2, 83.6, 107.4, 115.3, 121.0, 122.7, 124.3, 125.9, 130.7, 135.3, 149.8; ν_{max} 1607, 1734 cm^{-1}, that was in agreement with literature values.[231]

The preparation of 2-methyl-*N*-(*tert*-butoxycarbonyl)indole (168)

BOC protected *o*-toluidine **(158)** (0.25 g, 1.2 mmol) was dissolved in dry THF (20 ml), cooled to – 40 °C and *t*-BuLi (2.2 mol. eq.) was added dropwise so that the internal temperature did not rise above – 20 °C and the solution turned bright yellow. The reaction mixture was cooled to – 40 °C for 10 min and DMA (0.21 g, 2.4 mmol) was added. The bright yellow colour of the solution was not discharged so an excess of DMA was added and the solutions turned colourless. The solution was added to water (100 ml) and extracted with ether (2 x 50 ml). The crude alcohol was concentrated, dissolved in THF (50 ml) and hydrochloric acid (0.1 ml, 12 M) was added and the solution stirred at room temperature and followed by TLC. A further 0.5 ml of HCl was added and the solution stirred for another hour after which time TLC showed the full conversion of the alcohol. Ether (50 ml) was added and the solution washed with water and sat. aq. $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and columned (petrol / ether, 25 : 1) on a base treated column to give a clear oil identified as *2-methyl-N-(tert-butoxycarbonyl)indole* **(168)** (0.11 g, 0.5 mmol, 41 %) that showed δ_H 1.7 (9 H, s), 2.7 (3 H, s), 6.3 (1 H, s), 7.2-7.3 (2 H, m), 7.5 (1 H, d, J = 8.2 Hz), 8.2 (1 H, d, J = 7.6 Hz); δ_C 17.2, 28.3, 83.6 108.0, 115.5, 119.5, 122.6, 123.1, 129.4, 136.6, 137.8, 150.7; ν_{max} 1596,1731 cm^{-1}, that was in agreement with literature values.[257]

The attempted preparation of 2-ethyl-*N*-(*tert*-butoxycarbonyl)aniline (169)

2-Methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** (0.5 g, 2.4 mmol) was dissolved in dry THF (25 ml) and cooled to - 40 °C for 5 min. *tert*-BuLi (2.2 mol. eq.) was added dropwise so as not to raise the internal temperature above – 20 °C. The solution was cooled back to - 40 °C for 5 min and then quenched with methyl iodide (0.75 g, 5.3 mmol) and the solution left to warm to room temperature. Water was added and the solution extracted with ether, dried ($MgSO_4$), filtered, concentrated *in vacuo* and columned (petrol / ether, 10 : 1) to yield a crude solid (525 mg) that was a mixture of starting material and product that was identified as *2-ethyl-N-(tert-butoxycarbonyl)aniline* **(169)** that showed δ_H 1.3 (3 H, t, J = 7.6 Hz), 2.6 (2 H, q, J = 7.6 Hz). Crude NMR showed the starting material / product to be in a ratio of 2 : 3. The crude material was columned (petrol / ether, 10 : 1), but did not isolate the product, only increase the ratio to 2 : 7. The same experiment was repeated with 3

mol. eq. of *tert*-BuLi and quenched with methyl iodide (1.7 g, 12 mmol). The reaction was worked up as above to, to give a mixture of products that was columned (petrol / ether, 10 : 1) to show an unseparated mixture (264 mg) of starting material / *2-ethyl-N-(tert-butoxycarbonyl)aniline* **(169)** in a ratio of 1 : 8.

The preparation of 2-heptyl-*N*-(*tert*-butoxycarbonyl)aniline (171)

2-Methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** (2.0 g, 9.6 mmol) was dissolved in dry THF (20 ml) under an argon atmosphere, cooled to – 40 °C and *t*-BuLi (2.0 mol. eq.) was added dropwise so as not to raise the internal temperature above – 20 °C. The reaction was cooled, kept at – 40 °C for 10 min and then bromohexane **(170)** (2.2 mol. eq., 3.5 g, 21.2 mmol) added and the solution allowed to warm slowly overnight in the cooling bath. The solution was added to water (50 ml) and extracted with ether (2 x 50 ml). The organic layer was dried ($MgSO_4$), filtered and columned (hexane / ether, 9 : 1) on a base treated column to give a colourless oil that slowly crystallised to give colourless crystals that were identified as *2-heptyl-N-(tert-butoxycarbonyl)aniline* **(171)** (1.7 g, 5.7 mmol, 59 %), m.p. 33 - 35 °C, (Required for $C_{18}H_{29}NO_2$; C, 74.2; H, 10.0; N, 4.8; found: C, 74.3; H, 10.0; N, 5.1), that showed δ_H 0.9 (3 H, t, J = 6.7 Hz), 1.3 (8 H, m), 1.5 (9 H, s), 1.6 (2 H, t, J = 7.3 Hz), 2.6 (2 H, t, J = 7.8 Hz), 6.3 (1 H, br.s), 7.0 (1 H, dt, J = 1.2, 7.5 Hz), 7.2 (2 H, m), 7.8 (1 H, br.d, J = 8.0 Hz); δ_C 14.1, 22.6, 28.3, 29.1, 29.4, 29.6, 31.3, 31.7, 80.3, 121.9, 123.9, 126.6, 129.3, 132.3, 135.6, 153.3; ν_{max} 1735, 3348 cm^{-1}.

The attempted preparation of 2-ethyl-3-hexyl-*N*-(*tert*-butoxycarbonyl)indole (173)

2-Heptyl-*N*-(*tert*-butoxycarbonyl)aniline **(171)** (0.96 g, 3.3 mmol) was dissolved in dry THF (20 ml) under an argon atmosphere, cooled to – 40 °C and *t*-BuLi (2.0 mol. eq.) was added dropwise so as not to raise the internal temperature above – 20 °C. The reaction mixture was cooled and kept at – 40 °C for 20 min and then quenched with *N,N*-dimethylpropionamide (0.67 g, 6.6 mmol) in dry THF (3 ml) and the solution allowed to warm to room temperature slowly overnight. Water was added and the solution extracted with ether, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow / green oil. The oil was dissolved in THF (20 ml) and HCl (1 M, 0.1 ml) was added and the reaction stirred overnight. Ether (50 ml) was added

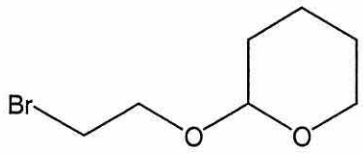
and the solution washed with water and sat. aq. $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and columned (hexane / ethyl acetate, 9 : 1) on a column that had been washed with triethylamine solution to give the recovery of the majority of the starting material (0.94 g, 3.3 mmol.

