The Fischer Indole Synthesis in Choline Chloride.2Zinc Chloride Ionic Liquid and the 1,3 Arene-Olefin Cycloaddition Reaction

University *of* Leicester

Thesis submitted for the degree of
Doctor of Philosophy
at the University of Leicester

by

Raúl Calderón Morales
Department of Chemistry
University of Leicester
December 2003

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

"La única batalla que se pierde, es la que se abandona"

"The only battle which is lost, is the only one which is given up"

Ismael Serrano

To my parents

A mis padres

Acknowledgement

First and foremost I would like to thank my supervisor Dr. P. R. Jenkins for his help, advice and endless enthusiasm over the last three years. I would like also to thanks Dr. S. Handa who has gone out of his way to encourage, teach and befriend me.

I am grateful to the other members of staff in the chemistry department who have helped me during my PhD, in particular Mick Lee for technical assistance, Dr. Graham Eaton or Mass Spectroscopy, Dr. Gerry Griffiths for NMR spectroscopy, Dr. John Fawcett for X-Ray crystallography and Ann Crane for helping me to improve my presentation skills.

Thanks also go to my friends in the lab, Richard, Ben and Simon for being a good friends and seeing through the first two years with me, and Toby, Manny and Kim for their friendship in the last year.

I would like also to thank all my Spanish friends who visited and supported me over the last three years including Terete, Manu, Hunclu, Monica, Tati and Queco in my first year and Emilio, Carmen, Javi, Gallino, Pipo, Chino, Foro and Cande in my second year. I would like also to thanks my housemates in my last year, Tom, Azz and Tully for their friendship and all those friends who passed by through the last three years including Faris (Jordan), Stefania (Italy), Javi (Vitoria) and Laurence (Newcastle).

Finally, I would like to thank five very special people, my girlfriend Belen who has been there when I needed her and supported me through everything, and my family, Mum, Dad and my sister Sonia for all their support and love, and very special thanks to my nephew Alejandro who was born while I was studying in England.

Leicester, 9/12/2003

Agradecimientos

Primeramente me gustaría dar las gracias a mi supervisor Dr. P. R. Jenkins for su ayuda, consejos y entusiasmo puestos en la tesis en los últimos tres años. También me gustaría dar las gracias a Dr. S. Handa por su apoyo, ayuda y amistad en los últimos tres años.

Me gustaría agradecer a otros miembros del personal en el Departamento de Química quien me ayudaron durante mi PhD., en particular Mick Lee por asistencia técnica, Dr. Graham Eaton por espectroscopia de masas, Dr. Gerry Griffiths por espectroscopia de RMN, Dr. John Fawcett por cristalografía de Rayos-X y Ann Crane por ayudarme a mejorar mis tecnicas de presentacion.

Las gracias también van a mis amigos en el laboratorio incluyendo Richard, Ben, Simon y Alicia en mi primer año por ser buenos amigos y estar ahí cuando se los necesitaba y Toby, Manny, Kim, Paula y Ángel por su amistad en el último año.

Me gustaría agradecer a todos mis amigos en España quienes me visitaron y me apoyaron en estos tan importantes tres años en Inglaterra especialmente a Terete, Manu, Hunclu, Monica, Tati y Queco en mi primer año y Emilio, Carmen, Javi, Gallino, Pipo, Chino, Foro y Cande en mi segundo año. Quiero agradecer a mis compañeros de casa Tom, Azz y Tully por su apoyo y amistad en mi último año y a todos aquellos amigos q fueron pasando a lo largo de tres años incluyendo Faris (Jordania), Stefania (Italia), Javi (Vitoria) and Laurence (Newcastle).

Finalmente, quiero dar gracias especiales a cinco personas muy importantes para mi, a mi novia y amiga Belén quien ha estado ahí cuando la necesitaba y me apoyó a superar momentos difíciles, y a mi familia, mi madre, mi padre y mi hermana Sonia por todo su apoyo y amor, y por último gracias a mi sobrinito Alejandro quien nació mientras estaba viviendo en Inglaterra.

9/12/2003

Leicester

Statement

The accompanying thesis submitted for the degree of Ph.D. entitled "The Fischer Indole Synthesis in Choline Chloride.2Zinc Chloride Ionic Liquid and The 1,3 Arene-Olefin Cycloaddition Reaction" is based on work conducted by the author in the Department of Chemistry at the University of Leicester between the period of September 2000 to September 2003.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references. None of the work has been submitted for another degree in this or any other university.

Signed: ..... Date: .....17/02/2004....

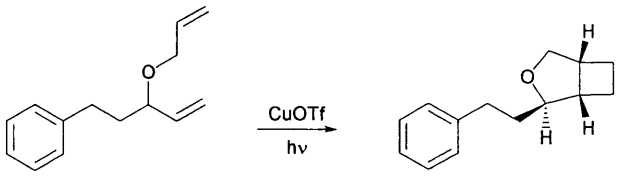
Parts of this work have been published:

The regiospecific Fischer indole reaction in choline chloride.2$ZnCl_2$ with product isolation by direct sublimation from the ionic liquid; Raul Calderon Morales, Vasuki Tambyrajah, Paul R. Jenkins,* David L. Davies and Andrew P. Abbott.

Abstract

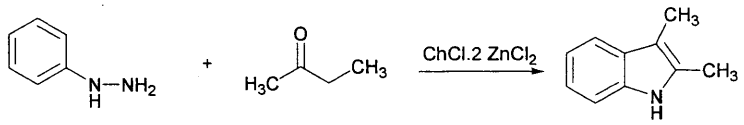
The Fischer Indole Synthesis in Choline Chloride.2 Zinc Chloride Ionic Liquid and The 1,3 Arene-Olefin Cycloaddition Reaction by Raul Calderon Morales.

We have utilised the copper(I) triflate catalysed intramolecular [2+2] photocycloaddition reaction to cyclise diene **53** to afford the *exo* product **54** in 60% yield (Chapter 2).



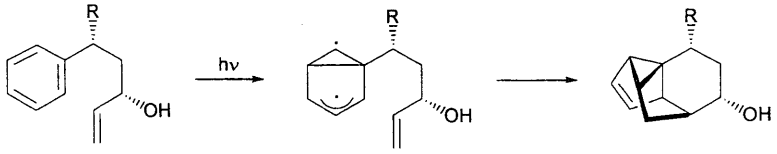
53 54

Using choline chloride.2zinc chloride ionic liquid we have carried out a one pot Fischer Indole synthesis. Phenyl hydrazine **149** was reacted with ethylmethylketone **298** to give 2,3-dimethyl-indole **273** as the only product in 80% yield. The product **273** was directly sublimed from the ionic liquid. 10 more examples of this reaction were carried out with direct sublimation of the product from the ionic liquid with yields between 48-90% (Chapter 3).



149 298 273

A single diastereoisomer **517** was obtained from the 1,3 arene-olefin cycloaddition reaction of the substrate *(S,S), (R,R)* **508.** This is arising from a prefulvene diradical **511**. The structure of the product was confirmed by X-ray crystallography and the finding was confirmed by repeating the reaction with an analogous substrate *(R,S), (S,R)* **534** to give the single product **540** (Chapter 5).



508 *(S,S),(R,R)*, R = vinyl.
534 *(R,S),(S,R)*, R = ethyl.

511

517, R = vinyl.
540, R = ethyl.

Contents

Abbreviations

Ac	acetyl
AIBN	azobisisobutyrylnitrile
Bn	benzyl
Bz	benzoyl
ChCl	choline chloride
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
de	diastereomeric excess
DEAD	diethylazodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyltetrahydro-2(1*H*)-pyrimidone
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI	electron ionization
ES	electrospray
FAB	fast atom bombardment
FG	functional group
GLC	gas liquid chromatography
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HOMO	highest occupied molecular orbital
J	coupling constant
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
MCPBA	*meta*-chloroperbenzoic acid
Ms	mesyl
NMR	nuclear magnetic resonance

nOe	nuclear Overhauser effect
ppm	part per million
RCM	ring closing metathesis
rt	room temperature
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl
UV	ultraviolet

Chapter 1

Cyclobutanation Reactions:

A brief overview

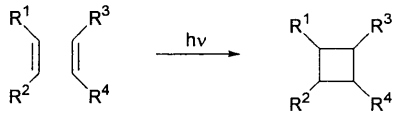
1.1 Background.

The first [2+2] photocycloaddition reaction was reported by Ciamicin in 1908, when he observed that carvone **1** was converted to carvone camphor **2** on prolonged exposure to 'Italian Sunlight'.[1] The distinctive smell of each isomer led to this discovery, however Buchi confirmed the isomerisation when he reinvestigated the reaction some five decades later.[2]

1
carvone

2
carvone camphor

Since the discovery the field has expanded very rapidly, and at the present there are thousands of examples of light mediated processes including geometric isomerisation, hydrogenation, oxidation and the [2+2] cycloaddition. The [2+2] photocycloaddition reactions is one of the most valuable to the synthetic chemist as it is a concerted process where the two π bonds from two unconjugated olefin moieties are converted to two new σ bonds in a cyclobutane product after absorbing energy from a source of radiation as shown below.[3]



The [2+2] cycloaddition reaction differs from most other common pericyclic reactions, such as the Diels-Alder reaction, in that it is a suprafacially disallowed thermal process. There are two discrete types of [2+2] cycloaddition reactions: the first is when a ketene can add to an olefin in an antarafacial ring closure. The other type of [2+2] ring closure is between two simple olefins, or an olefin and an enone, where the system requires excitation by the absorption of photons of light to allow the reaction to proceed.

Cycloadditions occur via a concerted mechanism in which the lowest unoccupied molecular orbital (LUMO) of one reacting component overlaps with the highest occupied molecurlar orbital (HOMO) of another. For this to occur, the two reacting orbitals must be in phase, hence the thermal reaction of two alkenes is disallowed as a suprafacial process (Fig. 1).

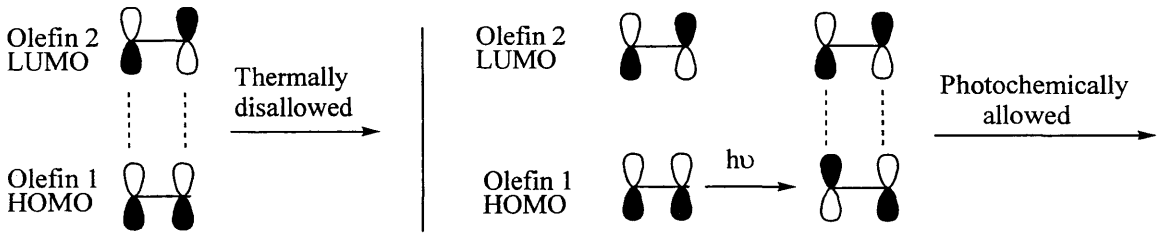


Figure 1

On the contrary, [2+2] reactions are allowed photochemically as irradiation of the molecules with light of energy hν promotes an electron from the ground state HOMO to the next highest molecular orbital, thus changing the phase of the HOMO and allowing in-phase overlap (Fig. 2). Cyclobutanes cannot, therefore, be formed from a concerted [2+2] thermal cycloaddition of two olefins. When considering thermal formations of cyclobutanes, it becomes evident that the thermal reductive elimination of a metallocyclopentane is a viable route to the formation of cyclobutane products.

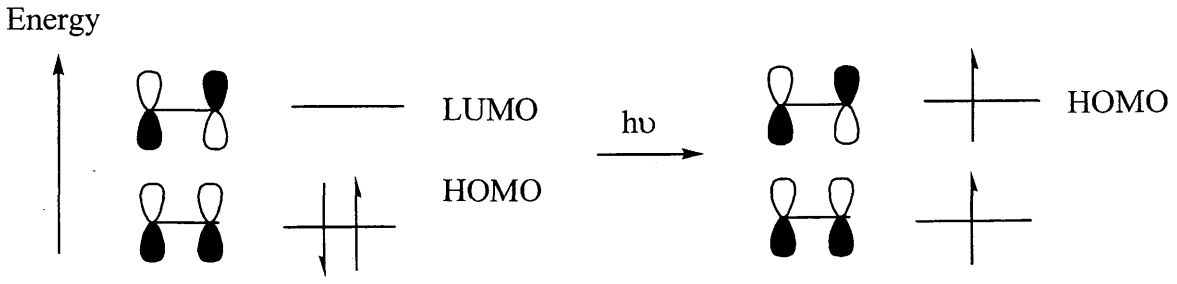
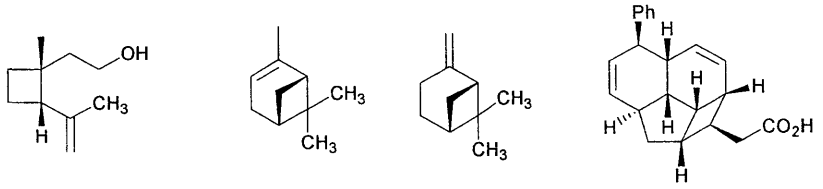


Figure 2

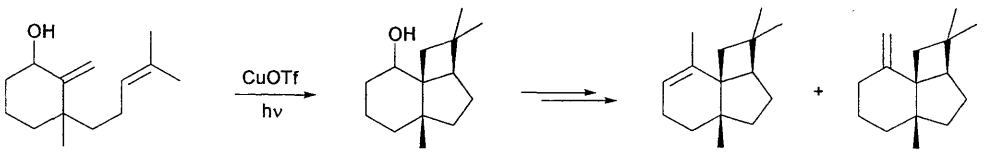
1.2 Natural cyclobutanes

Cyclobutanes, though not as abundant in natural products as the common cyclopentanes and cyclohexanes, are found in nature in a diverse range of compounds that are used for a wide range of applications. For example, grandisol **3** is a boll weevil pheromone and its synthesis has previously been reported many times.[4-8] Other relatively simple, naturally occurring cyclobutanes include structural isomers of the terpenes α-pinene **4** and β-pinene **5**. More complex in chemical structure are the endiandric acids. Endiandric acid A **6** was isolated from the leaves of *Endiandra introrsa (Lauraceae)* some twenty years ago, along with endriandric acids B-G. These novel polycyclic structures contain eight asymmetric centers and all contain a cyclobutane moiety, but most interestingly, they all exist naturally in a racemic rather than enantiomerically pure form. This is due to the fact that all are formed from the same intermediate in a complex series of non-enzymatic electrocyclisations. The syntheses of all eight of these natural products are reported in a series of four publications by Nicolaou and co-workers.[9-12]



3 4 5 6

Sesquiterpene α and β panasinsene **9** and **10**, extracts from root ginger, are derived from cyclohexanol **7**. Intramolecular photocycloaddition of **7** gives tricycle **8** in 55% yield; this cycloaddition is facially selective giving only the *cis* stereochemistry. Cyclic alcohol **8** is a mixture of diastereoisomers, and the authors conclude that the hydroxyl group does not coordinate to the copper during the ring closure to obtain this stereochemistry.[13] Further oxidation followed by alkylation and dehydration led to **9** and **10** in a 2:5 ratio in 50% yield overall from **8**.



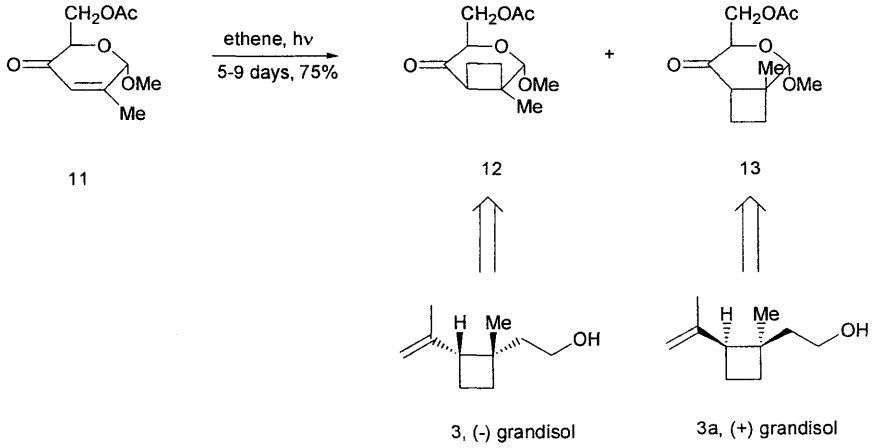
7 8 9 10

2 : 5

1.3 [2+2] Photocycloaddition Reactions of Carbohydrate Derivatives.

Enatiomerically pure cyclobutanes can be prepared by starting with a chiral starting material. Carbohydrates provide a readily available source of chirality and they are easily adapted for use in cyclobutanation.

Light mediated [2+2] photocycloaddition reactions have been used extensively in the synthesis of natural products,[14] however, there are few examples of their utility in reactions involving carbohydrates. Fraser-Reid and co-workers successfully prepared the two isomers **12** and **13** from the intermolecular [2+2] photoaddition of ethene to 2,3-dideoxy-2-C-methyl-α-D-glycero-hex-2-enopyranosid-4-ulose **11**. Each diastereoisomer represents a synthetic building block for the naturally occurring pheromone (-) grandisol **3** and its enantiomer **3a.**[15]

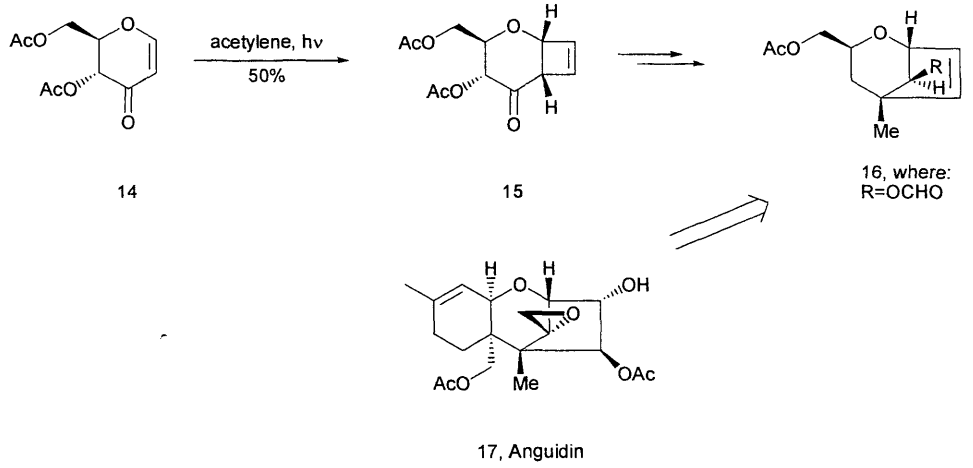


11 12 13

3, (-) grandisol 3a, (+) grandisol

Another example of an intermolecular [2+2] photocycloaddition to a sugar derived enone was proposed by Fetizon in their attempts to synthesise a class of natural products known as trichothecenes. This diverse family of mycotoxins exhibits a wide range of biological activity including anticancer activity. Photocycloaddition of

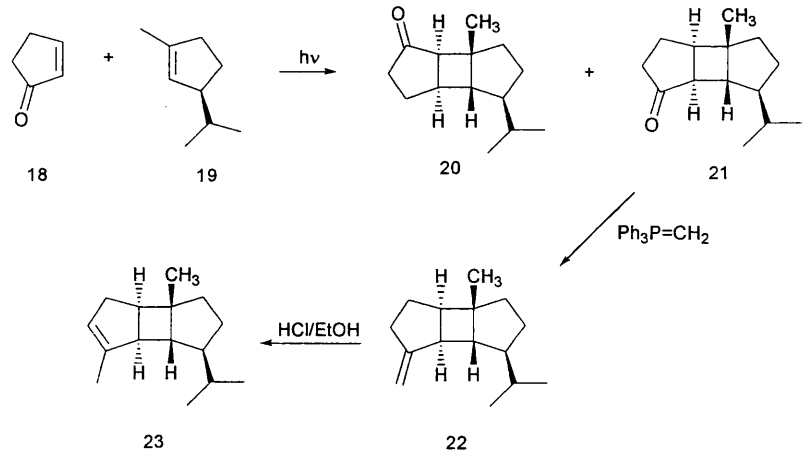
acetylene to enone **14** in acetone gave the cyclobutene adduct **15** in 50% yield. Deacetoxylation followed by alkylation with methyl lithium then ring expansion yielded **16** which is a chiron with correct stereochemistry for the B and C rings of anguidin **17** and other related trichothecenes.[16] Somewhat surprisingly, in this reaction sequence, cyclobutene **15**, is the only diastereoisomer reported, although there is no rational explanation for the observed stereochemistry.