The preparation of 2-[3-(tetrahydro-pyran-2-yloxy)-propyl]-*N*-(*tert*-butoxycarbonyl)aniline (174)

2-Methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** (1.0 g, 4.8 mmol) was dissolved in dry THF under an argon atmosphere and cooled to – 40 °C. *Tert*-BuLi (2.0 mol. eq.) was added dropwise so as the internal temperature was not raised above – 20 °C and the solution stirred for 10 min. The reaction was quenched with 2-(2-bromo-ethoxy)-tetrahydropyran **(174a)** (2.0 g, 9.6 mmol) and allowed to warm up slowly overnight in the cooling bath. The solution was added to water (50 ml) and extracted with ether. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo* and columned on a base treated column (hexane / ethyl acetate, 9 : 1) to give a colourless oil that was identified as *2-[3-(tetrahydro-pyran-2-yloxy)-propyl]-N-(tert-butoxycarbonyl)aniline* **(174)** (0.91 g, 2.7 mmol, 56 %), (required for $C_{19}H_{29}NO_4$: C, 68.0; H, 8.7; N, 4.2; found: C, 67.9; H, 8.7; N, 4.4), that showed δ_H 1.5 (9 H, s), 1.6 – 1.9 (8 H, m), 2.6 - 2.8 (2 H, m), 3.4 (1 H, m), 3.5 (1 H, m), 3.7 (1 H, m), 3.9 (1 H, m), 4.6 (1 H, br.t, J = 3.7 Hz), 7.0-7.2 (4 H, m), 7.8 (1 H, br.d, J = 7.9 Hz); δ_C 19.8, 25.4, 26.8, 28.4, 30.1, 30.6, 62.7, 64.9, 80.1, 98.7, 122.6, 124.0, 126.6, 129.6, 131.6, 136.4, 153.7; ν_{max} 1732, 3336 cm^{-1}.

The preparation of 2-(2-bromo-ethoxy)-tetrahydro-pyran (174a)

Bromoethanol (5.0 g, 40.0 mmol) was dissolved in dichloromethane under an argon atmosphere and 3,4-dihydro-2H-pyran (6.7 g, 80 mmol, 7.32 ml) and pyridinium-*p*-toluenesulfonate (0.1 mol. eq., 1.0 g, 4.0 mmol) were added and the solution stirred overnight. The solution was washed with water and sat. aq. sodium hydrogen carbonate. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo*, columned on a base treated column (petrol / ether, 5 : 1) and dried in a desiccator to give a colourless oil that was identified as *2-(2-bromo-ethoxy)-tetrahydro-pyran* (5.3 g, 25.4 mmol, 64 %) that showed δ_H 1.5 - 1.9 (6 H, m), 3.5 (3 H, m), 3.7 - 4.1 (3 H, m), 4.7 (1 H, br.t, J = 3.1 Hz); δ_C 19.2, 25.3, 30.4, 30.8, 62.2, 67.5, 98.9; ν_{max} 1124 cm^{-1}, that was in agreement with literature values.[258]



174a

The preparation of *N,N*-dimethylpropionamide (178)

Propionyl chloride **(177)** (6 g, 64.8 mmol) was added slowly to a dimethylamine **(176)** solution in water (7.9 M, 25 ml) and stirred for 1 h, after which time the exothermic reaction had ceased. The solution was extracted with ethyl acetate (3 x 50 ml), concentrated *in vacuo*, dissolved in DCM (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a white solid. Hexane (50 ml) was added to precipitate more solid, which was filtered and the solution was concentrated to give a colourless oil that was identified as *N,N-dimethylpropionamide* **(178)** (4.1 g, 40.3 mmol, 62 %) that showed δ_H 1.1 (3 H, t, J = 7.3 Hz), 2.3 (2 H, q, J = 7.3 Hz), 3.0 (6 H, s); δ_C 9.3, 26.5, 22.6, 30.9, 173.9; m/z 101, 72, 57; ν_{max} 1644 cm^{-1}, that was in agreement with literature values.[259]

The preparation of *N,N*-dimethylbutyramide (179)

Freshly distilled butyryl chloride (6.0 g, 56.3 mmol) was added slowly to a dimethylamine **(176)** solution in water (7.9 M, 25 ml) and the reaction stirred for 1 h. The solution was extracted with ethyl acetate (3 x 50 ml) and concentrated *in vacuo* to give a white solid. DCM (100 ml) was added and the solution dried ($MgSO_4$), filtered and the solvent evaporated to give a slushy white solid. Hexane was added to precipitate white crystals which were filtered off and the solvent was evaporated to give a colourless oil that was identified as *N,N-dimethylbutyramide* **(179)** (4.1 g, 35.9 mmol, 64 %) that showed δ_H 0.9 (3 H, t, J = 7.3 Hz), 1.6 (2 H, m), 2.3 (2 H, t, J = 7.5 Hz), 3.0 (6 H, s); δ_C 14.0, 18.6, 22.6, 31.6, 35.3, 173.2; m/z 115; ν_{max} 1650 cm^{-1}, that was in agreement with literature values.[260]

The attempted preparation of 2-ethyl-*N*-(*tert*-butoxycarbonyl)indole (180)

2-Methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** (0.5 g, 2.4 mmol) was dissolved in dry THF (25 ml) under an argon atmosphere, cooled to – 40 °C and *t*-BuLi (2.2 mol. eq.) was added dropwise so as not to raise the internal temperature above – 20 °C.

The reaction was cooled and kept at – 40 °C for 10 min and the quenched with *N,N*-diethyl-propionamide **(205)** (0.93 g, 7.2 mmol). The reaction was kept at – 40 °C for 5 min and then allowed to slowly warm to room temperature overnight in the cooling bath. After this time, water was added and the solution extracted with ether. TLC showed none of the required alcohol product. This was confirmed with analysis of the crude NMR spectrum.

The attempted preparation of 2-ethyl-*N*-(*tert*-butoxycarbonyl)indole (180)

2-Methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** (0.5 g, 2.4 mmol) was dissolved in dry THF (25 ml) under an argon atmosphere, cooled to – 40 °C and *t*-BuLi (2.2 mol. eq.) was added dropwise so as not to raise the internal temperature above – 20 °C. The reaction mixture was cooled and kept at – 40 °C for 10 min and the quenched with 4-propionyl-morpholine **(206)** (1.0 g, 7.2 mmol) which eventually decolourised the solution. The solution was allowed to slowly warm up to room temperature overnight, after which time, water was added and the solution extracted with ether. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent evaporated to give only starting materials.