1.4 [2+2] Photocycloadditions as Common Routes to Cyclobutane Products

Common synthetic methods to prepare cyclobutanes include photocycloadditions and such methodologies have been used as direct routes to cyclobutane products. White reported the syntheses of the natural products α-bourbonene **23** and β-bourbonene **22** from one such [2+2] photocycloaddition.[17] Both are sesquiterpenoids isolated from *Geranium bourbon* oil and *Metha piperita*.

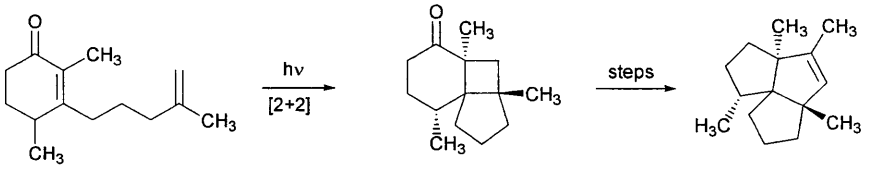
The [2+2] photocyclisation of cyclopent-2-enone **18** with 3-isopropyl-1-methylcyclopentene **19** proceeds in a 64% yield to give a mixture of both head-to-tail and head-to-head isomers each in racemic form. Treatment of these cyclobutane products with triphenylphosphine methylene yields β-bourbonene **22** as the solitary product as only ketone **21** (not **20**) reacts in the Wittig reaction. The terminal olefin is then readily isomerised with hydrochloric acid in ethanol to yield the trisubstituted α-bourbonene product **23** as a racemate.



18 19 20 21 22 23

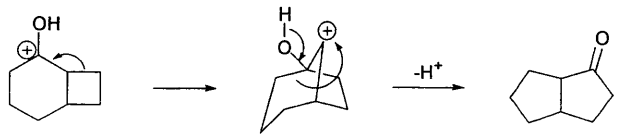
1.5 Application of Cyclobutane Precursors to the Synthesis of Larger Rings.

It is not just their presence in significant natural compounds that makes cyclobutanes so interesting but also their applications to the formation of other ring sizes. For example, isocomene **26** was prepared in racemic form from a cyclobutane precursor **25** as reported by Pirrung and co workers in 1981.[18] The key step in the synthesis is the intramolecular [2+2] photocycloaddition to give the tricyclo[6.3.3.0]undecanone cyclobutane-containing product **25** which can then be converted to the isocomene target and Pirrung reports two such methods.

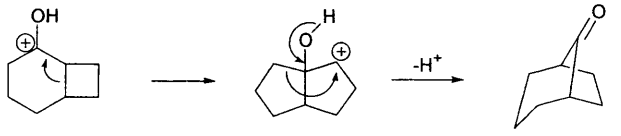


24 25 26

Utilising methods previously reported by Cargill,[12] the fused cyclobutyl carbinyl ketone precursor **25** was formed from a [2+2] photocycloaddition. Such systems are susceptible to acid catalysed rearrangement by alkyl migration to relieve ring strain in the cyclobutane moiety. In the first case, alkyl migration in the cyclobutyl carbinyl cation **27** occurs to give the bridged [3.2.1] product with a bridgehead hydroxy group **28**. Subsequent loss of a proton and concomitant rearrangement yields the [3.3.0] ketone product **29**.



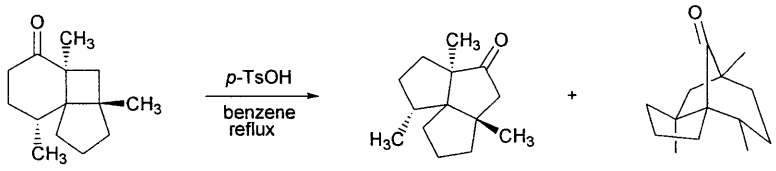
27 28 29



27 30 31

In the second case, alternative alkyl migration produces a [3.3.0] product **30**, again with a bridgehead hydroxy group. Loss of a proton and second rearrangement now give the corresponding [3.2.1] product with bridging carbonyl group **31**.

Pirrung *et. al.* realised the potential of applying the Cargill approach to the synthesis of isocomene from **25**. Treatment of **25** with TsOH in refluxing benzene yielded the two corresponding [3.3.0] and [3.2.1] products in 75% and 15% yields respectively. Migration to the bridged product is favoured as overlap of the migrating bond with the *p*-orbital at the carbinyl center is greatest via this pathway. Thus, formation of the [3.2.1] product **33** as the minor component renders its subsequent conversion to isocomene as unpractical. With this in hand, the [3.3.0] product **32** was treated with MeLi to afford a mixture of tertiary alcohols in quantitative yield. Subsequent treatment with formic acid at room temperature transformed the alcohols to the [3.3.0] isocomene product **26**, thus demonstrating the importance of cyclobutanes as useful precursors to natural products.



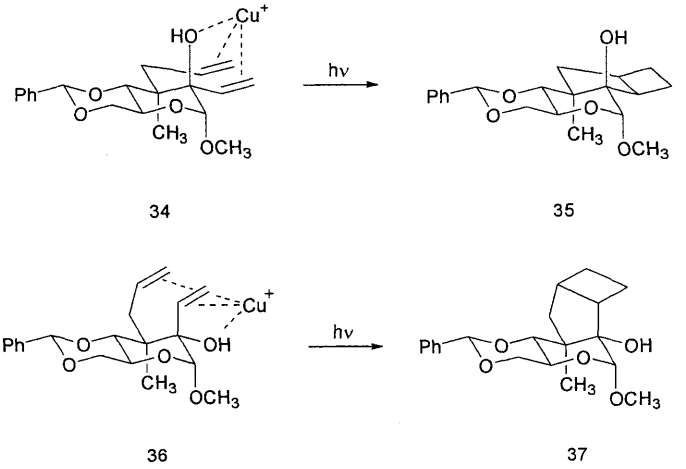
25 32, 75% 33, 15%

1.6 Catalytic Asymmetric Cyclobutanation Reactions.

Having now seen some of the ways in which synthetic chemists commonly prepare cyclobutanes and in some cases, subsequently utilise these as precursors to

other compounds of interest, it is readily apparent that there are many challenges that the modern chemist must embrace when considering accompanying stereochemistry of products formed. For example, the concerted nature of the [2+2] photocyclisation of cyclopent-2-enone **18** with 3-isopropyl-1-methylcyclopentene **19** described in the formation of the bourbonene **23** products above, generates some inherent stereoselectivity in the products formed i.e. the olefinic H's from the enone are always *cis* to each other in the product. Likewise, the H and methyl group from 3-isopropyl-1-methylcyclopentene **19** also result in a *cis* geometry in the product but are *trans* to the H's from the enone. Thus some selectivity is observed, however, the addition gives not only a head-to-head and a head-to-tail reaction to yield two products but also gives the two regioisomers in racemic form providing the method non-totally-selective.

Most naturally occurring compounds, such as the bourbonene **23**, occur as single enantiomers and in general, synthetic duplication of the selectivity observed in nature is often extremely difficult and this is also true of the synthetic preparation of cyclobutanes and derivatives. Recent work of the Jenkins group has addressed these issues by studying the selective formation of asymmetric cyclobutanes such as those shown in Scheme 1.[19] The scheme illustrates the hypothesis that the copper triflate catalyst chelates to the neighbouring hydroxy group as well as coordinating to the two olefins involved in the photocycloaddition. This proposal accounts for the fact that the two diastereoisomeric diene precursors give diastereoisomeric cyclobutane products *selectively* by controlled chelation of the metal catalyst to the neighbouring hydroxy moiety to afford a cyclobutane ring on the same side of the molecule as the hydroxy group in the product.



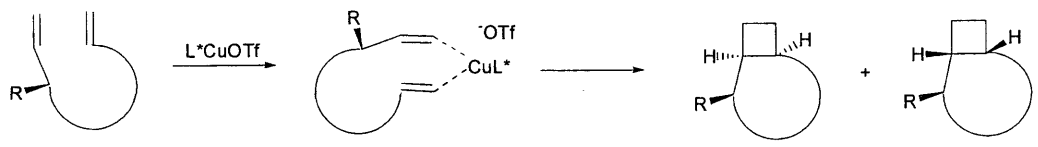
Scheme 1. Chelation control of copper triflate catalyst in photocyclisation reaction to achieve facial selecticity of cyclobutanes formed.

In the example of the enone-olefin photocycloaddition above, the product **25** is formed as a single diastereoisomer. If enantioselective formation of this cyclobutane precursor could be achieved then in theory, the following diastereoselective processes could be carried out enantioselectively. The synthesis of cyclobutane and polycyclic natural product targets as single enantiomers would then be possible.

To make the use of copper catalysts more widely applicable to the [2+2] photoaddition reaction of two olefins, the Jenkins group subsequently conducted studies of similar reactions utilising chiral ligands on the metal to give a 'chiral copper' reagent. It was suggested that such ligands would induce chirality and so the reaction could be employed more widely, now potentially in situations where chelation to a neighbouring group is not possible. Such chirality is induced as coordination of a chiral metal complex to two enantiomeric faces of a diene will produces two diastereotopic metal complexes. Whereas using an achiral copper catalyst produces two *enantiomeric* complexes where the R and S configurations are the same in energy, the diastereotopic complexes formed from the chiral catalyst differ in energy. Accordingly, the diastereoisomer with the lowest energy will be favoured and in the extreme case, will be formed exclusively.

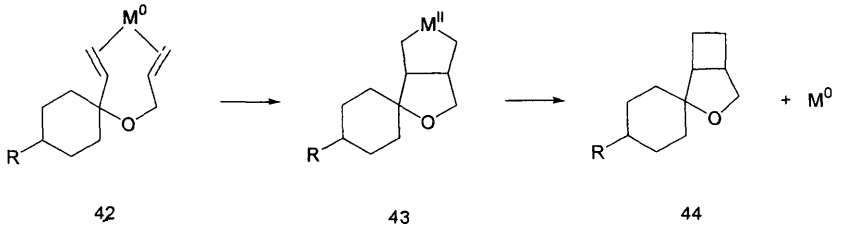
For example, the diene **38** is asymmetric and the complex **39** would be formed as a mixture of diastereoisomers. By controlling the ratio of these isomeric intermediates formed, the ratio of cyclobutane products **40** and **41** is also controlled.

This is a powerful concept and if realised, would be put on a pedestal with other prestigious asymmetric methodologies to have been developed of late, such as Evans' asymmetric aziridinations and Sharpless's epoxidations, both of which also use metal catalysts with chiral ligands.[20,21]



38 39 L* = chiral ligand 40 41

Trial studies proved the chiral copper approach to be unsuccessful. In all cases that were tested, the chiral copper failed to produce any significant enantiomeric excess and reaction rates were slow when compared to unligated copper triflate. It was postulated that, as the reactions were faster with the unligated copper triflate, it was possible that the products formed were derived from this and not the chiral copper and this would account for the formation of racemates. Alternatively, perhaps the chiral copper was involved in the activation of the dienes but not in the actual cycloaddition, hence no chiral induction was observed.[19]



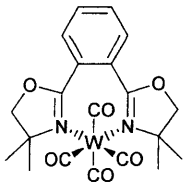
42 43 44

Scheme 2. formation of cyclobutanes via metallocycle intermediate.

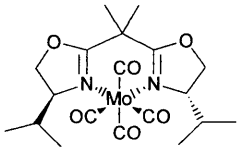
With these facts in hand, the Jenkins group changed the tactic and began to experiment with other metals in the catalysis of cyclobutane formation. In particular, the group VI transition metals, Cr, Mo and W were studied, along with Fe, a group VII transition metal. Grounds for proceeding with these projects came from the fact that the group VI transition metals have a tendency to undergo oxidative addition reactions with alkenes to form metallocycles. It was anticipated that this new development of the Jenkins group's strategy should overcome the problems associated with the chiral copper methodology by now incorporating the chiral metal complex directly into the reaction mechanism as a metallocycle intermediate (Scheme 2). Hence the metal would have a direct influence on the chiral centers being formed during the oxidative addition with the olefins to form the metallocycle and also in the reductive elimination to form the cyclobutane product.

The idea was put into practice, and indeed, cyclobutane products derived from **44** were formed from reaction of derivatives of the diene **42** with $Fe_2(CO)_9$ catalyst under photolytic conditions. The metallocycles **43** were not isolated but the group was confident that they were likely intermediates due to the precedent provided by

Hoffmann.[22] Jenkins *et. al.* did, however, isolate the tungsten complex **45** and the molybdenum complex **46** and structures were confirmed by X-ray crystallography.

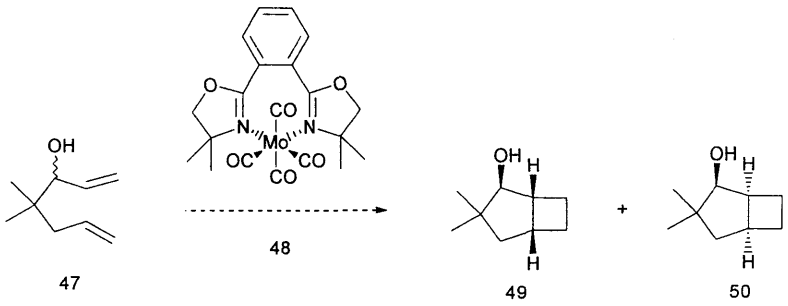


45



46

Test reactions were carried out with the hexacarbonyls of Cr, Mo and W with various dienes to determine whether cyclisation could be achieved and results were positive in all cases. Conditions for the preparation of both the chiral molybdenum complex **46** and achiral analogue **48** were optimised but neither complex gave satisfactory results when used in the photocyclisation reactions of dienes to yield cyclobutanes. For example, the reaction in Scheme 3 failed to show any enantiomeric excess in the products formed, possibly because the chiral ligands are decomplexed upon irradiation of **48** with ultraviolet light. Thermal cyclobutanations with such complexes were also unsuccessful.



47 48 49 50

Scheme 3, Formation of cyclobutane products from a metal catalysed photoaddition of a diene

Chapter 2:

Results & Discussion

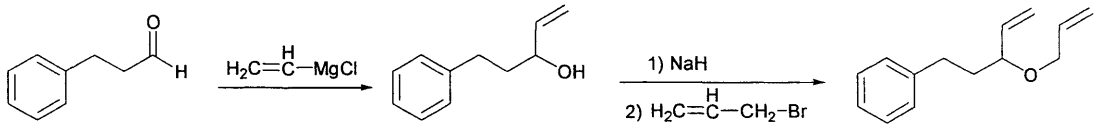
of

Cyclobutanation Reactions.

2.1 Cyclobutanation using CuOTf.

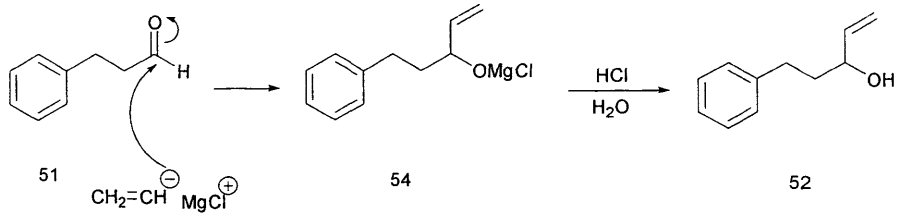
The objective of this project is to study the copper triflate catalyst [2+2] photochemical cycloaddition reaction with the chiral ligand. We used the racemic diene **53** in the reaction with the aim of obtaining kinetic resolution.

The synthesis of the model system investigated is shown in the sequence **51-53**.



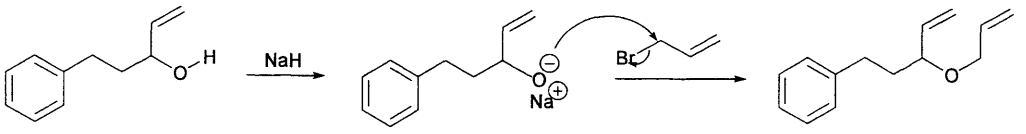
51 52 53

The aromatic diene (3-allyloxypent-4-enyl)benzene **53** was synthesised using a two-step procedure. 3-Phenylpropionaldehyde **51** was reacted with vinylmagnesium chloride to yield 5-phenylpent-1-en-3-ol **52** in 59% yield. This mechanism goes by non-stereoselective attack of the Grignard reagent ("CH_2=CH^-") on the carbonyl carbon to give 5-phenylpent-1-en-3-ol **52**.



51 54 52

After characterisation of 5-phenylpent-1-en-3-ol **52** it was alkylated with allyl bromide to yield (3-allyloxypent-4-enyl)benzene **53** in 60% yield. This mechanism requires deprotonation of the 5-phenylpent-1-en-3-ol **52** with a strong base (NaH). The resulting alkoxy anion **55** is prone to agregation, so addition of DMPU is required to produce a monomeric alkoxide before it can perform S_N2 attack on the allylic bromide.

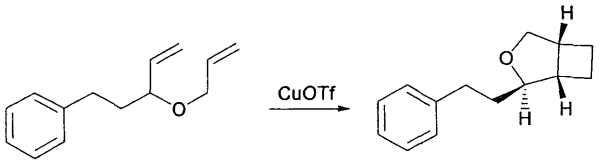


52 55 53

Now with the (3-allyloxypent-4-enyl)benzene **53** for study, small-scale reactions could be done with CuOTf catalyst.

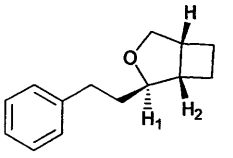
2.1.1 Preparative Photoannulation Reactions with the Aromatic Diene 53.

In order to study the [2+2] cycloaddition reaction with new catalysts, a racemic reference compound is needed so that it can be screened for in small-scale reactions. Photoannulations using the CuOTf catalyst produce the racemic product. (3-Allyloxypent-4-enyl)benzene **53** was reacted with CuOTf and yielded 60% of the racemic *exo*-2-benzyl-3-oxabicyclo[3.2.0]heptane **56**.



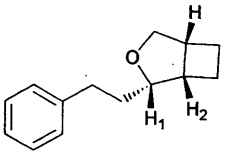
53 56

Exo-2-benzyl-3-oxabicyclo[3.2.0]heptane **56** was characterised by NMR assignment and signal correlation with previously assigned spectra. 2D NMR was used to assign the *exo* product **56**. The methine proton next to oxygen in exo-2-benzyl-3-oxabicyclo[3.2.0]heptane **56** appears at doublet-doublet in the proton NMR. We explain this by coupling only to the adjacent diastereotopic methylene protons and no coupling to the *exo* bridge-head proton (H_2). The reason for this is that dihedral angle between the two protons (H_1 and H_2) is 90° and the coupling constant between these two protons is zero. This would not be the case in the *endo* isomer **57** where the corresponding dihedral angle is 0° between H_1 and H_2 and the coupling constant by Karplus curve would expected to be 9 Hz.



exo, 120°

56



endo, 0°

57

This result is supported by decoupling experiments. If the downfield proton (H-1) is decoupled, the signal at δ~ 2.4 ppm (H-2) remains the same. This means that H-1 and H-2 are not coupled as shown in Figure 3.

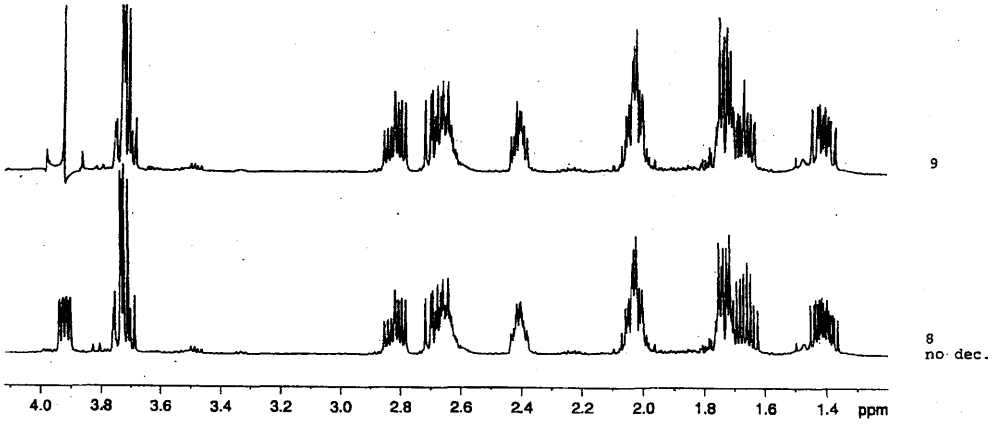


Fig. 3. Decoupling of exo-2-benzyl-3-oxabicyclo[3.2.0]heptane **56.**

According to our plan to obtain cyclobutanation reaction with other metals, we carried out the photochemical annulation of (3-allyloxy-pent-4-enyl)-benzene **53** with several other metals.

2.1.2 Investigative Photoannulations with the Aromatic Diene 53.

To study comparable with the CuOTf catalysed reactions, a catalytic amount of metal complex was used in the following cases. A set of three trial reactions were set up using the carousel of quartz tubes. (3-Allyloxypent-4-enyl)benzene **53** was irradiated with a number of catalysts in dry benzene.

After irradiation each reaction mixture were passed through a small plug of silica to remove degraded catalyst. The result showed that in the cases, W and Mo complex, only starting material was obtained. A faint spot consistent with cyclobutane **56** was

obtained in the reaction correspond with $PdCl_2(CH_3CN)_2$. The reaction was scaled up and the cyclobutane **56** was isolated in 67% yield by flash chromatography. The required product was characterised by NMR assignment and signal correlation with previously assigned spectra. 2D NMR spectrum showed that the product was the *exo* product with the same signals as the *exo* product with CuOTf.

N°	Catalyst/ Amount	solvent	Diene/amount	TLC
1	$PdCl_2(CH_3CN)_2$/14mg (10 mol %)	benzene	100 mg	SM + cyclobutane
2	W $(CO)_6$ / 12 mg (10 mol %)	benzene	100 mg	SM
3	Mo $(CO)_6$ / 16 mg (10 mol %)	benzene	100 mg	SM
4	$PdCl_2(CH_3CN)_2$/135 mg stoichiometric	benzene	100 mg	SM + cyclobutane

2.1.3 Thermal Cyclisation Reactions of Diene 53.

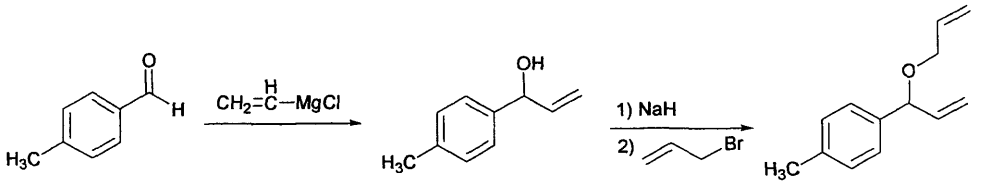
A reaction was set up to see if the $PdCl_2(CH_3CN)_2$ could catalyse a thermal reaction with the aromatic diene (3-allyloxypent-4-enyl)benzene **53**. As mentioned earlier, the [2+2] cycloaddition is forbidden thermally and should not occur here. If the reaction is to occur it must be via an alternative oxidative addition-reductive elimination mechanism via a metallocyclopentane intermediate. In such a case, the metal centre would lose two Cl ligands to become coordinatively unsaturated, and then coordinate the two allylic groups. As two σ-bonds are made to the metal it is oxidised. The achiral Pd catalyst and aromatic diene (3-allyloxypent-4-enyl)benzene **53** were refluxed in solvent (THF) for 24 hours. Reactions with 10% of the Pd complex and a stoichiometric amount were conducted at the reflux temperature for the solvent used.

N°	catalyst	Cat/diene	Solvent/temp	Diene amt	TLC
1	$PdCl_2(CH_3CN)_2$	1:1	THF / 80°C	200 mg	SM
2	$PdCl_2(CH_3CN)_2$	0.1:1	THF / 80°C	200 mg	SM

The reaction mixture were analysed by TLC and compared with an authentic sample of cyclobutane *exo*-2-benzyl-3-oxabicyclo[3.2.0]heptane **56**. In both cases only starting material was obtained.

2.1.4 Preparative Photoannulation Reactions with the Aromatic Diene 60.

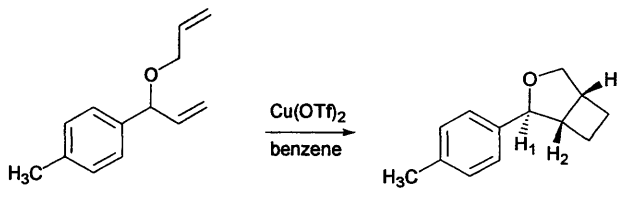
The synthesis of a new model system was investigated.



58 59 60

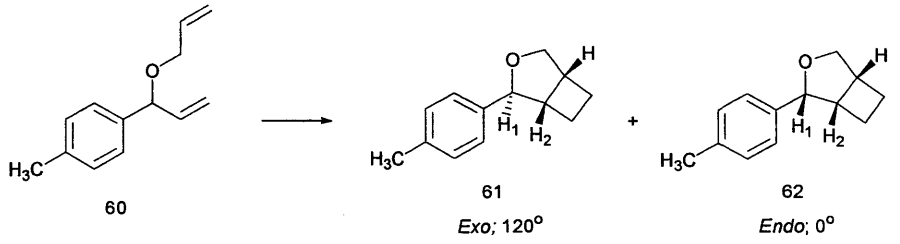
p-Toluenaldehyde **58** was reacted with vinylmagnesium chloride to yield 1-(4-methylbenzene)prop-2-en-1-ol **59** in 58% yield. This mechanism also goes by non-stereoselective attack of the Grignard reagent ("CH_2=CH^-") on the carbonyl carbon to yield 1-*p*-tolylprop-2-en-1-ol **59**. The mechanism is shown in the synthesis of 5-phenylpent-1-en-3-ol **52**.

After characterisation of 1-(4-methylbenzene)prop-2-en-1-ol **59** it was alkylated with allyl bromide to yield 1(1-allyloxyallyl)-4-methylbenzene **60** in 70% yield. This mechanism is also shown in the synthesis of (3-allyloxypent-4-enyl)benzene **53.** 1(1-Allyloxyallyl)-4-methylbenzene **60**, diethyl ether and a catalytic amount of $Cu(SO_3CF_3)_2.C_6D_6$ were added to a quartz photochemistry tube and *exo*-oxa-bicyclo[3.2.0]heptane **61** was obtained in 55% yield.



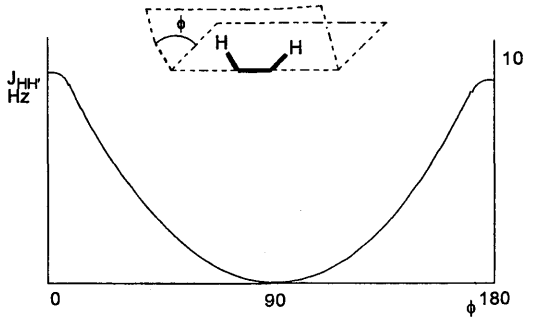
60 61

Once again, two possible diastereoisomers can be the result of this reaction but only *exo* product was obtained. This result can be explained by the methine proton (H_1) next to oxygen in product **61,** which appears at 5 ppm as a singlet. This means that the dihedral angle with H_2 is 90° again and there is not coupling to the *exo* bridge-head proton, furthermore the coupling constant is zero. In case we had obtained the *endo* diastereoisomer, the methine proton next to the oxygen in product **62** would appear as a doublet and the dihedral angle would also be 0° with a coupling constant of 8 Hz according to the Karplus curve.



60 61 62

Exo; 120° *Endo;* 0°



Karplus curve

2.1.5 Investigative Photoannulations with the Aromatic Diene 60.

To study again comparable with the CuOTf catalysed reactions, a catalytic amount of metal complex was used in the next reactions. A set of three trial reactions were set

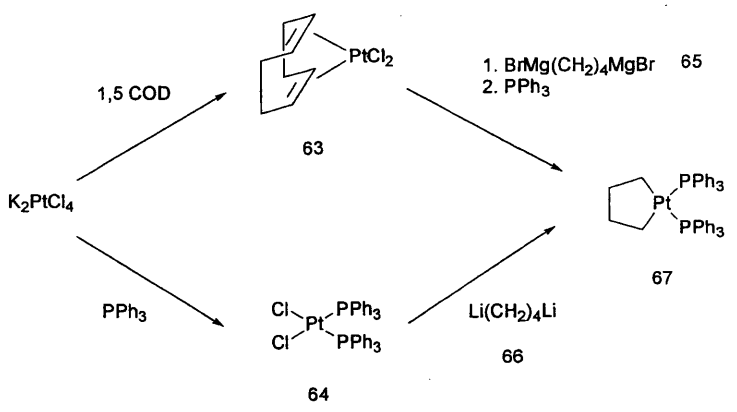
up using the carousel of quartz tubes. 1(1-Allyloxy-allyl)-4-methylbenzene **60** was irradiated with a number of catalysts in dry benzene.

N°	Catalyst/ Amount	solvent	Diene/amount	TLC
1	$PdCl_2(CH_3CN)_2$/14mg (10 mol %)	benzene	100 mg	SM
2	W $(CO)_6$ / 12 mg (10 mol %)	benzene	100 mg	SM
3	Mo $(CO)_6$ / 16 mg (10 mol %)	benzene	100 mg	SM
4	$PdCl_2(CH_3CN)_2$/135 mg stoichiometric	benzene	100 mg	SM

After irradiation each reaction mixture were passed through a small plug of silica to remove degraded catalyst. The result showed that in all cases as W, Mo and Pd complex, only starting material was obtained.

2.2 Platinocycles and Reductive Elimination.

The basis of this project comes from a previous study of the thermal decomposition of organometallic platinocycles as reported by Whitesides *et. al.* in 1976.[23] Two routes to the formation of these platinocycles were reported (Scheme 4).



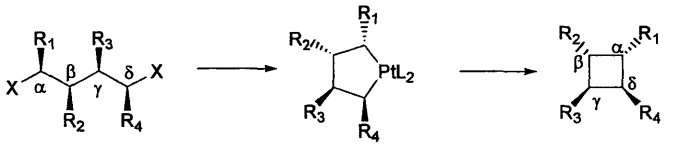
Scheme 4, Preparation of 1,4-Tetramethylenebis(triphenylphosphine)platinum(II).

The original work of Whitesides used 1,5-cyclooctadiene (COD) complexes in reactions with Grignard reagents. Work up of the reactions in the presence of triphenylphosphine yielded the metallocycle products such as **67** with two phosphine ligands. Alternatively, bisphosphine complexes such as **64** were reacted with alkyllithium reagents **66** and this method would also undergo the formation of platinum-carbon bonds. The formation of metallocycles depends upon the use of a bisnucleophile, such as a bisGrignard reagent. In principle, once the first Grignard component of a molecule of reagent has reacted with the platinum electrophile, substitution of the second could occur *intra*molecularly with the same platinum center or *inter*molecularly with a different platinum centre. Whitesides did not observe any dimerisation or indeed, any polymerisation in such reactions. However, monoalkylated platinum(II) compounds were being formed in some cases. For example, in the addition of bisGrignard reagents to dichloro(1,5-COD)platinum(II) **63**, the second substitution did not always occur. In such cases, it was found that the desired disubstituted, cyclic complex could be made by reaction of the alkyllithium analogue of the Grignard reagent with the corresponding dichlorobis(phosphine)platinum(II) complex **64**.

Each of the two methods has advantages and disadvantages. Whitesides commented that the Grignard reagents were easier to prepare and are more stable than the alkyllithium compounds. However, yields were higher when alkyllithium reagents were used and unlike in the cases with the Grignard reagents, chromatographic purification was often not necessary. The dilithium reagents were also less soluble in hydrocarbon solvents than Grignard reagents but were easier to use in terms of their reaction with bisphosphine complexes **63** rather than COD complexes **64** as with Grignard reagents.

It was felt that a range bis(phosphine)platinocyclopentane analogues similar to those reported by Whitesides could be prepared utilising the same methodology. The study of their thermal reductive elimination reaction may then produce a new procedure for the preparation of cyclobutane derivatives. To carry this out, the two carbon nucleophiles must clearly be in a α-δ relationship to eventually form the four-membered cyclobutane ring. Substituents on any of the carbon atoms α, β, γ or δ would potentially be acceptable but may exhibit electronic or steric related problems during the formation of the platinocyclopentane **69** and/or its reductive elimination but this may depend on the size and chemical nature of the group. However, prior to experimental proof, it is

anticipated that the relative stereochemistry at all centers α-δ would be controlled (though not necessarily *maintained*) in both the platinocycle and cyclobutane formed. One reasonable proposal is that the reaction of the organonucleophile with platinum will proceed by S_N2 mechanism (inversion of configuration at C_α and C_δ) and that reductive elimination, being a concerted process, would maintain the relative configuration in the platinocycle. This and similar hypotheses may form the basis of later projects. The important element of the reaction though, is the *control* of the stereochemistry of the products formed.

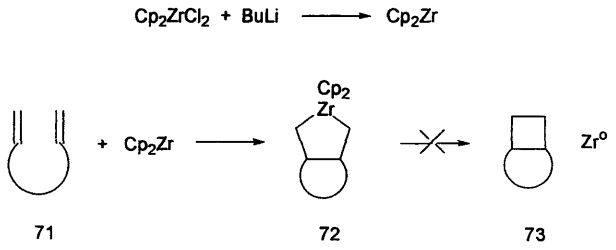


68 69 70

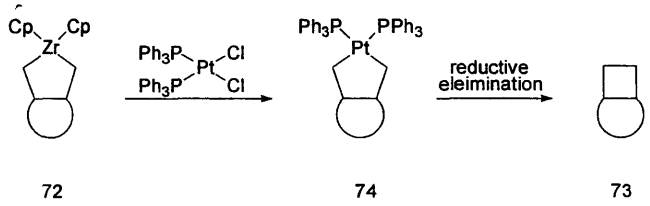
Whitesides reported the formation of a totally unsubstituted cyclobutane. In practice, repetition of this work was challenging. Formations of 1,4-butanedi(magnesiumbromide) **65** and 1,4-dilithiobutane **66** were achieved but reaction of these nucleophiles with platinum did not proceed in accordance with those reactions reported. For example, reaction of the organolithium reagent, 1,4-dilithiobutane, with dichlorobis(triphenylphosphine)platinum(II) **64** gave a product that did not melt below 320°C (for tetramethylenebis(triphenylphosphine)platinum (II), **67** (lit. mp = 197 °C))[23] and had misleading ^1H and ^{31}P NMR spectra. Additionally, no evidence of the expected parent ion was detected by mass spectrometry. It was not obvious from the data obtained as to what exactly had happened in the reaction. More experiments were necessary to ascertain the nature of the chemical transformations that had taken place.