The preparation of 2-ethyl-*N*-(*tert*-butoxycarbonyl)indole (180)

2-Methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** (0.5 g, 2.4 mmol) was dissolved in dry THF (25 ml) under an argon atmosphere, cooled to – 40 °C and *t*-BuLi (2.2 mol. eq.) added dropwise so as not to raise the internal temperature above – 20 °C. The reaction was cooled and kept at – 40 °C for 10 min and the quenched with *N,N*-dimethyl-propionamide **(178)** (0.49 g, 4.8 mmol) in dry THF (5 ml). The reaction was kept at – 40 °C for 5 min and then allowed to slowly warm to room temperature overnight in the cooling bath. After this time, water was added and the solution extracted with ether. The crude alcohol was concentrated *in vacuo* and dissolved in THF (50 ml). Hydrochloric acid (0.5 ml, 12 M) was added and the reaction stirred for 2 h until the alcohol was converted to indole. Ether (50 ml) was added and the solution washed with water and sat. aq. $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and columned (petrol / ethyl acetate, 9 : 1) on a column that had been washed with triethylamine solution to give a clear oil that was identified as *2-ethyl-N-(tert-butoxycarbonyl)indole* **(180)** (0.46 g, 1.9 mmol, 78 %), (Required for

$C_{15}H_{19}NO_2$: C, 73.4; H, 7.8; N, 5.7; found C, 73.8; H, 7.8; N, 6.1), which showed δ_H 1.4 (3 H, t, J = 7.3 Hz), 1.7 (9 H, s), 3.1 (2 H, q, J = 7.3 Hz), 6.4 (1 H, s), 7.2 - 7.3 (2 H, m), 7.5 (1 H, m), 8.2 (1 H, br. d, J = 7.3 Hz); δ_C 13.3, 23.5, 28.2, 83.6, 106.1, 115.5, 119.7, 122.5, 123.2, 129.4, 136.7, 144.1, 150.6; ν_{max} 1732 cm^{-1}.

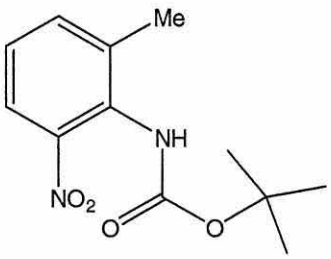
The preparation of 2-propyl-*N*-(*tert*-butoxycarbonyl)indole (181)

2-Methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** (0.5 g, 2.4 mmol) was dissolved in dry THF (25 ml) under an argon atmosphere, cooled to – 40 °C and *t*-BuLi (2.2 mol. eq.) was added dropwise so as not to raise the internal temperature above – 20 °C. The reaction mixture was cooled and kept at – 40 °C for 10 min and the quenched with a solution of *N,N*-dimethylbutyramide **(179)** (0.56 g, 4.8 mmol) in dry THF (5 ml). The reaction was kept at – 40 °C for 5 min and then allowed to warm up to room temperature over 90 min in the cooling bath. After this time, the internal temperature was 10 °C and the reaction had a slight yellow tinge. Therefore a further equivalent of *N,N*-dimethylbutyramide **(179)** (0.28 g, 2.4 mmol) was added and the solution allowed to warm to room temperature. Water was added and the solution extracted with ether. The crude alcohol was concentrated and dissolved in THF (50 ml). Hydrochloric acid (0.2 ml, 12 M) was added and the reaction left to stir at room temperature for a couple of hours, followed by TLC. Ether (50 ml) was added and the solution washed with water and sat. aq. $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and columned (hexane / ethyl acetate, 9 : 1) on a base treated column to give a clear oil identified as *2-propyl-N-(tert-butoxycarbonyl)indole* **(181)** (0.41 g, 1.6 mmol, 66 %), (Required for $C_{16}H_{21}NO_2$: C, 74.1; H, 8.2; N, 5.4; found: C, 74.1; H, 8.4; N, 5.2), which showed δ_H: 1.1 (3 H, t, J = 7.3 Hz), 1.7 (9 H, s), 1.8 (2 H, m), 3.0 (2 H, t, J = 7.6 Hz), 6.3 (1 H, s), 7.1 - 7.2 (2 H, m), 7.5 (1 H, m), 8.1 (1 H, br. d, J = 7.3 Hz); δ_C: 14.2, 22.1, 28.2, 32.2, 83.5, 107.1, 115.5, 119.6, 122.5, 123.1, 129.4, 136.6, 142.3, 150.6; ν_{max} 1732 cm^{-1}.

The attempted preparation of 2-methyl-6-nitro-*N*-(*tert*-butoxycarbonyl)aniline (182a)

2-Methyl-6-nitroaniline **(182)** (1.5 g, 10 mmol) was dissolved in THF (25 ml) and BOC_2O **(167)** (2.4 g, 11 mmol) added and the solution refluxed for 3 h. The reaction was cooled to room temperature and the solvent evaporated to give a solid that was

recrystallised from hexane to give a bright orange powder that was identified by NMR as starting material.



182a

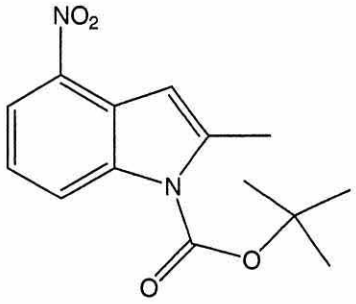
The preparation of 2-methyl-3-nitro-*N*-(*tert*-butoxycarbonyl)aniline (184)

2-Methyl-3-nitroaniline **(183)** (1.5 g, 10 mmol) was dissolved in THF (25 ml), BOC_2O **(167)** (2.4 g, 11 mmol) added and the solution heated at reflux for 3 h. The reaction was cooled to room temperature and the solvent evaporated. Ethyl acetate was added and the solution washed with 1 M citric acid and brine. The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated to give a solid that was washed with hexane and recrystallised from DCM / petrol to give a white flakes that were identified as *2-methyl-3-nitro-N-(tert-butoxycarbonyl)aniline* **(184)** (1.1 g, 4.3 mmol, 43 %), m.p. 129 - 131 °C that showed δ_H 1.5 (9 H, s), 2.4 (3 H, s), 6.4 (1 H, br. s), 7.3 (1 H, t, J = 9.0 Hz), 7.5 (1 H, d, J = 8.2 Hz), 8.0 (1 H, d, J = 8.3 Hz); δ_C 13.3, 28.2, 81.4, 119.4, 125.6, 126.7, 138.0, 152.7; ν_{max} 1684 cm^{-1}, that was in agreement with literature values.[261]

The attempted preparation of 2-methyl-3-nitro-*N*-(*tert*-butoxycarbonyl)indole (184a)

2-Methyl-3-nitro-*N*-(*tert*-butoxycarbonyl)aniline **(184)** (0.21 g, 0.79 mmol) was dissolved in dry THF (15 ml) under an argon atmosphere and cooled to – 40 °C. *tert*-BuLi (2.2 mol. eq.) was added dropwise to give a yellow coloured solution immediately. Further addition changed the colour of the solution from dark yellow to brown that ended up dark yellow again upon complete addition. The reaction was quenched with DMA (0.18 g, 2.4 mmol) and left to warm up slowly in the cooling bath over an hour to give a brown solution. Water was added and the solution extracted with ether. The organic phase was concentrated and dissolved in THF (50 ml). Hydrochloric acid (0.2 ml, 12 M) was added and the solution stirred at room

temperature overnight after which time TLC showed no reaction had occurred. Ether (50 ml) was added and the solution was washed with water and sat. aq. $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow / brown oil; the crude NMR showed the reaction not to have worked.