2.2.1 The Application of Sulphonamide Zirconium Cyclisation to Cyclobutanation.

The formation of metallocyclopentane structures is well known for zirconium chemistry.[24]

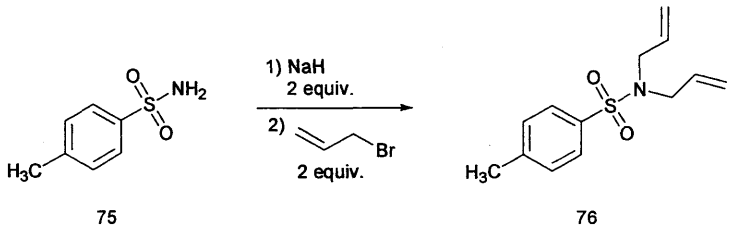


The *in situ* formation of zirconecene Cp_2Zr is followed by reaction with the diene **71** to produce the metallocyclopentane **72**. The reductive elimination of the zirconium in **72** to produce the cyclobutane **73** has not been observed. Our aim in this part of the project is to transmetallate the zirconium in **72** to another metal which can undergo a reductive elimination to form a cyclobutane. One example of such a metal would be platinum.

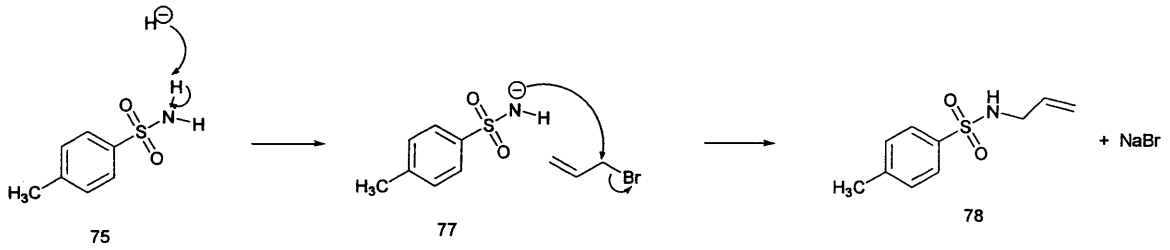


2.2.1a *N,N*-Diallylsulphonamide (76) Synthesis.

We first synthesised a simple model compound to study the zirconation reaction. *N,N*-Diallyl-*p*-toluenesulphonamide **76** was synthesised using one step procedure.



4-Methyl-benzenesulphonamide **75** was reacted with 2 equivalents of NaH. This mechanism requires deprotonation of the amine with a strong base to produce the sulphonamide anion **77** which then undergoes allylation by an S_N2 process to produce *N,N*-diallyl-4-methylbenzenesulphonamide **78**. Repetition of this process leads to the diallyl sulphonamide **76** in 38% yield.

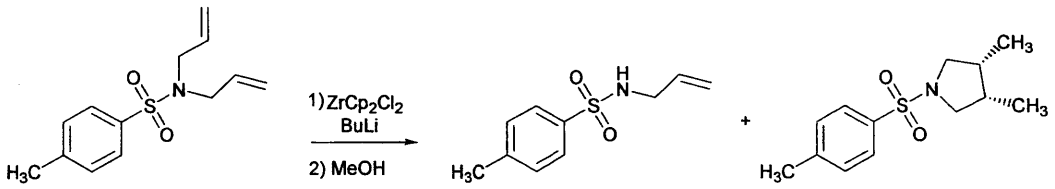


75 77 78

2.2.1b Diallylsulphonamide (76) Ziconium Reaction.

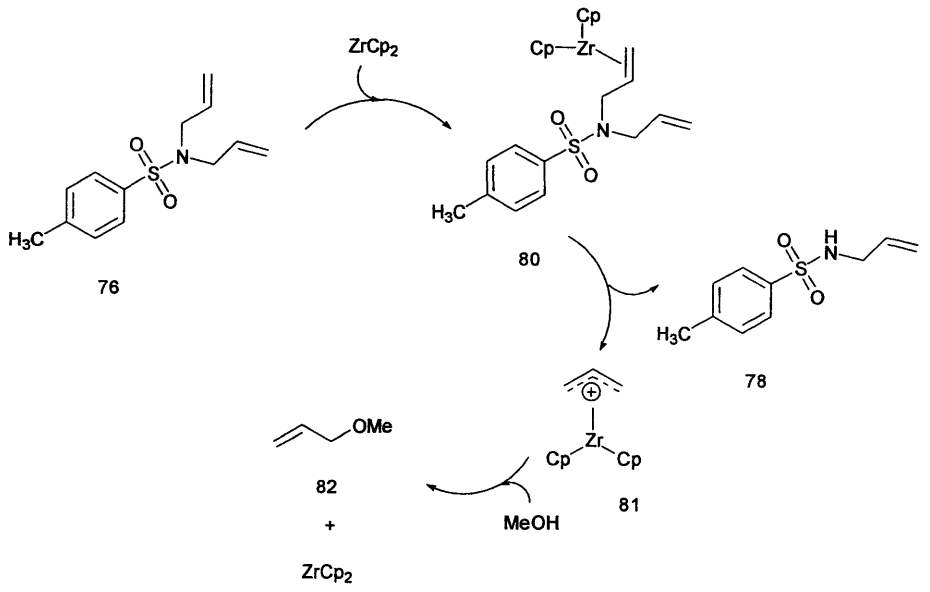
Diallyl sulphonamide **76** was reacted with $ZrCp_2Cl_2$ complex and BuLi under nitrogen using a vacuum line to give the zirconium metallocycle and then MeOH was added to the reaction to yield 3,4-dimethyl-1-(toluene-4-sulphonyl)pyrrolidine **79** in 4% yield and *N*-allyl-4-methyl-benzenesulfonamide **78** in 7% yield.

$$ZrCp_2Cl_2 + BuLi \longrightarrow ZrCp_2$$



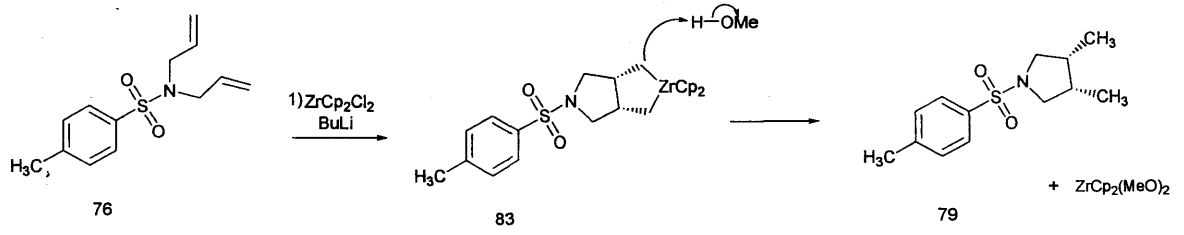
76 78 79

^{1}H NMR of *N*-allyl-4-methylbenzenesulphonamide **78** showed signals at 5.25 ppm as one olefinic hydrogen and at 4.40 ppm as NH hydrogen which indicates the resulting product was deallylation of the starting material. We propose the same mechanism for the deallylation of product **78.**



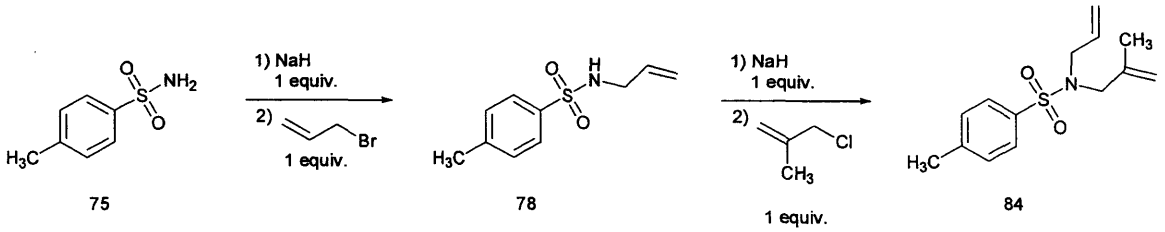
The first step is the coordination of the zirconecene Cp_2Zr to one of the olefinic bonds in diallyl sulphonamide **76**. Then there is elimination of *N*-allyl-4-methyl-benzenesulfonamide **78** which acts as a leaving group. Treatment of cation **81** with MeOH gives to product **82**.

The formation of 3,4-dimethyl-1-(toluene-4-sulphonyl)pyrrolidine **79** goes through a metallocyclopentane mechanism. After addition of zirconecene Cp_2Zr the zirconacycle **83** is formed. Both methylenes α to zirconium can undergo nucleophilic attack on the MeOH and 3,4-dimethyl-1-(toluene-4-sulphonyl)pyrrolidine **79** was obtained in poor yields. Special conditions are required as the zirconium ring is very sensitive to the air.



2.2.1c *N*-Allyl-4-methyl-*N*-(2-methyl-allyl)-benzenesulphonamide (84) Synthesis.

N-Allyl-4-methyl-*N*-(2-methylallyl)benzenesulphonamide **84** was synthesised in a two-step procedure. The first step consisted in the synthesis of allyl sulphonamide **78**. It was obtained in 17% yield. The mechanism is shown in the synthesis of diallyl sulphonamide **76** above.

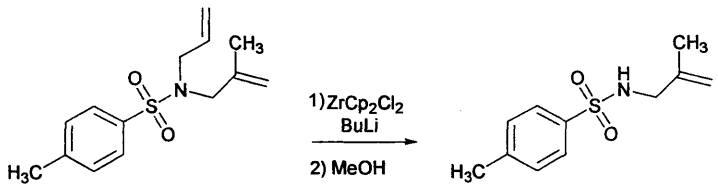


75 78 84

The synthesis of *N*-allyl-4-methyl-*N*-(2-methylallyl)benzenesulphonamide **84** followed the same procedure but after addition of sodium hydride, 3-chloro-2-methyl-1-propene was added instead. The mechanism is also the same as synthesis of diallyl sulphonamide **76** above. *N*-Allyl-4-methyl-*N*-(2-methylallyl)benzenesulphonamide **84** was obtained in 82% yield.

2.2.1d *N*-Allyl-4-methyl-*N*-(2-methylallyl)benzenesulphonamide (84) Zirconium Reaction.

$ZrCp_2Cl_2$ was reacted with BuLi to give zirconecene $ZrCp_2$. *N*-Allyl-4-methyl-*N*-(2-methylallyl)benzenesulphonamide **84** was added to the mixture with the aim of forming the zirconium metallocycle. However, after adding MeOH, 4-methyl-*N*-(2-methylallyl)benzenesulphonamide **85** was obtained in poor yield as the only isolated product.

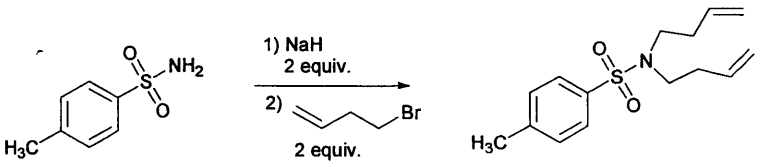


84 85

The ^1H NMR clearly indicated that 4-methyl-*N*-(2-methylallyl)benzenesulphonamide **85** had been obtained as there were only 2 olefinic protons. No evidence of products arising from metallocyclopentane intermediate was obtained.

2.2.1e *N,N*-Di-but-3-enyl-4-methylbenzenesulphonamide (86) Synthesis.

N,N-Di-but-3-enyl-4-methylbenzenesulphonamide **86** was prepared from the reaction of 4-methylbenzenesulphonamide **75** and 2 equivalents of 4-bromo-1-butene to yield *N,N*-di-but-3-enyl-4-methylbenzenesulphonamide **86** in 20% yield. The mechanism is shown in the synthesis of diallyl sulphonamide **76** above.

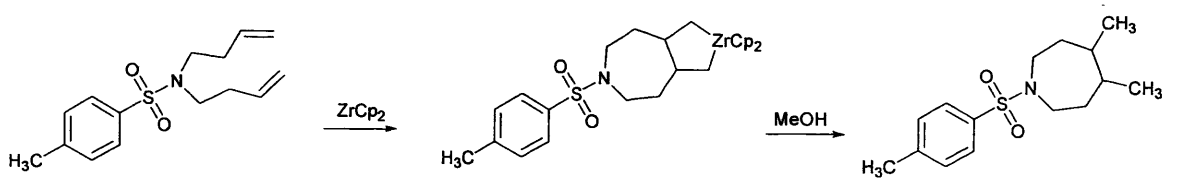


75 86

The ^1H NMR of **86** showed signals at 5.75 ppm as ddt (2H) and 4.93-5.16 ppm as multiplet (4H) which clearly demonstrates that double alkylation has occured. The product had 5 non aromatic signals in the ^{13}C NMR. We can, therefore study the formation of the zirconocycle.

2.2.1f *N,N*-Di-but-3-enyl-4-methylbenzenesulphonamide (86) Zirconium Reaction.

N,N-Di-but-3-enyl-4-methylbenzenesulphonamide **86** was reacted with $ZrCp_2Cl_2$ complex and BuLi. After adding MeOH to the reaction 4,5-dimethyl-1-(toluene-4-sulphonyl)azepane **88** was obtained in 5% yield. The product showed a signal at 0.92 ppm as doublet (6H) which corresponds to 2 x CH_3 in the ^1H NMR. The product had 5 non aromatic signals in the ^{13}C NMR. The MS was 282 (100%) which corresponds to 4,5-dimethyl-1-(toluene-4-sulphonyl)azepane **88**. Only one diastereoisomer was obtained but it is not possible to say if we obtained *cis* or *trans* isomer. We can propose the following mechanism for the reaction:

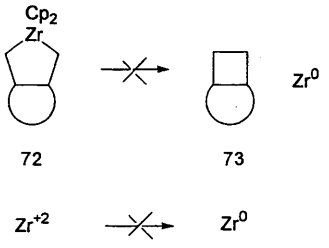


86 87 88

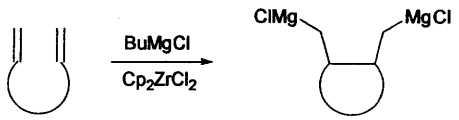
According to these results, zirconecene diene complexes are formed in low yields. One possible explanation for this is the electron withdrawing effect of the *N*-tosyl-group. Our next objective was to synthesise substrates with an allyl group on the nitrogen.

2.2.2 The Application of Benzylamine Zirconium Cyclisation to Cyclobutanation.

Earlier, it was explained that zirconium-promoted cyclizations of dienes. These cyclizations are useful in synthetic organic chemistry. The aim of this project was to work with zirconium-catalysed carbomagnesation and cyclization in the presence of Grignard reagent. In general, when a stoichiometric amount of zirconium complex is used for cyclisation, a thermodynamic zirconocycle generated, and in a zirconium-catalyzed cyclization using Grignard reagent, a kinetic zirconocycle is produced. When a thermodynamic zirconacycle is furnished, it is impossible to obtain a thermal reductive-elimination reaction of the zirconametallocycle.[24]

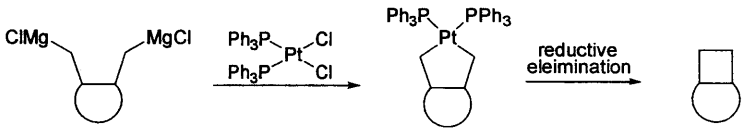


As described above zirconocene can be used in stoichiometric quantities to generate zirconocyclopentane intermediate. Zirconocene may also be used in catalytic amounts to catalyse the conversion of a diene **71** into cyclic bis Grignard reagents **89**.[24]



71 89

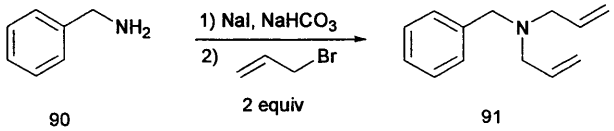
In the new method, we will then try to study the thermal reductive elimination reaction of the platinocyclo **74**, which leads to cyclobutane **73**.



89 74 73

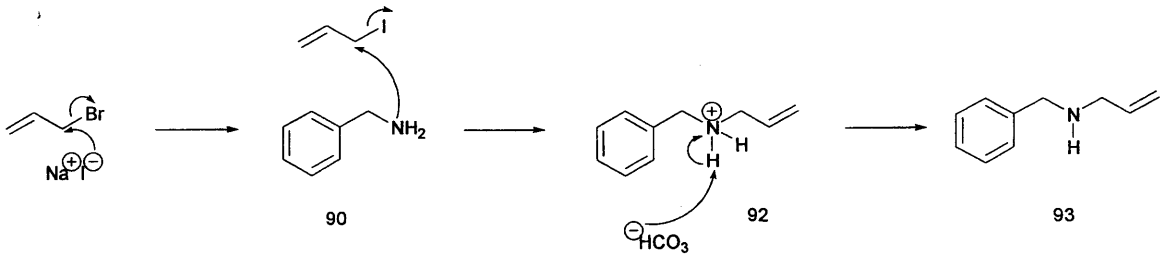
2.2.2a *N,N*-Diallylbenzylamine (91) Synthesis.

Benzylamine **90** was reacted with 2 equivalents of allyl bromide to give *N,N*-diallylbenzylamine **91** in 61% yield.



90 2 equiv 91

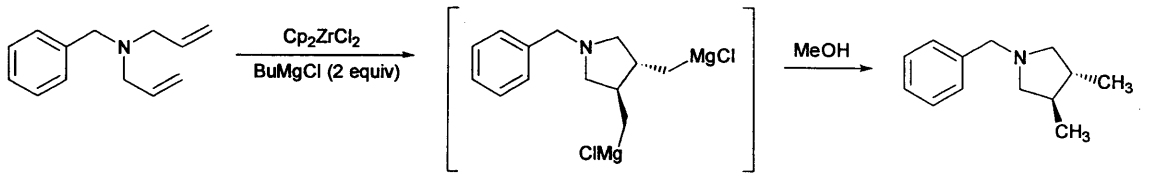
Sodium iodide undergoes nucleophilic attack on the allylic bromide and the more reactive allyl iodide was obtained. Benzylamine **90** can perform S_N2 attack on the allyl iodide to give intermediate **92**. Sodium hydrogencarbonate takes a proton in the intermediate **92** to give *N*-allyl-*N*-benzylamine **93.** The same process is carried out to get the final product *N,N*-diallylbenzylamine **91**.



90 92 93

2.2.2b *N,N*-Diallylbenzylamine (91) Zirconium Reaction.

N,N-diallylbenzylamine **91** was reacted with Cp_2ZrCl_2 (10%) in the presence of BuMgCl (2 equiv).[24]

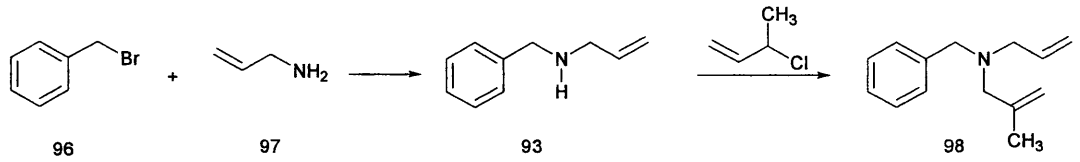


91 94 95

MeOH was added to the reaction and 1-benzyl-3,4-dimethylpyrrolidine **95** was obtained in 20% yield. The ^{1}H NMR of 1-benzyl-3,4-dimethylpyrrolidine **95** showed a main signal at 1.04 ppm as doublet (2 x CH_3). The accurate mass was 185.2357 and the product had 4 non aromatic signals in the ^{13}C NMR.[25]

2.2.2c *N*-Allyl-*N*-benzyl-*N*-(2-methylallyl) (98) Synthesis.

A second substrate was obtained by reacting allyl amine **97** with benzylbromide **96** to give *N*-allyl-*N*-benzylamine **93** in 80% yield.

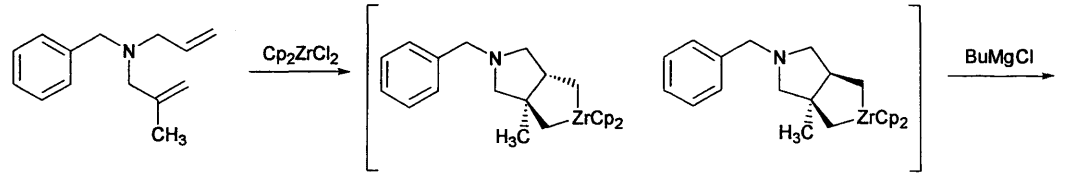


96 97 93 98

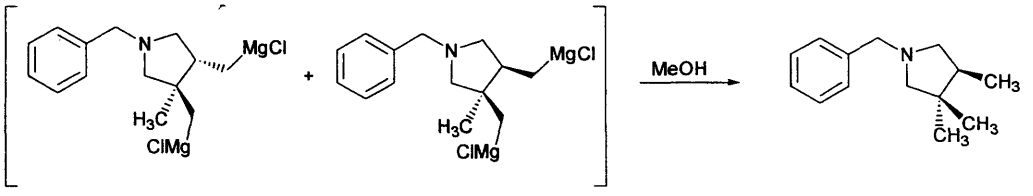
This mechanism goes by S_N2 attack. After purification, *N*-allyl-*N*-benzylamine **93** was reacted with methylallyl chloride to furnish the *N*-allyl-*N*-benzyl-*N*-(2-methylallyl)amine **98** in 65% yield. The ^{1}H NMR of **98** showed one olefinic signal at 6.05 ppm as ddt (1H) and multiplet (4H) respectively. The product had 8 non aromatic signals in the ^{13}C NMR.

2.2.2d *N*-Allyl-*N*-benzyl-*N*-(2-methylallyl)amine (98) Zirconium Reaction.

Compound **98** was reacted with Cp_2ZrCl_2 and BuMgCl. *N*-Allyl-*N*-benzyl-*N*-(2-methylallyl) amine **98** was treated in a similar manner to *N,N*-diallylbenzylamine **91**. The mechanism goes through zirconacycle intermediates **99** and **100**. Transmetallation from BuMgCl leads to the Grignard intermediates **101** and **102** and addition of MeOH produces 1-benzyl-3,3,4-trimethylpyrrolidine **103** in 33% yield.[24]

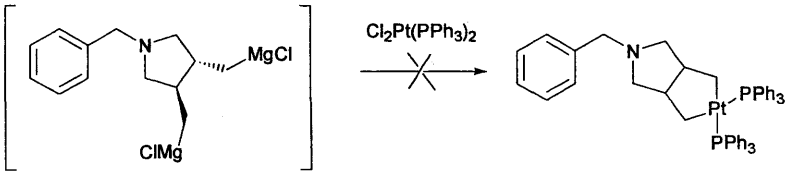


98 99 100



101 102 103

The same reaction was repeated with compounds **91** and **98** in order to get the transmetallation of the Grignard intermediate with the platinum complex and final reduction elimination to the cyclobutane. Both reactions were not successful and transmetallation was not observed.

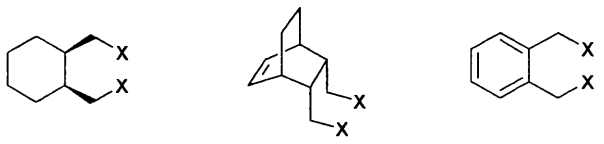


94 104

As this chemistry was not successful we transferred our attention to alternative platinocycle precursors.

2.2.3 Alternative Platinocycle Precursors.

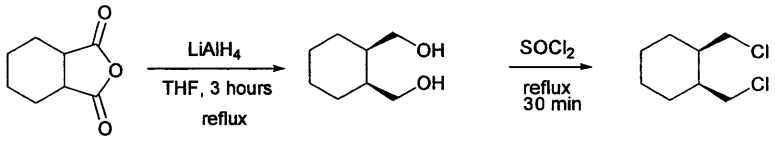
One of the problems in studying the formation of cyclobutane is that it is relatively volatile (lit. bp = 11-13 °C [26, 27]). By studying cyclobutanes of higher molecular weight, isolation and characterisation of final product will be easier.



105 106 107

Three platinocycle precursors **105**, **106** and **107** were considered to be useful starting points which would lead to non volatile cyclobutane products. The compounds based on cyclohexane target structure **105** was synthesised first.

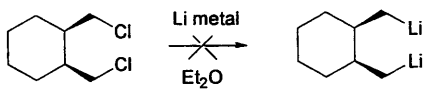
Cyclohexane-1, 2-dicarboxylic anhydride **108** was reacted with lithium aluminium hydride to give the diol **109** in 79% yield.



108 109 110

The diol **109** was converted into the dichloride **110** in 72% yield using thionyl chloride.

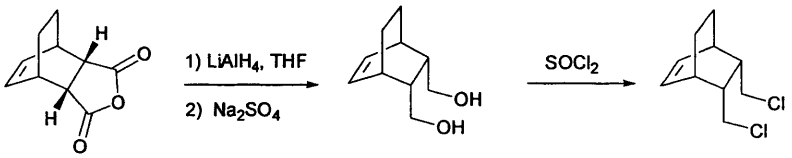
The dichloride **110** was treated with lithium that had been flattened, cleaned and suspended in ether, no reaction took place.



110 111

A new precursor was synthesised. *Endo*-bicyclo[2.2.2]oct-2-ene-5,6-dicarboxylic anhydride **112** was reduced with $LiAlH_4$ to produce diol **113**. By minimising aqueous

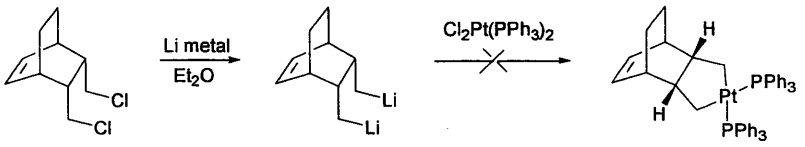
work-up the overall yield for the reaction was maximised and 98% yield was observed. As before with the cyclohexyl analogue **110** the dichloride **114** was made by treatment of the diol precursor with thionyl chloride. The dichloride **114** was obtained in 83% yield as white needles.



112 113 114

All attempts to make the corresponding bis(magnesiumchloride) Grignard reagents of cyclohexyl system **105** and the [2.2.2]bicyclooct-2-ene system **106** failed despite careful purification of the dichloride used. All reagents were kept dry and reactions were carried out under inert conditions, however, reactions with magnesium could still not be initiated.

Preparation of the dilithio derivative **115** was carried out. Following the same process as with dichloride **110**, lithium metal was flattened and cleaned in a nitrogen free atmosphere then suspended in diethyl ether. The dichloride **114** was added to the metal and initiation appeared to occur. After stirring overnight, the solution was filtered to remove lithium salts, the reaction mixture was added to dichlorobis(triphenylphosphine)-platinum(II) showed non of the desired platinocycle formation by NMR and MS. After work-up dichloride **114** was recovered in 55% yield.

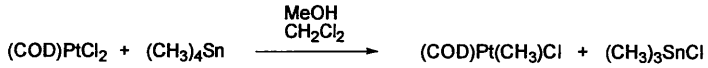


114 115 116

2.2.3a Alternative Organometallic Precursors.

Due to the difficulty experienced with the formation of bis-Grignard reagents of **105** and **106** and the reaction of alkyllithium reagents **111** and **115** with platinum(II) compounds, it was decided to consider alternative strategies for the formation of platinocyclopentanes. Decker and co-workers have reported that alkylstannanes

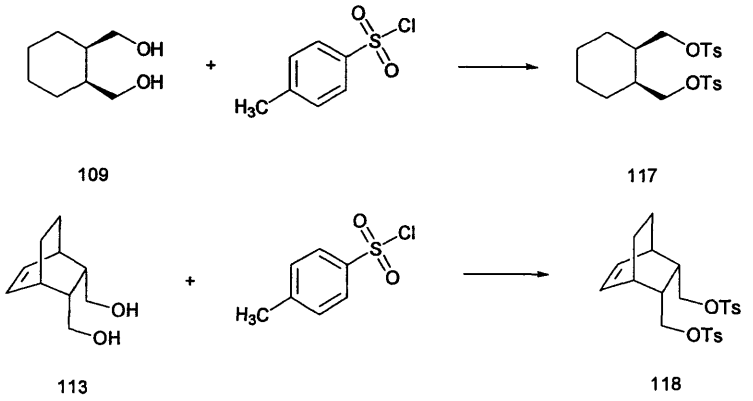
undergo substitution reactions with platinum(II) electrophiles to produce platinum-carbon bonds.[28]



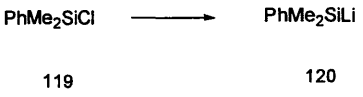
Additionally, although no precedent for their substitution reaction with platinum has been found thus far, a plethora of organsilicon compounds have been made and it was anticipated that such compounds could be prepared in the laboratory. Although silicon is not a metal as it lies on the non-metal side of the border in the periodic table, it is more electropositive than carbon and so the δ- carbon may undergo nucleophilic reactions with platinum electrophiles. As such, organotin and organosilicon nucleophiles became the next class of compounds to be studied in nucleophilic substitution reactions with platinum(II) compounds.

In order to form the organotin and organosilicon reagents, suitable precursors were made and reacted with the appropriate tin and silicon nucleophiles. Chloride is not a particularly good leaving group although there is some literature precedent to support formation of organosilicon compounds by reaction of alkylchlorides with silicon nucleophiles.[29] Additionally, there is precedent for the formation of alkylstannanes from alkylhalide precursors.[30] However, to increase the likelihood of reaction, corresponding tosylate and triflate analogues of the bicyclic system and cyclohexyl system were made.

The cyclohexyl system was converted firstly to a ditosylate. Treatment of the diol **109** with 2 equivalents of *p*-toluenesulphonylchloride with triethylamine yielded the ditosylated product **117** in 71%. Formation of the ditosylate **118** was carried out in a similar fashion by treatment of diol **113** with *p*-toluenesulphonylchloride and triethylamine base. After column chromatography only 15 mg of the desired ditosylate product were obtained, the majority of the reaction appeared to have given a mono-tosylate product.

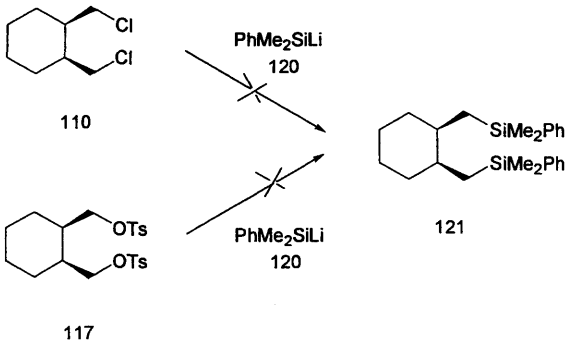


A literature search provided precedent for the formation of stannyllithium and silyllithium reagents and their reaction as nucleophiles to form corresponding alkylstannane and alkylsilane products.[30, 31] In the case of formation of the dimethylphenylsilyllithium reagent **120**, reactions were carried out under argon atmosphere for 16 hours at 8 °C. As before, the use of argon atmosphere prevented formation of nitride layer on the lithium metal. The metal was flattened in paraffin with a hammer and washed with absolute THF under argon to produce a large, shiney surface on the metal. Dimethylphenylsilyl chloride **119** was then added to the metal at –8 °C as a solution of THF and the reaction left in the cold room where it gradually warmed to 8 °C. After maintaining this temperature overnight, the mixture had turned to a blood-red coloured solution that was quenched with water and titrated to determine the quantity of silyllithium compound present.

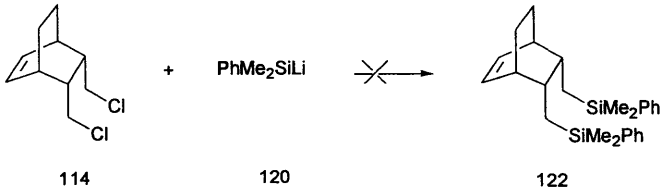


Several attempts were required to optimise the reaction. In the first cases the reaction was not initiated satisfactorily and even after stirring under argon atmosphere for up to four days at a time, the reaction mixture did not turn red. With the addition of more clean lithium, the reaction often initiated and after stirring for an additional day the reaction then yielded the required red solution. By cleaning the metal in paraffin and then washing the shiny surface under argon as described above and by using dry solvents, the reactions proceeded much more readily and gave resulting solutions of higher concentration.

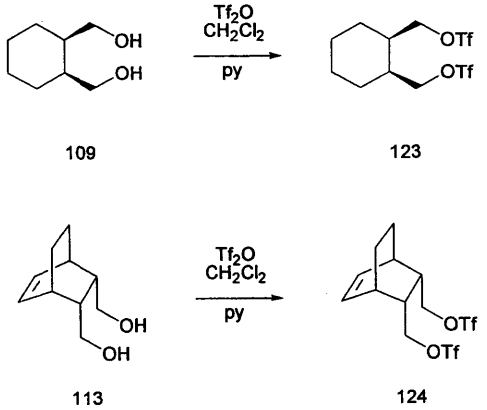
Reaction of the silyllithium compound **120** with the dichloride **110** did not give the product **121**. The reaction was carried out with the tosylate **117** in parallel with the reaction of the dichloride **110**. Both reactions were carried out identically – i.e use of the same reagents and conditions but the tosylate reaction yielded non of the desired product **121**.



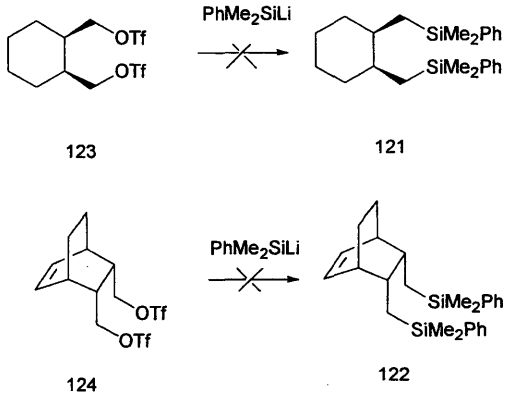
Reaction of the silyllithium compound **120** with the dichloride **114** did not give the desired product **122.**



The triflates **123** and **124** were prepared in parallel by treatment of the diol **109** and **113** with trifluoromethanesulphonic anhydride in dichloromethane with pyridine base.[32] The products were obtained in modest yields (**123** in 24%, **124** in 27%).



Reaction of the triflates **123** and **124** with $PhMe_2SiLi$ were carried out in an experiment to determine whether the use of a better leaving group than tosylate and dichloride compounds would yield the desired silyl products, the experiments were carried out in parallel. Results for the two reactions were negative; neither reaction showed even a trace of product. Perhaps, there was a problem with the silyllithium solution and this may have been the source of the problem. However, this is unlikely as the solution had been made and used on the same day and had turned red on formation as before. This indicates that the desired $PhMe_2SiLi$ product had formed and also, as the quenched solution was titratable with acid this also suggests that there was some of the silyllithium product present. Although every effort was made to ensure that the reactions were carried out under the same conditions as before, clearly there was a problem somewhere and it could have originated from a number of sources. For example, if solvents or syringes hadn't been dried properly, the reactions would not have worked as expected as the $PhMe_2SiLi$ compound would have hydrolysed and been unreactived towards the alkyl electrophiles. Therefore, no conclusion as to the utility of triflates in the reaction with such silyllithium reagents can be drawn.



2.2.3b Stannyllithium Nucleophiles.

Precedent for the formation of stannyllithium species came from a publication by Kitching.[30] Trimethylstannyllithium was prepared in a fashion analogous to that for the formation of the silyllithium compound discussed above. Lithium metal was flattened with a hammer in paraffin and washed with anhydrous THF several times under an argon atmosphere. The metal was then suspended in the solvent and trimethyltin chloride was added as a solution of THF. After stirring at room temperature for 2

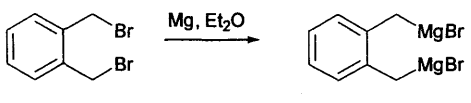
hours, the reaction mixture turned from colourless to a dark green colour. As with the silicon derivative, the tin solution was then filtered through celite under inert conditions to remove excess lithium and salts formed during the reaction. An aliquot of the green solution was then quenched with water to liberate LiOH which was titrated against a standardised aqueous acid solution to allow the concentration of Me_3SnLi **126** solution to be determined.

As before with the $PhMe_2SiLi$ solution, the tin nucleophile was added to the two chlorides **110** and **114** and the two triflates **123** and **124**. None of the reactions appeared to work. Crude ^1H NMR of all reaction mixtures after evaporation showed essentially dichloride or ditriflate starting materials.

2.2.3c α,α'-Dibromo-*o*-xylene and Metallation Reactions.

The benzylic *o*-xylene derivatives **107** were also studied as a platinocycle precursors. In order to get results, repetition of reaction of the acyclic derivatives 1,4-dibromobutane and 1,4-dichlorobutane were undergo with magnesium and lithium.

Commercially available α,α'-dibromo-*o*-xylene precursor **127** was reacted with magnesium to produced the corresponding bis-Grignard reagent **128.** Reaction was carried out exactly as with cyclohexyl chloride **110** and the alkyl bicyclic dichloride **114** but where the formation of bis-Grignard reagent had failed, the desired product was now being formed.