184a

The preparation of 2,4,6-trimethyl-*N*-(*tert*-butoxycarbonyl)aniline (186)

2,4,6-Trimethylaniline **(185)** (1.4 g, 10 mmol) was dissolved in THF (25 ml) and BOC_2O **(167)** (2.4 g, 11 mmol) was added and the solution heated at reflux for 3 h. The reaction was allowed to cool and the solvent evaporated. White needles were precipitated from hexane that were identified as *2,4,6-trimethyl-N-(tert-butoxycarbonyl)aniline* **(186)** (1.1 g, 4.8 mmol, 48 %), m.p. 68 – 70 °C (lit.,[262] 70 – 71 °C), that showed δ_H 1.5 (9 H, br. s), 2.2 (6 H, s), 2.3 (3 H, s), 5.8 (1 H, br. s), 6.9 (2 H, s); δ_C 18.3, 20.9, 28.3, 77.5, 128.8, 131.3, 135.5, 136.5, 154.0; ν_{max} 1702, 3251 cm^{-1} that was in agreement with literature values.[262]

The preparation of 2,6-dimethyl-*N*-(*tert*-butoxycarbonyl)aniline (187)

2,6-Dimethylaniline (1.2 g, 10 mmol) was dissolved in THF (25 ml), BOC_2O **(167)** (2.4 g, 11 mmol) added and the solution heated at reflux for 3 h. The reaction was allowed to cool and the solvent evaporated. Hexane was added to precipitate a small amount of blue / black solid that was filtered off. Colourless crystals were then precipitated from the hexane that were identified as *2,6-dimethyl-N-(tert-butoxycarbonyl)aniline* **(187)** (1.3 g, 5.9 mmol, 59 %), m.p. 75 - 77 °C, (Required for $C_{13}H_{19}NO_2$; C, 70.6; H, 8.7; N, 6.3; found: C, 70.9; H, 8.6; N, 6.6), that showed δ_H 1.5 (9 H, br. s), 2.3 (6 H, s), 5.9 (1 H, br. s), 7.1 (3 H, s); δ_C 18.3, 28.3, 79.8, 126.9, 128.1, 133.9, 135.8, 153.8; ν_{max} 1692, 3340 cm^{-1}.

The preparation of 2,7-dimethyl-*N*-(*tert*-butoxycarbonyl)indole (188)

2,6-Dimethyl-*N*-(*tert*-butoxycarbonyl)aniline **(187)** (0.24 g, 1.1 mmol) was dissolved in dry THF (20 ml) under an argon atmosphere and cooled to – 40 °C. *Tert*-BuLi (2.2 mol. eq.) was added dropwise so as not to raise the internal temperature above – 20 °C to give a bright yellow solution. The temperature cooled to – 40 °C and then the reaction was quenched with DMA (3 mol. eq.). The reaction was allowed to warm up over 2 h and then the solution was added to water (50 ml) and extracted with ether. The crude alcohol solution was concentrated and dissolved in THF (50 ml). Hydrochloric acid (0.5 ml, 12 M) was added and the reaction stirred at room temperature overnight after which TLC showed full conversion of the alcohol. Ether (50 ml) was added and the solution washed with water and sat. aq. $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and columned (hexane / ethyl acetate, 19 : 1) on column that had been washed with diethylamine solution to give a colourless oil that was identified as *2,7-dimethyl-N-(tert-butoxycarbonyl)indole* **(188)** (37 mg, 0.15 mmol, 14 %), (Required for $C_{15}H_{19}NO_2$: C, 73.4; H, 7.8; N, 5.7; found C, 73.3; H, 7.9; N, 5.6), that showed δ_H 1.7 (9 H, s), 2.5 (3 H, s), 2.5 (3 H, d, J = 0.9 Hz), 6.3 (1 H, d, J = 1.2 Hz), 7.0 (1 H, d, J = 7.0 Hz), 7.1 (1 H, t, J = 7.5 Hz), 7.3 (1 H, d, J = 7.6 Hz); δ_C 15.9, 20.8, 28.0, 83.6, 106.4, 117.3, 122.5, 123.9, 125.9, 130.2, 135.7, 137.0, 150.7; ν_{max}1737 cm^{-1}.

The preparation of 2,5,7-trimethyl-*N*-(*tert*-butoxycarbonyl)indole (189)

2,4,6-Trimethyl-*N*-(*tert*-butoxycarbonyl)aniline **(186)** (0.5 g, 2.1 mmol) was dissolved in dry THF (20 ml) under an argon atmosphere and cooled to – 40 °C. *tert*-BuLi (2.0 mol. eq.) was added dropwise so that the internal temperature did not rise above – 20 °C to give a bright yellow solution. The solution was stirred at this temperature and then quenched with DMA (0.56 g, 6.3 mmol). Water was added and the solution extracted with ether. TLC (hexane / ethyl acetate, 9 : 1) showed the presence of the expected alcohol which was concentrated, dissolved in THF, hydrochloric acid (0.5 ml, 12 M) added and the reaction stirred at room temperature overnight. Water was added and the solution extracted with ether. The organic layer was dried ($MgSO_4$), filtered, concentrated and columned (hexane / ethyl acetate, 9 : 1) on a base treated column to give a colourless oil that was identified as *2,5,7-trimethyl-N-(tert-butoxycarbonyl)-indole* **(189)** (0.2 g, 0.8 mmol, 38 %), (Required

for $C_{16}H_{21}NO_2$: C, 74.1; H, 8.2; N, 5.4; found C, 74.4; H, 8.2; N, 5.7),that showed δ_H 1.7 (9 H, s), 2.4 (3 H, s), 2.5 (3 H, s), 2.5 (3 H, s), 6.2 (1 H, s), 6.9 (1 H, s), 7.1 (1 H, s); δ_C 16.1, 20.7, 21.1, 28.0, 83.4, 106.4, 117.3, 123.6, 127.4, 130.6, 131.9, 134.1, 137.2, 150.7; ν_{max} 1732 cm^{-1}.

The preparation of 3-fluoro-2-methyl-*N*-(*tert*-butoxycarbonyl)aniline (191)

3-Fluoro-2-methylaniline **(190)** (0.65 g, 5.0 mmol) was dissolved in THF (25 ml). BOC_2O **(167)** (2.40 g, 11.0 mmol) was added and the solution heated at reflux overnight. The solution was concentrated, ethyl acetate added and the solution washed with 1M citric acid and brine solution. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo*, hexane added and the solution cooled to precipitate white flakes that were identified as *3-fluoro-2-methyl-N-(tert-butoxycarbonyl)aniline* **(191)** (0.89 g, 3.9 mmol, 79 %), m.p. 62 - 64 °C (lit.,[233] 62 - 64 °C) that showed δ_H 1.5 (9 H, s), 2.2 (3 H, s), 6.3 (1 H, br.s), 6.8 (1 H, t, J = 8.7 Hz), 7.1 (1 H, m), 7.6 (1 H, br.d, J = 8.3 Hz); δ_C 8.9 (d, J = 25.0 Hz), 28.3, 80.8, 110.3 (d, J = 95.0 Hz), 114.9 (d, J = 70.0 Hz), 116.4, 126.9 (d, J = 40.0 Hz), 137.8 (d, J = 25.0 Hz), 161.1 (d, J = 965.0 Hz), 206.9; ν_{max} 1690 cm^{-1}; m/z 225 (M^+), that was in agreement with literature values.[233]

The preparation of 4-fluoro-2-methyl-*N*-(*tert*-butoxycarbonyl)indole (192)

3-Fluoro-2-methyl-*N*-(*tert*-butoxycarbonyl)aniline **(191)** (207 mg, 0.9 mmol) was dissolved in dry THF (10 ml) under an argon atmosphere and cooled to – 40 °C. *tert*-BuLi (2.0 mol. eq.) was added dropwise so the internal temperature was not raised above – 20 °C and the solution turned bright yellow. After addition was complete the internal temperature of the reaction was lowered to below – 40 °C and the reaction left to stir for 10 min. The reaction was quenched with an excess of DMA (0.43 g, 5.0 mmol), after which the bright yellow colour dissipated very quickly. The reaction was left to slowly warm up over 2 h then the solution added to water (50 ml) and extracted with ether. The crude alcohol was concentrated and dissolved in THF (50 ml). Hydrochloric acid (0.5 ml, 12 M) was added and the reaction stirred at room temperature overnight after which time TLC showed full conversion of alcohol. Ether (50 ml) was added and the solution washed with water and sat. aq. $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and columned (hexane / ethyl acetate,

9 : 1) on a column washed with triethylamine solution to give a yellow oil that was identified as *4-fluoro-2-methyl-N-(tert-butoxycarbonyl)indole* **(192)** (53 mg, 0.21 mmol, 23 %), (Required for $C_{14}H_{16}NO_2F$: C, 67.5; H, 6.5, N, 5.6; found C, 67.6; H, 6.8; N, 5.4), that showed δ_H 1.7 (9 H, s), 2.6 (3 H, s), 6.4 (1 H, s), 6.9 (1 H, m), 7.2 (1 H, dt, J = 5.5, 8.2 Hz), 7.9 (1 H, d, J = 8.2 Hz); δ_C 17.1, 28.2, 84.07, 103.1, 107.8 (d, J = 75.8 Hz), 111.5 (d, J = 15.2), 118.1 (d, J = 87.2 Hz), 123.5 (d, J = 30.3 Hz), 137.8, 138.7 (d, J = 41.7 Hz), 151.7 (d, J = 629.3 Hz), 156.9; ν_{max} 1736 cm^{-1}.

The preparation of *N,N*-dimethyl-3-phenyl-propionamide (195)

3-Phenyl propionic acid **(193)** (1.0 g, 6.7 mmol) was dissolved in chloroform (100 ml), excess thionyl chloride was added and the reaction refluxed for 5 h. The solvent was evaporated, ether (50 ml) added and the solution washed with aq. sodium hydrogen carbonate and water. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo*, added slowly to an excess dimethylamine **(176)** solution in water (7.9 M, 25 ml) and stirred overnight. After this time the solution has turned blue / purple. The product was extracted with ethyl acetate (3 x 50 ml), the solvent evaporated, DCM added and the solution dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an oil that was columned on a base treated column (petrol / ether) to remove impurities and then the column was flushed with methanol to remove the product that was dried in a desiccator overnight to give a colourless oil identified as *N,N-dimethyl-3-phenyl-propionamide* **(195)** (0.8 g, 4.5 mmol, 68 %) that showed δ_H 2.6 (2 H, t, J = 7.9 Hz), 3.0 (8 H, m), 7.3 (5, m); δ_C 31.3, 35.3, 35.4, 37.2, 126.0, 128.4, 128.5, 141.4, 172.2; m/z 177, 105, 91; ν_{max} 1632 cm^{-1} that was in agreement with literature values.[263]

The preparation of *N,N*-dimethyl-benzamide (196)

An aqueous solution of dimethylamine **(176)** was extracted with portions of toluene and cooled on an ice bath. Benzoyl chloride (16.6 g, 118 mmol) was added dropwise so that HCl was evolved. The solvent was evaporated under high vacuum to give a colourless oil that was identified as *N,N-dimethyl-benzamide* **(196)** (13.6 g, 91 mmol, 77 %) that showed δ_H 3.0 (3 H, s), 3.1 (3 H, s), 7.4 (5 H, s); δ_C 35.3, 39.5, 127.0, 128.3, 129.5, 136.3, 171.6; ν_{max} 1633 cm^{-1}, that was in agreement with literature values.[264]

The preparation of *N*-(*tert*-butoxycarbonyl)-2-phenylethynyl indole (197)

2-Methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** (0.5 g, 2.4 mmol) was dissolved in dry THF (25 ml) and cooled to - 40 °C for 5 min. *tert*-BuLi (2.2 mol. eq.) was added dropwise so that the temperature did not exceed – 20 °C. The solution was cooled back to - 40 °C for 10 min and then quenched with *N,N*-dimethyl-3-phenyl-propionamide **(195)** (0.64 g, 7.2 mmol) to give a colourless solution. The solution was allowed to warm over 4 h. Water (2 ml) was added to precipitate a white solid and turn the slightly yellow solution completely colourless. The solid was filtered off and the solvent evaporated to give crude product (327 mg). A portion (63 mg) of this was dissolved in THF (5 ml) and hydrochloric acid (0.1 ml, 12 M) was added and left to stir overnight. Water was added and the solution extracted with ether. The organic layer was dried ($MgSO_4$), filtered and columned (hexane / ethyl acetate, 9 : 1) on a base treated column to give a clear oil that was identified as *N-(tert-butoxycarbonyl)-2-phenylethynyl indole* **(197)** (41 mg, 0.13 mmol, 69 %) that showed δ_H 1.7 (9 H, s), 3.1 (2 H, t, J = 7.9 Hz), 3.4 (2 H, t, J = 7.8 Hz), 6.4 (1 H, s), 7.2 – 7.4 (7 H, m), 7.5 (1 H, m), 8.1 (1 H, d, J = 7.9 Hz); δ_C 28.3, 31.8, 35.2, 83.8, 107.4, 115.6, 119.8, 122.6, 123.3, 126.0, 128.4, 128.4, 129.3, 136.5, 141.5, 141.7, 150.6; ν_{max} 1750 cm^{-1}, that was in agreement with literature values.[265]

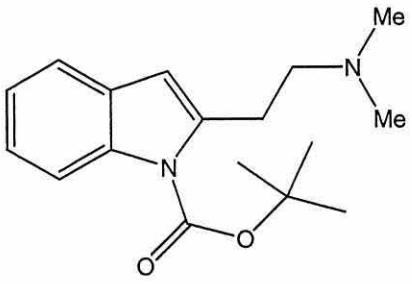
The preparation of *N*-(*tert*-butoxycarbonyl)-2-phenylindole (200)