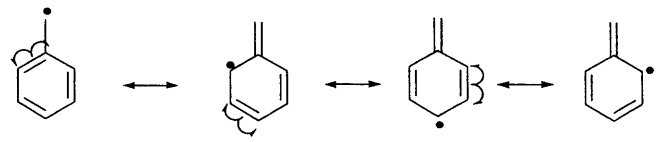


127 128

There are two factors which differ from the reactions of cyclohexyl chloride **110** and the alkyl bicyclic dichloride **114** to that with α,α'-dibromo-*o*-xylene **127**. Firstly, the most noticeable difference is the fact that the dibromide is being used for the

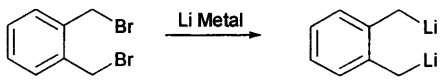
formation of the Grignard reagent. Considering the mechanism of formation of Grignard reagents via alkyl radicals, it is evident that as the halide leaves formally as an anion, X^-, then it might be expected that bromide analogues more easily form Grignard reagents than chlorides as Br^- is a better leaving group than Cl^-.

Additionally, where as before there was formation of an alkyl radical for the alkyl dichlorides **110** and **114**, the corresponding radical for the formation of the α,α'-di(magnesiumbromide)-*o*-xylene **128**, is a benzylic radical. Benzylic radicals are more stable than corresponding alkyl radicals as they can delocalise charge to stablilise these electron deficient intermediates.



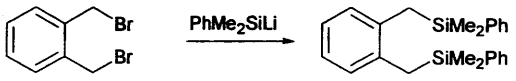
129 130 131 132

The benzylic dilithio compound **133** was also formed in a similar way to the alkyllithium compounds **111** and **115**. By cleaning and flattening the lithium metal under argon, a suitable surface for reaction with the dibromide **127** was created. Addition of the dibromide to the metal in diethyl ether and stirring at room temperature for 16 hours followed by filtration yielded the dilithio compound **133** as a solution of ether.



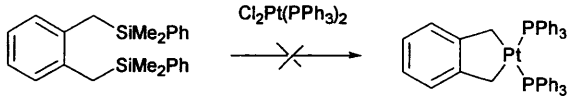
127 133

Reaction of the dilithio **133** with the tin and silicon nucleophiles, $PhMe_2SiLi$ **120** and Me_3SnLi **126** gave similar negative results to those of the reaction of the same nucleophiles with the alkyl dichlorides **110** and **114** and the ditriflates **123** and **124**. The reaction with Me_3SnLi did not yield any desired product but reaction with $PhMe_2SiLi$ did. The silyl compound **134** was formed in 17% yield on small scale (50 mg).



127 134

However, trial experiments by addition of the organosilicon compound **134** to dichlorobis(triphenylphosphine)-platinum(II) showed no desired platinocycle **135** formation by NMR and MS.

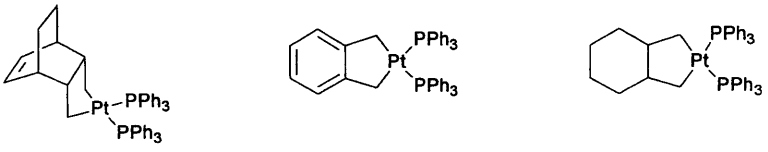


134 135

2.2.4 Concluding Remarks.

The aim of this project was to study the synthesis of organo-platinocycles and subsequent reductive elimination of such compounds. This project has provided the groundwork for further related projects and a great deal of information relating to the formation of alkyldimetal reagents has been uncovered.

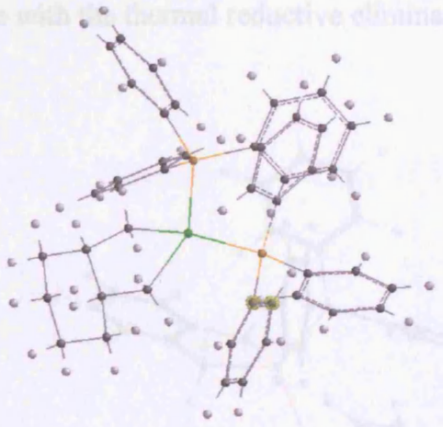
Based on the precedent provided by the work of Whitesides and co-workers,[23] it is possible that cyclobutane derivatives can be made via the reductive elimination of platinocyclopentane precursors. Although no such metallocycles were prepared as part of this project, model studies have been conducted to calculate dihedral angles of C_β-H – C_α-Pt bonds in the proposed platinocycles **116**, **135** and **136**. It was a previous concern that heating such complexes may result in undesired β-H elimination rather than desired reductive elimination. To alleviate such fears, molecular modelling of the complexes was accomplished using Spartan software.



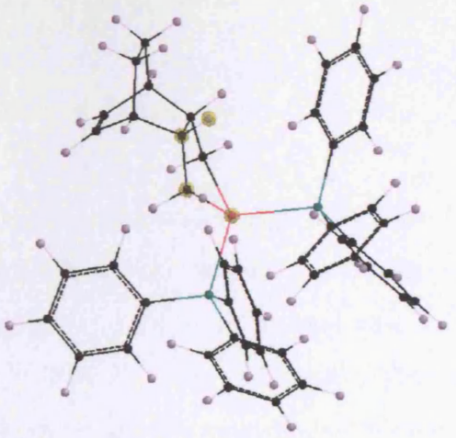
116 135 136

These are the structures of the platinocycle precursors **136** [5,6-bis(methylene)[2.2.2]bicyclooct-2-ene]bis(triphenylphosphine)platinum(II), **116** and [1, 2-bis(methylene)benzene]bis(triphenylphosphine)platinum(II) **135.**

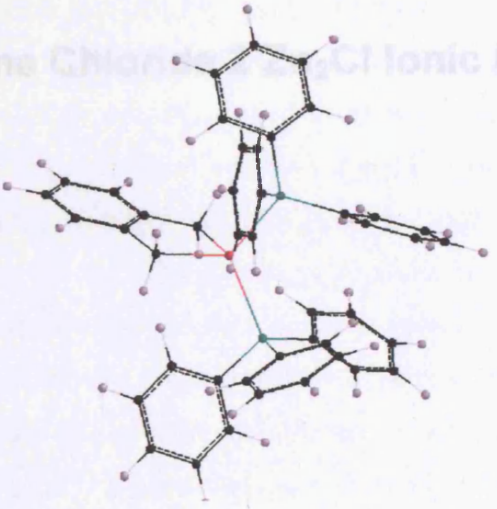
The model of the platinocycle precursor **136** is shown and the dihedral angle of the hydride on carbon β to the platinum center is shown by the gold highlights. Using the molecular modeling program, the dihedral angle is calculated to be 95.25 °. For β-hydride elimination of such a complex to occur, the C_β-H and Pt-C_α bonds must be approximately co-planar and *syn* (i.e. dihedral angle (θ), ~0 °). It is therefore anticipated that β-H elimination would not significantly compete with thermal reductive elimination should any such complexes be made in future projects.



Now it is shown the corresponding model for the platinocycle **116**. Once again the calculated dihedral angle (θ_{calc} = 97.5°) provides satisfactory evidence for proceeding to prepare the complex on the grounds that heating the complex to affect reductive elimination should not induce any significant β-H elimination competition. Gold highlights indicate dihedral angle of C-H_β – Pt-C_α bonds (θ_{calc} = 97.5 °).



Finally, it is shown [1,2-bis(methylene)benzene]bis(triphenylphosphine)platinum(II) **135**. The xylene moiety does not contain any H's which are β to the platinum center, thus β-H elimination cannot possibly compete with the thermal reductive elimination of this complex.



Chapter 3

The Fischer Indole Synthesis

in

Choline Chloride.2 Zn_2Cl Ionic Liquid.

3.1 Green Chemistry.

3.1.1 Introduction to Green Chemistry.

Green Chemistry, or environmentally benign chemistry, is focused on processes and products that reduce or eliminate the use and generation of hazardous substances. Major interest in green chemistry in the United States began in earnest with the passage of the Pollution Prevention Act of 1990 and with green chemistry becoming a formal focus of the EPA in 1991. Prior to this act, more than 100 environmental laws had been passed in the United States. However, these acts were of the command and control, or treatment and abatement, variety; that is, they tried to limit the spread of pollutants, deal with the cleanup of waste, or assess fines or penalties for those responsible for pollution.[33] All these laws were thus designed to deal with pollutants after they were formed. This is shown diagrammatically in figure 4.

The Pollution Prevention Act of 1990 was the first act to focus on preventing the formation of pollutants, with an eye toward eventual elimination of the need for treatment and abatement. This act encouraged industries and academics to devise novels technologies and processes that avoided the formation and/or the use of hazardous substances. In the field of chemistry, this has inspired chemists to devise greener reaction conditions for old syntheses (e.g., replacement of an organic solvent with water or the elimination of a solvent); develop greener syntheses for existing chemicals (e.g., syntheses that use biomass rather than petrochemical feedstocks or reactions that use catalysts rather than stoichiometric reagents); and design new compounds that are less toxic but have the same desirable properties as an existing compound (e.g., a new pesticide that is toxic only to target organisms and biodegrades to harmless substances).[33]

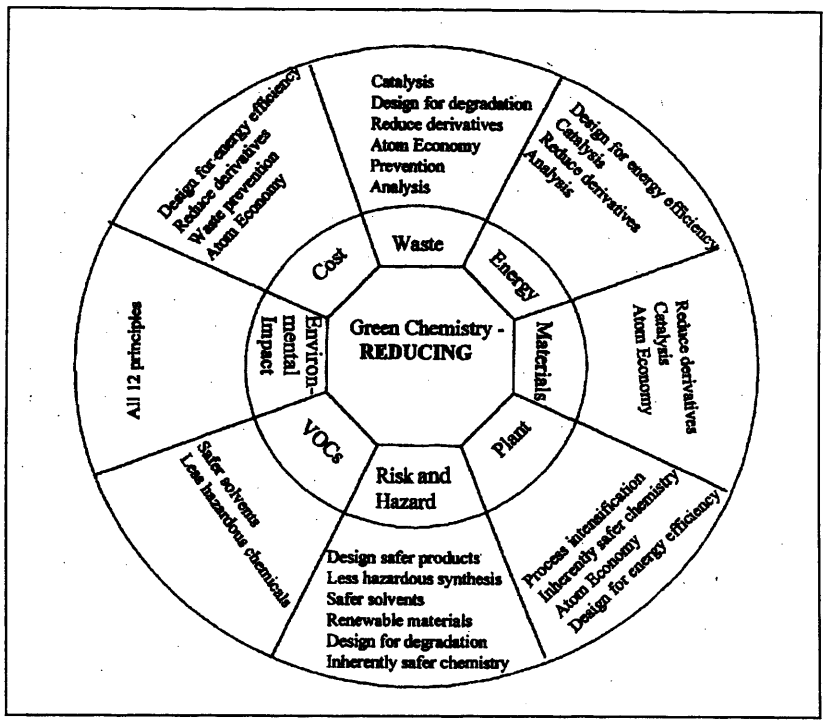


Fig 4, the green chemistry reducing

3.1.2 12 Principles of Green Chemistry.

Anastas and Warner have developed "The Twelve Principles of Green Chemistry".[33] These can serve as guide lines for practising chemists in developing and assesing how green a synthesis, compound, process, or technology is. The first principle supports the basic of green chemistry, namely, pollution prevention. Other principles deal with such topics as atom economy (how many reactant atoms end up in the desired product), toxicity, the use of solvents and auxiliary agents, energy use, renewable versus non-renewable feedstocks, and decomposition of compounds into nontoxic, environmentally bening subtances.

1. Prevention.

It is better to prevent waste than to treat or clean up waste after it has been created.

2. Atom Economy.

Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. Less Hazardous Chemical Synthesis.

Wherever practicable, synthetic methods should be designed to use and generate substances that posses little or no toxicity to people or the environment.

4. Designing Safer Chemicals.

Chemical products should be designed to effect their desired function while minimizing their toxicity.

5. Safer Solvents and Auxiliaries.

The use of auxiliariy substances (e.g., solvents or separation agents) should be made unnecessary whenever possible and innocuous when used.

6. Design for Energy Efficiency.

Energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. Use of Renewable Feedstocks.

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. Reduce Derivatives.

Unnecesary derivatization (use of blocking groups, protection/de-protection, and temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. Catalysis.

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Design for Degradation.

Chemical products should be designed so that at the end of their function they break into down into innocuous degradation products and do not persist in the environment.

11. Real-time Analysis for Pollution Prevention.

Analitycal methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Inherently Safer Chemistry for Accident Prevention.

Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

3.1.3 Atom Economy.

The concept of atom economy considers the amount of starting materials incorporated into the desired final product.[34] The aim of atom economy is to create syntheses in which most of the atoms of the reactants are incorporated into the desired final product and fewer waste byproducts are created. The yield of a reaction, which is perhaps the most common way of expressing the efficiency of a reaction, is a measure of the quantity of product formed versus the quantity of the limiting reagent. The percentage yield is generally calculated according to the following equation:

$$\% \text{ Yield} = \frac{\text{Actual yield of product}}{\text{Theoretical yield of product}} \times 100$$

where the theoretical yield is the maximum yield possible based on the quantity of limiting reagent that is used.

Although chemists have developed many reactions of high selectivity and high yields, many of these reactions earn low marks for the incorporation of reactants atoms into the desired product.[34] A significant portion of these atoms of the reactants are found in unwanted waste by products, even in reactions that are judged highly efficient based on their high selectivity and high yield.

Atom economy proposes that in addition to the selectivity and percent yield of the reaction, one must consider how efficiently atoms of the reactants are used in a chemical synthesis. The concept of atom economy is a consideration of "how much of the reactants end up in the final product."[34] Thus, atom economy takes a look at the atoms that are found in the reactants and then considers how many of them find their way into the desired product and how many of them result in the formation of waste by products.

The ideal situation, in terms of atom economy, is to create a synthesis in which all of the atoms in the reactants are incorporated into the final product, because this reaction, in theory, would not produce any waste by producs. When high atom economy results in significant loss of selectivity and/or lower yield then the goal is to create syntheses that generate the lowest quantity of waste and the most non toxic waste possible while maintaining high selectivity and high yield.[35]

Percentage atom utilization is calculated by dividing the molecular weight of the desired product by the molecular weights of all the products generated in a reaction.

$$\% \text{ Atom utilization} = \frac{\text{MW of desired product}}{\text{MW of (desired product + waste byproducts)}} \times 100$$

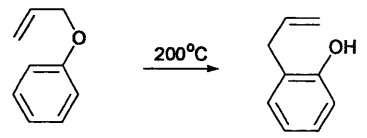
In many reactions, however, the identities of the waste by products are unknown or difficult to determine. Fortunately, conservation of mass allows us to calculate a number similar to the percentage atom utilization called percentage atom economy. It was proposed to calculate the percentage atom economy by totalling the formula weight of all the atoms in the reactants that are incorporated into the final product (atoms utilized) and divide this number by the total formula weight of all the reactants.

$$\% \text{ Atom economy} = \frac{\text{FW of atoms utilized}}{\text{FW of all the reactants used in the reaction}} \times 100$$

When we look at some common organic reactions (namely, the rearrangement, addition, substituion, and elimination reactions), we will find that some of these reactions are inherently more atom-economical than others. The rearrangement and addition reactions tend to be the most atom-economical, followed by the substitution reaction, and finally, the least atom-economical is the elimination reaction.[36]

A rearrangement reaction is one that changes the connectivity of the starting material, often resulting in a change in the carbon skeleton leading to the formation of the product. Because this reaction pathway simply changes the way the atoms in a molecule are connected (no atoms in the starting material are lost), it is considered an

atom-economical reaction.[36] An example of such a reaction would be the Claisen rearrangement.

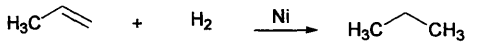


137 138

FW=134.17 FW=134.7

Because all the atoms were utilized in the final product, the percentage atom economy for the Claisen rearrangement is 100% (134.175/134.175 x 100 = 100%).

Addition reactions are also atom-economic reactions.[36] In the addition reaction, groups are added to a molecule usually across a double or triple bond. An example of such a reaction is the catalytic hydrogenation of propene.



139 140 141

FW=42.08 FW=2.016 FW=44.096

In this reaction, both of the hydrogens atoms **140** and all of the atoms in the propene molecule **139** are utilized in the final product. Calculating the total atomic weighs of the atoms of reactants that are utilized in the product. The percentage atom economy for this addition reaction is 100% (44.096/(42.08 + 2.016) x 100 = 100%). It should also be noted that the nickel used in this reaction is used only in catalytic (not stoichiometric) amounts and can be reused repeatedly.

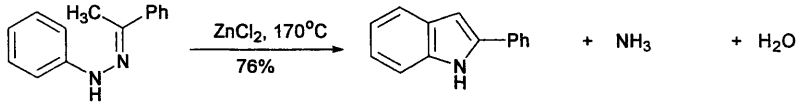
In a substituion reaction, one atom (or groups of atoms) is replaced by another atom (or group of atoms). Because the atom that is replaced is not utilized in the final desired product, the substitution reaction is less atom-economical than rearrangement or addtion reactons.[36] An example of a substitution reaction is the reaction of ethyl propionate **142** with methylamine **143**.

142 143 144 145

FW=102.132 FW=31.057 FW=87.120 FW=46

Note that in this reaction the leaving group (OCH_2CH_3) is not utilized in the desired amide products. In addition, one hydrogen atom on the amine is not utilized. The remaining atoms in the reactants are incorporated into the final products. The percentage atom economy for this reaction is 65.41% (87.12/133.189 x 100 = 65.41%).

The aim of our project is to find a new method of synthesis of indoles. We will study the Fischer indole synthesis in an ionic liquid. The Fischer synthesis involves the acid- or Lewis-acid-catalysed rearrangement of a phenylhydrazone with the elimination of ammonia. Furthermore, Fischer synthesis is an example of rearrangment reaction which is an atom economical reaction.

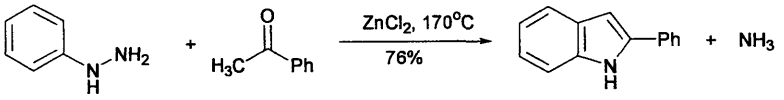


FW=210.353 FW=193.248 FW=17.031

146 147 148

The percentage atom economy for this reaction is 92% (193.248/210.353 x 100 = 92%).

We will also try the one pot Fischer reaction which involves the hydrazine **149** and the ketone **150** as a starting material.



FW=108.130 FW=120.152 FW=193.248 FW=17.031

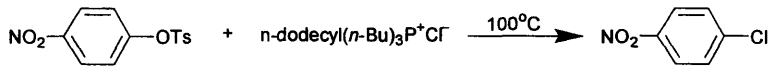
149 150 147 148

The percentage atom economy for this reaction is 85% (193.248/ (108.13+120.152) x 100).