2-Methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** (2.0 g, 9.6 mmol) was dissolved in dry THF (20 ml) under an argon atmosphere and cooled to - 40 °C for 5 min. *tert*-BuLi (2.0 mol. eq.) was added dropwise so that the temperature did not exceed – 20 °C. The solution was cooled back to - 40 °C for 30 min and then quenched with *N,N*-dimethyl-3-benzamide **(196)** (4.3 g, 28.8 mmol) to give a cloudy solution. This was allowed to warm with stirring over 1 h. Ether (50 ml) and water (2 ml) were added and the precipitate filtered off and the solvent evaporated under vacuum to give a solid that was purified by recrystallisation (petrol / DCM) to give a white solid identified as *N-(tert-butoxycarbonyl)-2-hydroxy-2-phenyl-2,3-dihydro indole* **(199)** (0.65 g, 2.1 mmol, 22 %), m.p. 102 - 105 °C. Required for $C_{19}H_{21}NO_3$; C, 73.3; H, 6.8; N, 4.5; found: C, 73.1; H, 6.6; N, 4.7, that showed δ_H 1.5 (9 H, s), 4.3 (2 H, s), 7.1 (1 H, t, J = 7.3 Hz), 7.2 – 7.3 (2 H, m), 7.4 – 7.7 (4 H, m), 7.8 (1 H, d, J = 8.3 Hz), 8.1 (2 H, d, J = 7.3 Hz); δ_C 28.3, 42.0, 80.2, 123.9, 124.3, 126.1, 127.0, 128.1,

128.8, 130.7, 133.8, 136.1, 137.6, 153.7, 199.1; ν_{max} 1713, 3365 cm^{-1}. A portion of this alcohol (230 mg, 0.74 mmol) was dissolved in THF (5 ml) and HCl (12 M, 0.1 ml) was added and the reaction stirred for 4 days. Water was added and the solution extracted with ether. The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated to give a green oil that was purified on a base treated column (petrol / ether, 1 : 1) to give pale yellow solid that was identified as *N-(tert-butoxycarbonyl)-2-phenylindole* **(200)** (179 mg, 0.61 mmol, 82 %), m.p. 74 - 75 °C (lit.,[266] 76 - 77 °C, that showed δ_H 1.3 (9 H, s), 6.6 (1 H, s), 7.2 – 7.4 (7 H, m), 7.6 (1 H, d, J = 7.6 Hz), 8.2 (1 H, d, J = 7.9 Hz); δ_C 27.5, 83.4, 109.9, 115.2, 120.4, 122.9, 124.3, 127.6, 127.8, 128.7, 129.2, 135.0, 137.4, 140.5, 150.2; ν_{max} 1730 cm^{-1}, that was in agreement with literature values.[266]

The attempted preparation of 2-(2-*N,N*-Dimethylamino-ethyl)-*N*-(*tert*-butoxycarbonyl)indole (202a)

2-Methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** (1.0 g, 4.8 mmol) was dissolved in dry THF under an argon atmosphere and cooled to – 40 °C. *Tert*-BuLi (2.0 mol. eq.) was added dropwise so as the internal temperature was not raised above – 20 °C and the solution was stirred for 20 min. The reaction was quenched with 3-dimethylamino-*N,N*-dimethyl-propionamide **(202)** (1.4 g, 9.6 mmol) and allowed to warm up slowly in the cooling bath overnight. After 18 h the solution was still bright yellow which suggested the reaction has not worked. The solution was then poured into water and extracted with ether (3 x 25 ml). The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo* and analysed to show the recovery of 2-methyl-*N*-(*tert*-butoxycarbonyl)aniline.



202a

The preparation of *N,N*-diethylacrylamide (203)

Acryloyl chloride **(201)** (4.0 g, 44.2 mmol) was added dropwise with stirring to diethylamine (30 ml) cooled on an ice bath and the solution stirred for 10 min to give a white precipitate. The salt was filtered off and the solution concentrated *in vacuo* to give an orange oil identified as crude *N,N-diethylacrylamide* **(203)** (2.8 g, 22.4 mmol, 51 %) that showed δ_H 1.1 (3 H, t, J = 7.2 Hz), 1.2 (3 H, t, J = 7.0 Hz), 3.4 (4 H, m), 5.6 (1 H, dd, J = 2.3, 10.4 Hz), 6.3 (1 H, dd, J = 2.3, 16.5 Hz), 6.5 (1 H, dd, J = 10.4, 16.8 Hz); δ_C 13.0, 14.8, 40.8, 42.2, 127.5, 127.9, 165.6; ν_{max} 1606, 1650 cm^{-1} that was in agreement with literature values.[267]

The preparation of *N,N*-di-*iso*-propylacrylamide (204)

Acryloyl chloride **(201)** (1.0 g, 11.1 mmol) was added dropwise to a solution of *N,N*-di-*iso*-propylamine (3.4 g, 33.3 mmol) in benzene with cooling on an ice bath and the solution was stirred for 30 min to give a white precipitate. The salt was filtered off and the benzene removed with distillation under vacuum. The remaining oil was columned on a base treated column (petrol / ether, 1 : 1) to give a colourless oil identified as *N,N-di-iso-propylacrylamide* **(204)** (1.2 g, 7.5 mmol, 67 %) that showed δ_H 1.3 (6 H, br.s), 1.4 (6 H, br.s), 3.8 (1 H, br.s), 4.0 (1 H, br.s), 5.6 (1 H, dd, J = 2.0, 10.5 Hz), 6.2 (1 H, dd, J = 2.0, 16.8 Hz), 6.5 (1 H, dd, J = 10.4, 16.8 Hz); δ_C 20.6, 21.3, 45.7, 48.1, 125.7, 130.7, 166.2; m/z 155, 140, 112; ν_{max} 1609, 1647 cm^{-1}; m/z 155(M^+), that was in agreement with literature values.[268]

The preparation of *N,N*-diethyl-propionamide (205)

Propionyl chloride **(177)** (6 g, 64.8 mmol) was added slowly to diethylamine (30 ml) cooled on an ice bath and stirred for 1 h, after which time a white solid had precipitated. The solid was filtered off and the solution concentrated *in vacuo* to give an oil that was columned on a short base treated column (ether) to give a red oil that was identified as *N,N-diethyl-propionamide* **(205)** (5.6 g, 43.4 mmol, 67 %) that showed δ_H 1.0 – 1.2 (9 H, m), 2.3 (2 H, q, J = 7.3 Hz), 3.2 (2 H, q, J = 7.3 Hz), 3.3 (2 H, q, J = 7.3 Hz); δ_C 9.5, 13.0, 14.2, 26.2, 40.0, 41.8, 172.9; m/z 101, 72, 57; ν_{max} 1643 cm^{-1}, that was in agreement with literature values.[269]

The preparation of 4-propionyl-morpholine (206)

Propionyl chloride **(177)** (6.4 g, 68.8 mmol) added dropwise to an excess solution of morpholine in toluene (100 ml) which was cooled with an ice bath. HCl fumes were evolved and a salt was precipitated whilst the reaction was run for 30 min. The salt was filtered off and the solution concentrated to give a crude oil that was columned (ether) to give a pale orange oil that was identified as *4-propionyl-morpholine* **(206)** (1.7 g, 11.6 mmol, 17 %) that showed δ_H 1.2 (3 H, t, J = 7.3 Hz), 2.4 (4 H, q, J = 7.3 Hz), 3.5 (2 H, m), 3.6 – 3.7 (6 H, m); δ_C 9.3, 26.3, 41.9, 45.8, 66.6, 66.9, 172.4; ν_{max} 1644 cm^{-1}, that was in agreement with literature values.[270]

The attempted preparation of *N,N*-dimethylacrylamide (207)

Acryloyl chloride **(201)** (4.0 g, 51.8 mmol) was added slowly to a solution of dimethylamine **(176)** in water (7.9 M, 30 ml) and the reaction stirred for 1 h. The solution was extracted with ethyl acetate (3 x 50 ml) and concentrated *in vacuo* to give a colourless oil that was neither starting material nor the desired product. The oil was identified as *3-dimethylamino-N,N-dimethyl-propionamide* **(202)** (1.7 g, 11.6 mmol, 22 %) that showed δ_H 2.2 (6 H, br.s), 2.4-2.6 (4 H, m), 2.9 (3 H, s), 3.0 (3 H, s); δ_C 31.7, 35.3, 37.2, 45.4, 55.1,171.7; m/z 144, 72, 58; ν_{max} 1645 cm^{-1}, that was in agreement with literature values.[271] The reaction was repeated with the addition of a few crystals of hydroquinone to prevent any polymerisation and the solution was cooled on an ice bath at all times during the reaction so as not to allow the internal temperature to rise upon addition of the acryloyl chloride. The reaction gave the same product as the previous reaction.

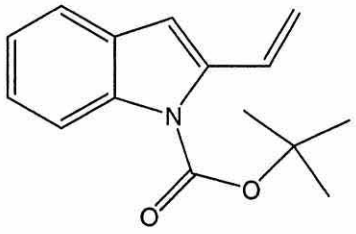
The preparation of *N,N*-dimethyl-acrylamide (207)

An aqueous solution of dimethylamine **(176)** in water (7.9 M, 30 ml) was extracted twice with benzene (2 x 20 ml). The organic layer was dried ($MgSO_4$), filtered and cooled on ice. A few crystals of hydroquinone was added and acryloyl chloride **(201)** (3.0 g, 34 mmol) was added dropwise so that HCl was evolved and a white solid was precipitated. The solid salt was filtered off, the benzene carefully distilled, ether added and evaporated to make sure all traces of benzene were removed. The crude oil was then columned (ether) on a base treated column to give a colourless oil identified as *N,N-dimethyl-acrylamide* **(207)** (2.2 g, 23 mmol, 66 %) that showed δ_H 3.0 (3 H, s), 3.1 (3 H, s), 5.7 (1 H, dd, J = 2.1, 10.4 Hz), 6.3 (1 H, dd, J = 2.1, 16.8

Hz), 6.6 (1 H, dd, J = 10.4, 16.8 Hz); δ_C 35.6, 37.3, 127.5, 127.6, 166.6; m/z 99, 84, 72, 55; ν_{max} 1612, 1648 cm^{-1}, that was in agreement with literature values.[272]

The attempted preparation of 2-vinyl-*N*-(*tert*-butoxycarbonyl)indole (207a)

2-Methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** (1.0 g, 4.8 mmol) was dissolved in dry THF (20 ml) and cooled to –40 °C under an argon atmosphere. *tert*-BuLi (2.2 mol. eq.) was added dropwise so as not to raise the internal temperature above – 20 °C and the solution was stirred for 30 min after which time the reaction was quenched with *N,N*-diethylacrylamide **(203)** (1.8 g, 14.5 mmol). The solution's yellow colour was not dissipated by this addition so it was left to warm up with stirring for 6 h. After this time water was added, the solution extracted with ether and ethyl acetate, dried ($MgSO_4$), filtered and concentrated to give a solid that was identified as starting material.



207a

The attempted preparation of 2-vinyl-*N*-(*tert*-butoxycarbonyl)indole (207a)

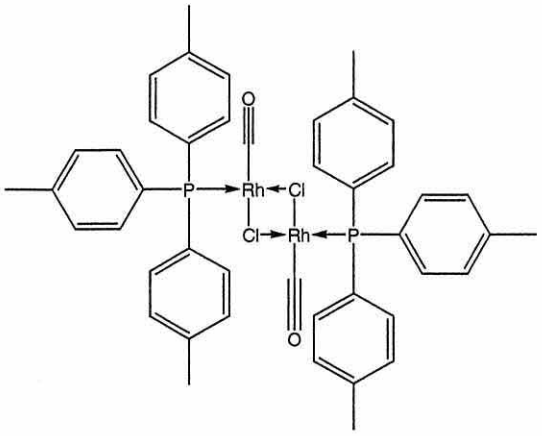
2-Methyl-*N*-(*tert*-butoxycarbonyl)aniline **(158)** (0.51 g, 2.5 mmol) was dissolved in dry THF (15 ml) and cooled to –40 °C under an argon atmosphere. *tert*-BuLi (2.2 mol. eq.) was added dropwise so as not to raise the internal temperature above – 20 °C and the solution was stirred for 10 min after which time the reaction was quenched with *N,N*-di-*iso*-propylacrylamide **(204)** (0.76 g, 5.0 mmol) in dry THF (3 ml). The solution colour remained yellow so the solution was left to stir and warm up overnight. After this time water was added, the solution extracted with ether, dried ($MgSO_4$), filtered and concentrated to give a solid that was identified as starting material.

The attempted preparation of 2-vinyl-*N*-(*tert*-butoxycarbonyl)indole (207a)

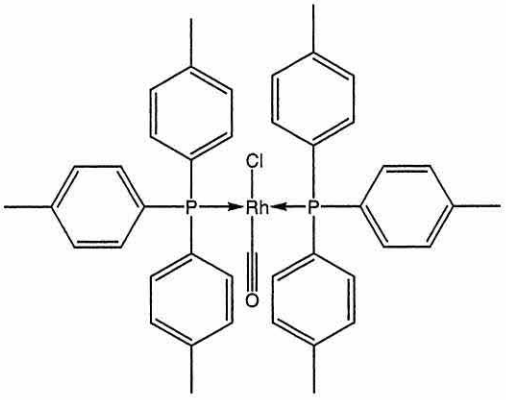
2-Methyl-*N*-(tert-butoxycarbonyl)aniline **(158)** (0.5 g, 2.4 mmol) was dissolved in dry THF under an argon atmosphere and cooled to – 40 °C. *Tert*-BuLi (2.2 mol. eq, 2.4 mmol) was added dropwise so as the internal temperature did not rise above – 20 °C and the solution turned bright yellow. The solution was stirred at this temperature for 20 min and the reaction quenched with *N,N*-dimethyl-acrylamide **(207)** (3 mol. eq, 0.72 g, 7.23 mmol). The yellow colour did not quite disappear and the reaction is allowed to warm slowly. As the temperature rose the colour started to fade. At 0 °C a further equivalent of *N,N*-dimethyl-acrylamide **(207)** was added. Water was added and the solution extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated to give a crude oil (0.4 g) that was identified by NMR as starting material with no alkene signals present.