3.2 Reactions in Ionic Liquids.

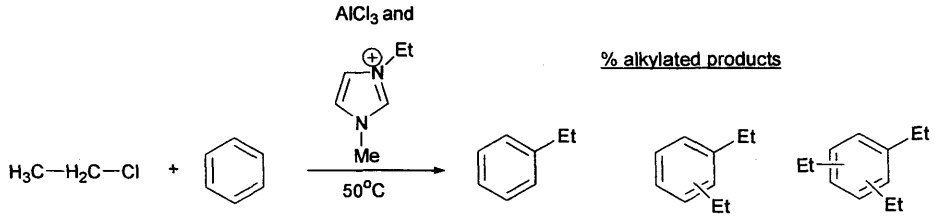
The motivation for studying reactions in ionic liquids was to reduce the use of volatile organic solvents "VOC's" in the environment and in some cases improved selectivity, for this reason ionic liquids have become known as 'Green Solvents.'

An ionic liquid is a liquid that consists entirely of ions.[37] The first ionic liquid, $[EtNH_3]^+[NO_3]^-$ with a freezing point of 12°C was reported in 1929.[38] The nucleophilic aromatic substitution of *p*-nitro-tosylate **151** in molten dodecyltributylphosphonium chloride **152** at 100°C leading p-nitro-chloro-benzene **153** was published in 1985, this was the first example of the used of an ionic liquid to carry out an organic reaction.[39]



151 152 153

This was followed in 1986 by the Friedel-Crafts alkylation reaction in ambient-temperature molten salts, formed from mixtures of 1-methyl-3-ethylimidazolium chloride and aluminium chloride.[40] The alkylation was tested by reacting ethyl-chloride with benzene and the results shows that mono-, di, and tri- alkylations of benzene were obtained with 25, 20 and 55% respectively.

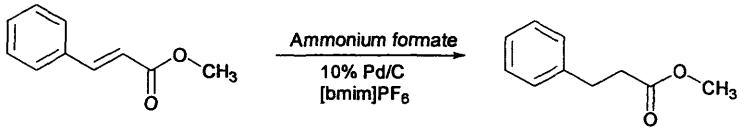


154 155 mono 24.8% di 19.9% tri 55%

156 157 158

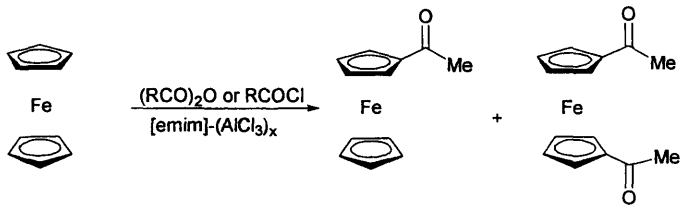
Since these early studies, ionic liquids made from *N,N'*-dialkylimidazolium and *N*-alkylpyridinium salt has been used as solvents in several reactions. One example is the catalytic transfer hydrogenation of *(E)*-methyl cinnamate **159** which was carried out in

N-butyl-*N'*-methylimidazolium hexafluorophosphate ionic liquid at room temperature heated by microwave irradiation with 99% yield.[41]



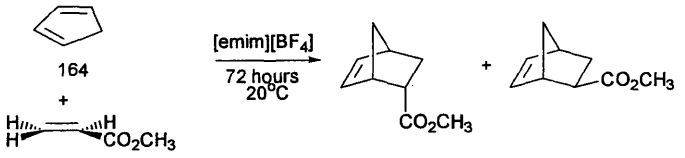
159 160

Ethyl-3-methylimidazolium halogenoaluminate was used as a solvent for Friedel-Crafts acylations of ferrocene **161** to give acetylcyclopentadienyl(cyclopentadienyl)iron(II) **162** and bis(acetylcyclopentadienyl)iron(II) **163**.[42]



161 162 163

The Diels-Alder cycloaddition reaction between methyl acrylate **165** and cyclopentadiene **164** was carried out in [emim][BF_4] ionic liquid to yield the endo product **166** in 84% yield and the *exo* product **167** in 14% yield after 72 hours at 20°C.[43]

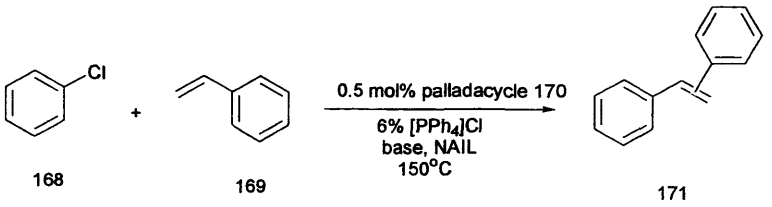


164 + 165

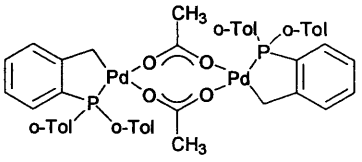
166, *endo* 5.3

167, *exo* 1

Palladium-catalyzed Heck-vinylation reaction was carried out in [NBu_4]OAc ionic liquid with 54% yield after 14 hours.[44] One example is the olefination of chlorobenzene **168** with styrene **169** and palladacycle **170** to give product **171**.



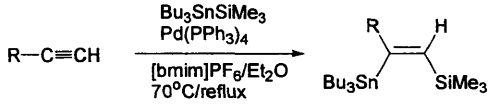
168 169 171



170

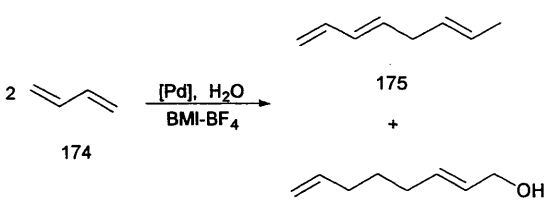
Phosha-Palladacycles

Trimethylsilyltributylstannane can be regioselectively added *cis* across terminal alkyne **172** in a quantitative fashion to produce **173** in the presence of a palladium(0) catalyst immobilised in the [bmim]PF_6 ionic liquid which can be recycled without loss of activity.[45]



172 173

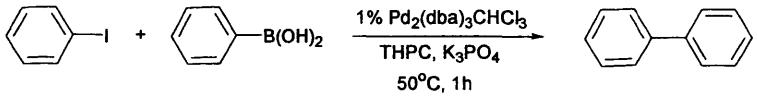
Palladium(II) compound dissolved in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (BMI-BF_4) ionic liquid was used to catalyse the hydrodimerization of 1,3-butadiene **174** to give 1,3-butadiene dimer 1,3,6-octatriene **175** in 11% yield and octa-2,7-dien-1-ol **176** in 89% yield.[46]



174 175 + 176

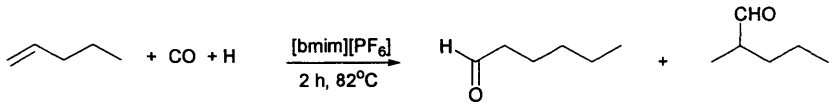
Linear dimers from but-1-ene were obtained using different 4-methylpyridinium(4-MBPCl)-chloroaluminate ionic liquid systems.[47]

The Suzuki cross-coupling of iodobenzene **177** and phenylboronic acid **178** was carried out in the phosphonium salt ionic liquid tetradecyltrihexylphosphonium chloride (TMPC) to give biphenyl **179** in 95% yield. In a range of examples yields from 17% to 100% were obtained.[48]



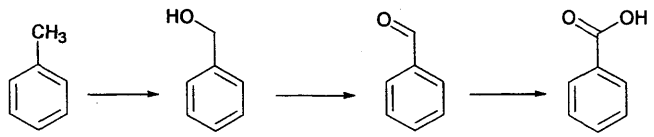
177 178 179

A hydroformylation process for unsaturated compounds such us monoolefins and diolefins is carried out in 1-butyl-1-methylimidazolium hexafluorophosphate ionic liquid with good yields. 1-Pentene **180**, CO and H gave 75% yield of hexanal **181** and 24% yield of 2-methylpentanal **182**.[49]



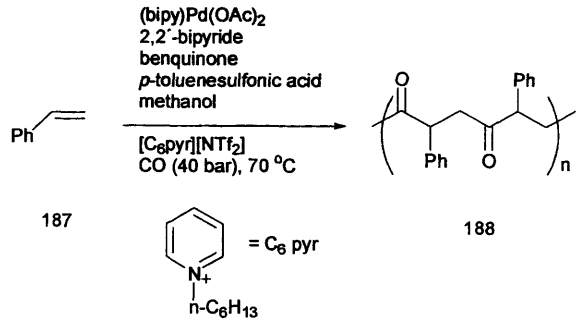
180 181 182

The oxidation sequence from toluene **183** to benzylalcohol **184**, benzaldehyde **185** and benzoic acid **186** is an important industrial process. Seddon and Stark have studied this oxidation using palladium catalyst and oxygen in imidazolium ionic liquids. The factors governing the various stages of this process have been identified as the chloride ion concentration and water content.[50]



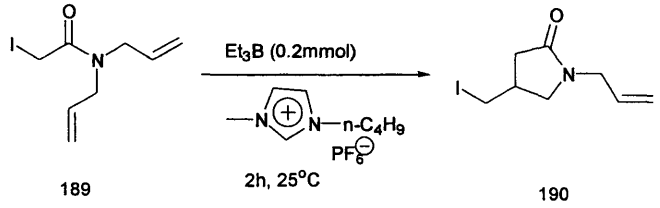
183 184 185 186

Increased molecular weights and yields were improved in the palladium-catalyzed copolymerization of styrene and CO in the 1-hexylpyridinium bis(trifluoromethanesulfonyl)imide ionic liquid.[51]



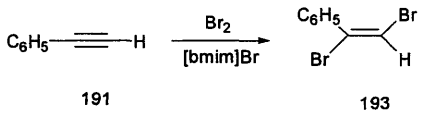
187 188

Radical cyclization reaction of *N,N'*-dialkyl-2-iodoacetamide **189** to give γ-lactam **190** was carried out in 1-butyl-3-methylimidazolium hexafluorophosphate with 82% yield. The mechanism consists on an iodine atom-transfer radical transfer in [BMIM][PF_6] ionic liquid.[52]

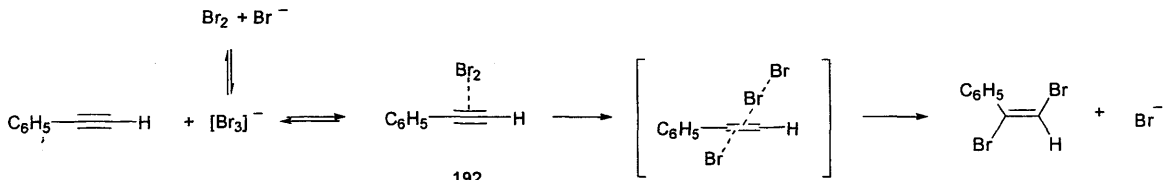


189 190

Br_2 was added to alkyne **191** in [bmim]Br ionic liquid in an *anti*-stereospecific addition at room temperature.[53] The mechanism does not involve ionic intermediates and occurs through attack by bromide on the olefin-Br_2 π complex.



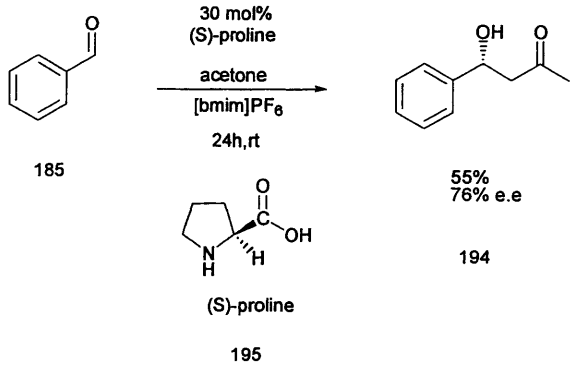
191 193



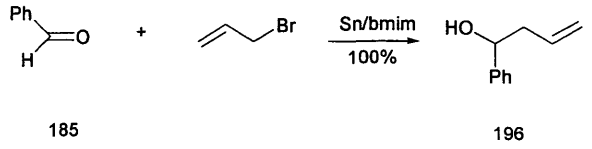
191 192 193

Proline **195** catalysed asymmetric direct aldol reactions of benzaldehyde **185** with acetone at room temperature in 1-*n*-butyl-3-methylimidazolium hexafluorophospate ionic liquid gave 55% yield of aldol product **194** in enantioselectivity 76% e.e.

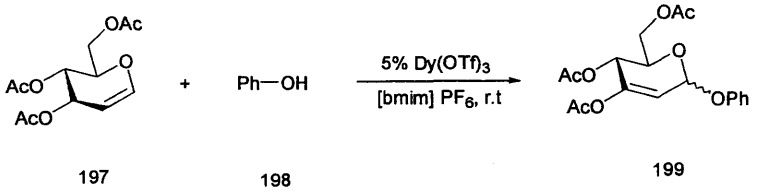
Immobilisation of the catalyst in the ionic liquid enable the product isolation and reuse of the catalyst in further reactions.[54]



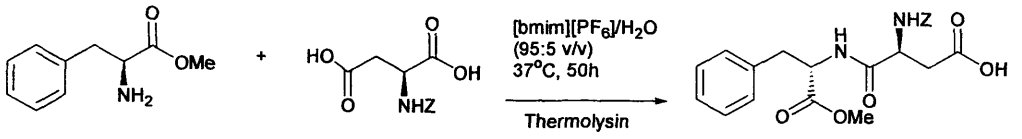
[Bmim][BF_4] or [emim][BF_4] have been used in the Sn mediated allylation reaction of benzaldehyde **185** at room temperature to provide the corresponding homoallylic alcohol **196** in yields between 48 and 100%.[55] In a range of examples yields between 48% and quantitative were obtained.



3,4,6-Tri-O-acetyl-D-glucal **197** was reacted with phenol **198** in the presence of 5 ml% dysprosium triflate immobilized in 1-butyl-3-methylimidazolium hexafluorophosphate under mild conditions to give the corresponding 2,3-unsaturated glycopyranoside **199** in 89% yield with high α-selectivity (ratio 10:1). The catalyst was immobilized in the ionic liquid which was recycled in several reactions without loss of activity. In a range of examples yields between 80 and 95% were obtained.[56]



Finally, isolated enzymes were used in thermolysin-catalysed biosynthesis in [bmim][PF_6]/H_2O ionic liquid allowing high levels of efficiency, good solubility and no volatility.[57]

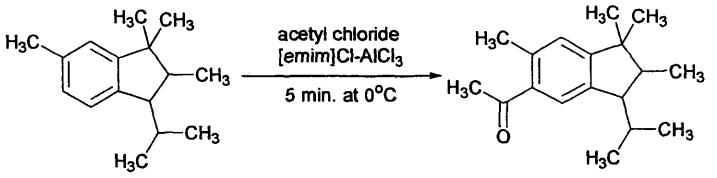


L-Phe — 200

Z-L-Asp — 201

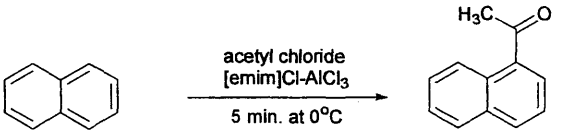
95% yield Aspartame percursor — 202

When acid catalysed reaction is required then the alkylimidazolium/aluminium chloride mixtures have been studied extensively, particularly in Friedel-Crafts reaction.[37d] Acetylation of 1,1,2,6-tetramethyl-3-isopropylindane **203** and naphthalene **205** were carried out in [emim]Cl-$AlCl_3$ (X=0.67) as solvent to produce **204** in 99% yield and **206** in 89% yield. In the acetylation of naphthalene **205**, the ionic liquid gives the highest known selectivity for the 1-position.



203

204, 99%



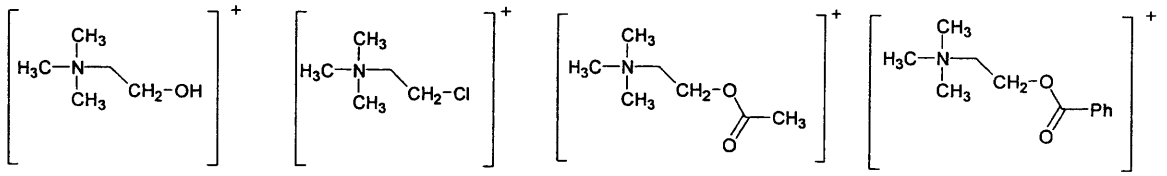
205

206

89% 1-isomer
2% 2-isomer

However, these chloroaluminate(III) ionic liquids are moisture sensitive and the product isolation from them can be difficult. Recent studies at Leicester have demonstrated that quaternary ammonium salts may be used to produce moisture-stable Lewis acidic ionic liquids.[58] They have been prepared by mixing appropriate molar ratios of MCl_2 (M = Zn and/or Sn) and quaternary ammonium salts of formula

$[Me_3NC_2H_4Y]Cl$ (Y = OH **207**, Cl **208**, OC(O)Me **209**, OC(O)Ph **210**); the influence of substituent Y and metal M on the physical properties of the melts has been investigated.

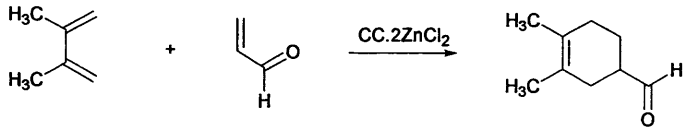


207 208 209 210

To investigate the parameters necessary for a salt to be liquid at or near room temperature, a range of ammonium salts with zinc chloride in a 1:2 molar ratio were heated. Using salts of symmetrical cations, H_4NCl and Me_4NCl, no liquid is formed below 200°C whereas with the longer chain NEt_4Cl the freezing point was *ca.* 90 °C. It has been established in the imidazolium system that reducing the symmetry of the cations leads to a lower freezing point for the ionic liquid, thus, the "Green Group" at the University of Leicester has examined cations of the general formula Me_3NR^+. Using Me_3NEt^+ gives a freezing range of 53-55 °C, *i.e.* a reduction of *ca.* 35 or 140 °C compared with Et_4N^+ and Me_4N^+ respectively. However, it was found that functionalised ethyl chains, $Me_3NC_2H_4Y^+$, give even lower freezing points; *e.g.* if Y = OH or Cl, room temperature liquids are observed with freezing points of 23-25 °C. Even when the substituent is significantly larger, *e.g.* Y = OC(O)Me or OC(O)Ph, the salts formed have lower freezing points than for Me_3NEt^+. These results suggest that both lower symmetry and the presence of a functional group reduce the freezing point of the salt formed, though the exact role of the functional substituent is not yet clear. In all cases the liquids formed are viscous and hygroscopic but moisture-stable so can be easily prepared and stored without the need for specialist equipment.