Appendix 1

Rhodium catalysts tested to trial the iodoaniline and phenylacetylene coupling reaction.



208



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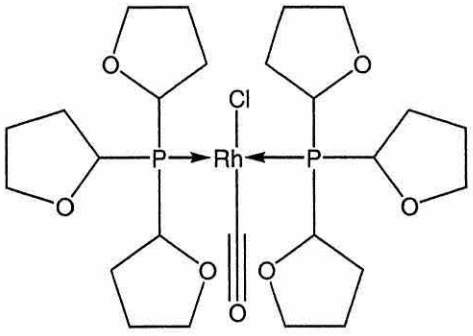

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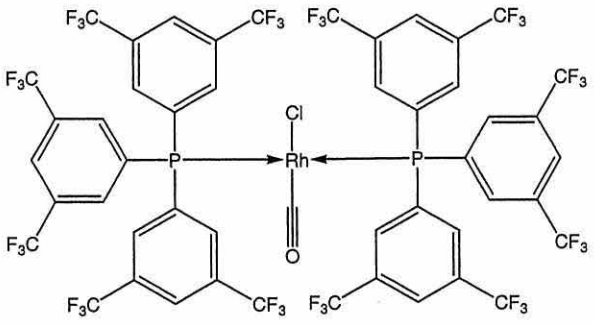
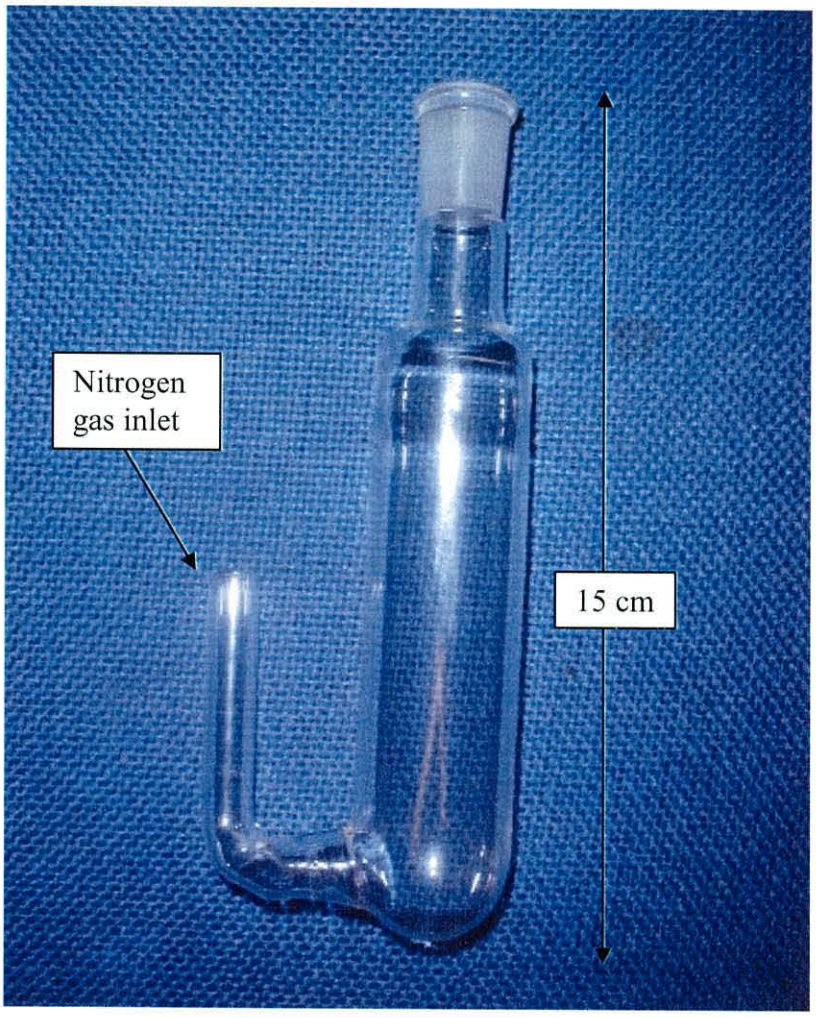


211

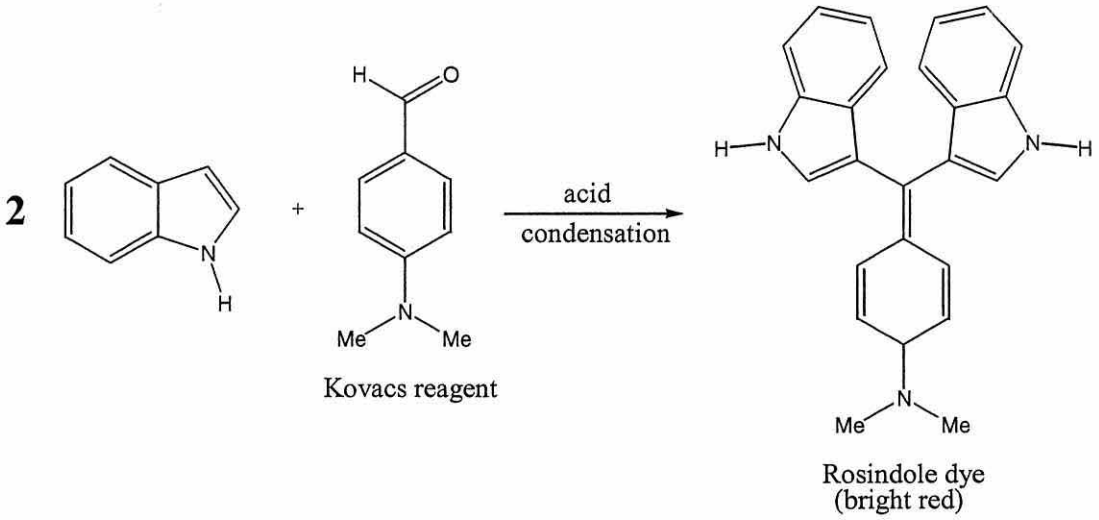
Appendix 2

The customised glassware used for Okuro's copper catalyst reactions.



Appendix 3

The mechanism for the reaction of an indole with no substitution at the 3-position with Kovacs reagent (dimethylaminobenzaldehyde) to give a bright red colour for a positive test due to conjugation. The test was developed to detect the breakdown of tryptophan **(42)** to indole by bacteria.



Kovacs reagent

Rosindole dye
(bright red)

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