Since choline chloride, $[Me_3NC_2H_4OH]Cl$, gave the lowest freezing point the system was characterised in more detail. Heating mixtures of choline chloride and zinc chloride in molar ration between 1:1 and 1:3 gave rise to clear colourless liquids, with the freezing points varying between *ca.* 65 °C (1:1), 25 °C (1:2) and 45 °C (1:3).

The combination of choline chloride **207**, a cheap readily available quaternary ammonium salt, with $ZnCl_2$ or $SnCl_2$ in a ratio 1:2 can be used as a Lewis acidic solvent for the Diels-Alder reaction.[59]

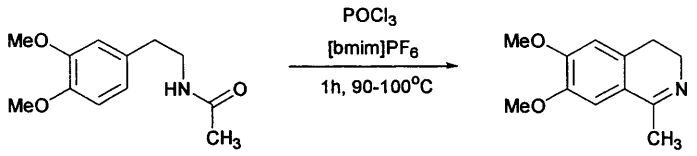


211 212 213

2,3-Dimethylbutadiene **211** reacts with acrolein **212** to give product **213** in 91% yield as single isomer using the choline chloride.2 $ZnCl_2$ ionic liquid. The reaction occurs in two hours whereas the uncatalysed reactions are reported to take at least 1000 times longer. In a range of examples yields between 85 and 94% were obtained.

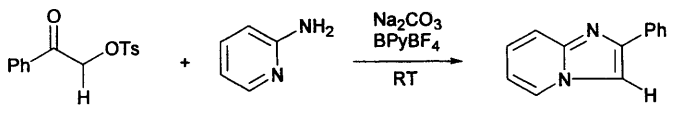
More recently, the novel solvent properties of choline chloride/urea ionic liquids have been reported.[60] Mixtures of urea and a range of quaternary ammonium salts are liquid at ambient temperatures and have interesting solvent properties.

In seeking new applications of the choline chloride.2$ZnCl_2$ our attention was taken by some recent publications on the synthesis and reactions of heterocyclic compounds in ionic liquids, these included the preparation of isoquinolines derivatives **215** through Bischler-Napieralski cyclization which were carried out in 1-butyl-3-methylimidazolium hexafluorophosphate([bmim][PF_6]) ionic liquid with 87% yield.[61]



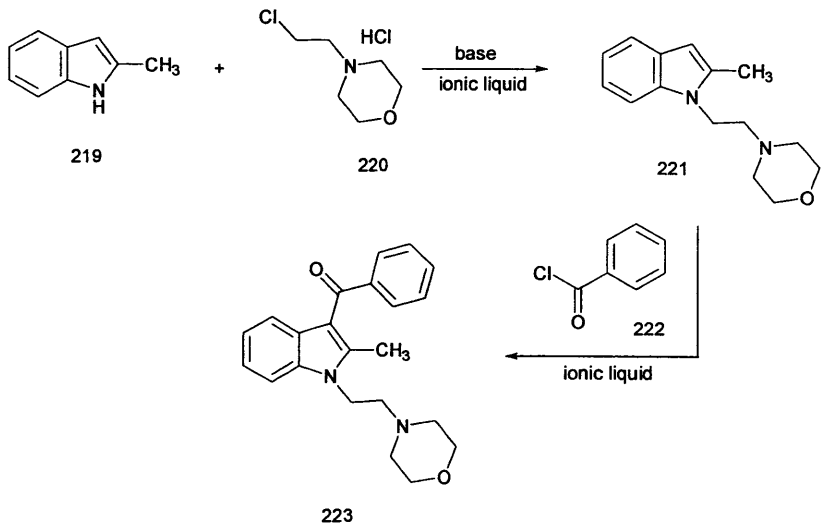
214 215

The room temperature ionic liquid *n*-butylpyridinium tetrafluoroborate ($BPyBF_4$) was used for the cyclocondensation of α-tosyloxyketone **216** with 2-aminopyridine **217** in the presence of sodium carbonate to form the corresponding imidazo[1,2-*a*]pyridine **218** with 81% yield.[62]



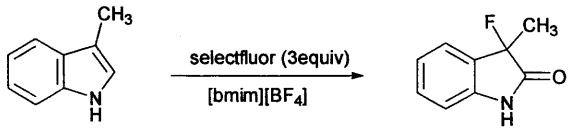
216 217 218

Total synthesis of the pharmaceutical Pravadoline **223** is achieved in 90% yield in the ionic liquid [bmim][PF_6].[63]



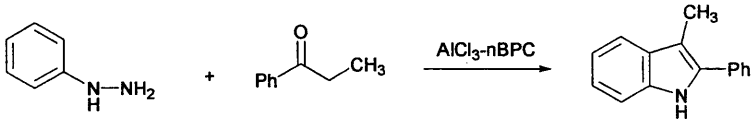
219 220 221 223

Electrophilic fluorination of 3-methylindole **224** was achieved using Selectfluor^{TM} (F-TEDA-BF_4) which is soluble in [bmim] [PF_6] to yield fluorinated oxoindole **225** in 99%.[64]



224 225

We were particularly interested in carrying out the Fischer indole synthesis in an ionic liquid, there was one report of this reaction using different ketones in 1-butylpyridinium chloride-$AlCl_3$ (*n*-BPC-$AlCl_3$) ionic liquid.[65] This synthesis worked with yields between 41 and 92%. A mixture of phenylhydrazine **149** and propiophenone **226** gave 2-phenyl-3-methylindole **227** in 73% after 1 hour reaction at 180°C.



149 226 227

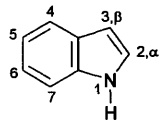
The Fischer indole reaction is a good candidate for ionic liquids as it is normally carried out in hot poly-phosphoric acid, product isolation is by addition to water and filtration of the product, disposal of the phosphoric acid residues can have a considerable environmental impact. To avoid the use of strong acid by carrying out the Fischer indole synthesis in an environmentally friendly ionic liquid is the aim of this project.

3.3 The Fischer Indole Synthesis.

3.3.1 Introduction to the Fischer Indole Synthesis.

3.3.1a Indole.

Indole was first prepared in 1866 by zinc dust distillation of oxindole. The word indole is derived from the word India: a blue dye imported from India became known as indigo in the 16th century, and chemical degradation of this gave rise to indoxyl, oxindole, and then to indole.



228

Indole **228** and the simply alkyl indoles are colourless crystalline solids. Many simple indoles are commercially available and all of these are produced by synthesis. Indole, for example, is made by the high temperature vapour-phase cyclizing dehydrogenation of ortho-ethylaniline. Indole is planar with a conjugated system of 10-π electrons – two from the nitrogen and eight from the carbons – and hence is a heteroaromatic molecule. In simple resonance terms indole is a hybrid of the main canonical forms given in Scheme 5, with lesser contributions from structures with the negative charge on the indole α-position and the benzene ring. Thus the nitrogen atom carries a fractional positive charge.

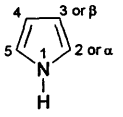
228 229 230 231

Scheme 5, Simple resonance description of indole.

Most indoles are quite stable in air with the exception of those which carry a simple alkyl group at C 2. 2-Methylindole, for example, autooxidizes quite readily even in a dark brown bottle.

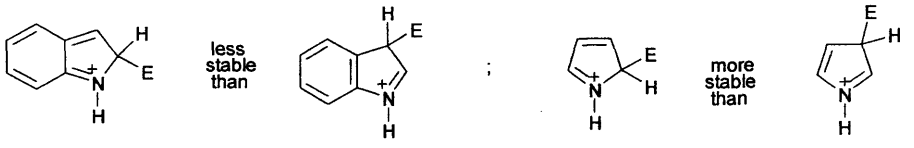
3.3.1b Reactivity and Comparison with Pyrroles.

Pyrrole **232** and indole **228** have similar chemical properties. They are both electron rich aromatic systems which undergo electrophilic attack and they do not undergo attack by nucleophiles.



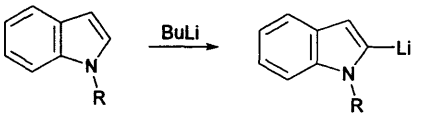
232

The main difference between pyrrole and indole is in the position of greatest reactivity to electrophilic substitution, which in pyrrole **232** is at an α-position (C-2) and in indole **228** is at the β position (C-3). The preferred C-3 reactivity of indoles is a consequence of the presence of a benzene ring. Addition of an electrophile E^+ to C-2 of indole would generate a non benzenoid 2H-indolium cation **233**, whereas attack at C 3 affords the more stable 3H-indolium cation **234** in which the aromaticity of the benzene ring is retained. A 3H-indolium cationic intermediate is also more stable than the 3H-pyrrolium cation **236**, making indole β-substitution faster than pyrrole β-substitution.

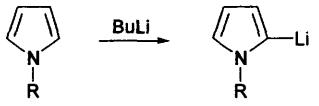


233 234 235 236

In contrast with this clear differentiation in the position of favoured electrophilic substitution, C-deprotonation of the N-alkylated heterocycles occurs at C2 in both cases, since this involves the generation of a negative charge which is stabilized by induction by the electronegative nitrogen atom, and not by mesomeric delocalization, since it does not form part of the π-electronic system.



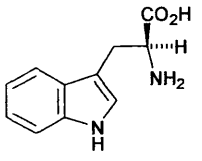
237 238



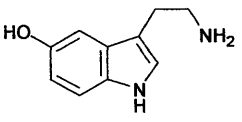
239 240

3.3.1c Natural Products Containing an Indole Ring.

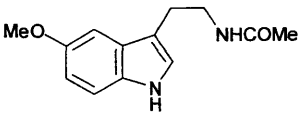
Indole based rings are important as they occur in many important natural products. Tryptophan **241** is an essential amino acid and such is a constituent of many proteins. In animals, tryptophan **241** also serves as a precursor for two chemically closely related hormones: serotonin (5-hydroxytryptamine) **242** is a powerful vasoconstrictor and regulates gastric secretion and intestinal peristalsis. It is believed that serotonin may also play a role in the central nervous system and melatonin **243** is believed to play a part in regulating the day and night rhythms of the human body.[66]



241



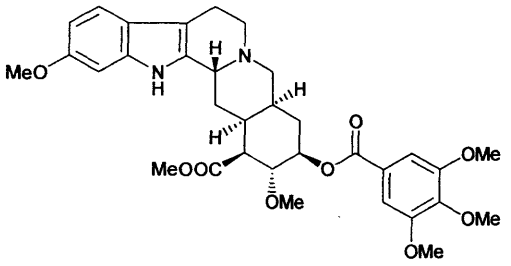
242



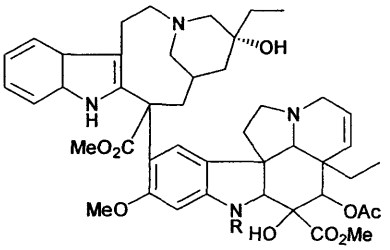
243

A number of indole derivatives have significant clinical use, several of the alkaloids are particularly important. Reserpine **244** is an important tranquilizer, the dimeric indole alkaloids vincristine **245** and vinblastine **246** are anticancer agents which

have clinical use in the treatment of choriocarcinoma and certain forms of leukaemia and Hodgkins disease.[67, 68]

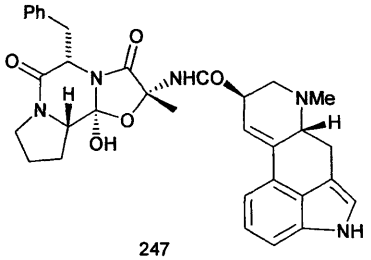


244



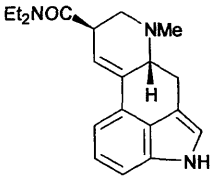
245 R = H
246 R = CHO

The lygersic acid derivative ergotamine **247** is used as a vasoconstrictor in relief of migraine.[69]

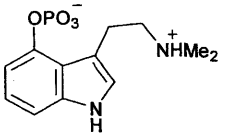


247

The activity of the semi-synthetic derivative LSD (lysergic acid diethylamide) **248** is notoriously well known; the less familiar hallucinogen psilocybin **249** occurs naturally in a central American mushroom.

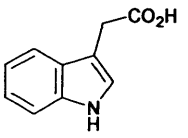


248

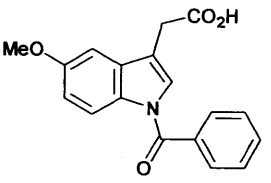


249

The β-indolylacetic acid **250** derivative indomethacin **251** is of value in the treatment of rheumatoid arthritis.



250

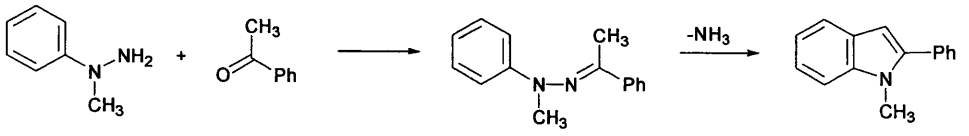


251

3.3.1d Synthesis of Indole Compounds.

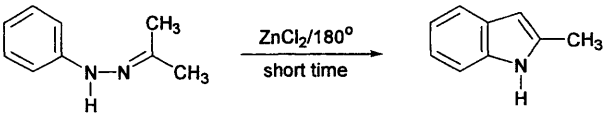
There are five main general routes for the synthesis of the indole ring systems from non-heterocyclic precursors all begin with benzene derivatives.

The Fischer indole synthesis is by far the most widely used indole synthesis. It consists of heating a phenylhydrazone, most often with acid, though sometimes in an inert solvent alone. This involves the acid-catalysed rearrangement of a phenylhydrazone with the elimination of ammonia.



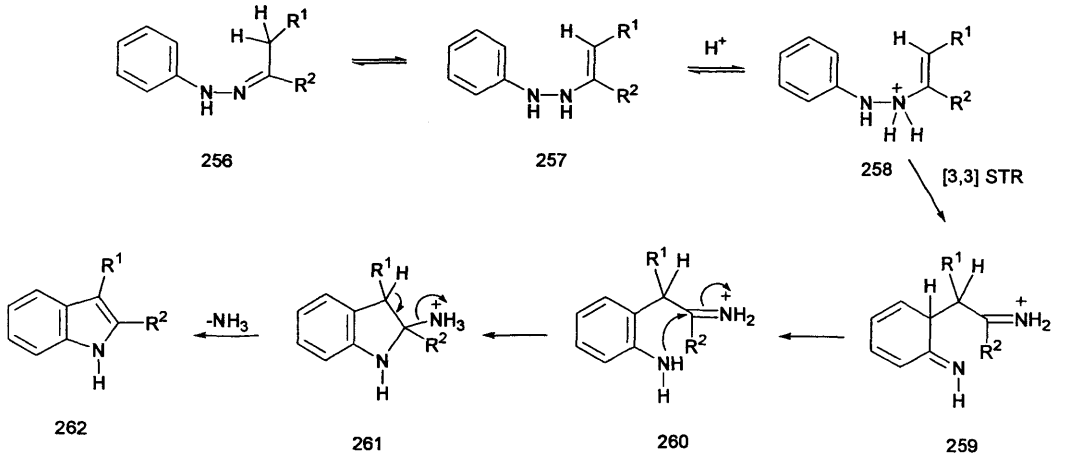
252 150 253 254

The reaction can be carried out in one pot by mixing aldehyde or ketones with one mole equivalent of phenylhydrazine in acetic acid, and refluxing. The formation of phenylhydrazone **255** and its subsequent rearrangement thus take place without the isolation of the intermediate. Here we have the synthesis of 2-methylindole **219**.[70]

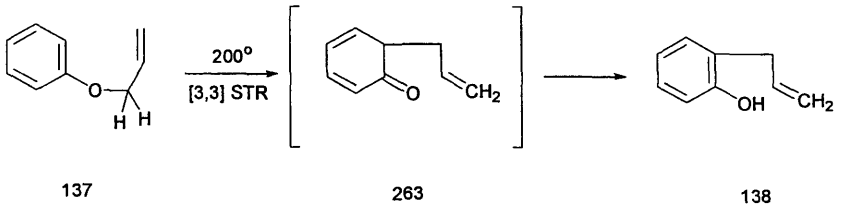


255 219, 60%

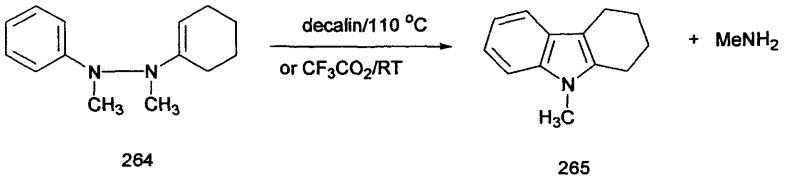
Indole cannot be obtained from acetaldehyde phenylhydrazone under the usual liquid phase reaction conditions, but this has now been achieved in vapour phase at 300 °C over zinc chloride. The full details of the mechanism of this multi-step reaction have not been worked out, but there is considerable evidence to suggest the following sequence.[71]



The most important step in the mechanism is the formation of a new a carbon-carbon bond in a [3,3] sigmatropic rearrangement (**258** to **259**). This step is very likely to be electrocyclic in character and thus analogous to the Claisen rearrangement of phenyl allyl ethers.[72]

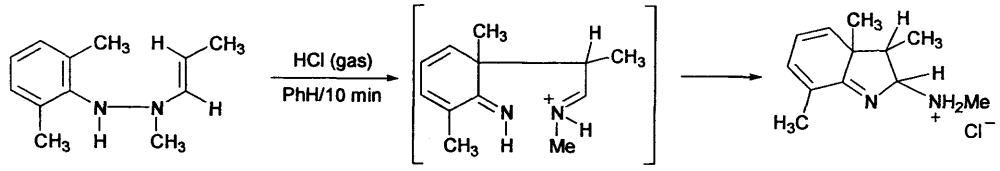


Support for this view comes from the observation that in many cases the Fischer synthesis may be achieved simply by heating a phenylhydrazone to 200 °C in the absence of the acid. Recently, indolization has been achieved thermally at a temperature as low as 100 °C in the special case of ene-hydrazines **264**: the first step of the normal sequence has already been achieved for these compounds.[73]



The reaction does occur more rapidly, however, by weak acid catalysis, in which proton adds to the aliphatic nitrogen to give a cation **267** which then undergoes

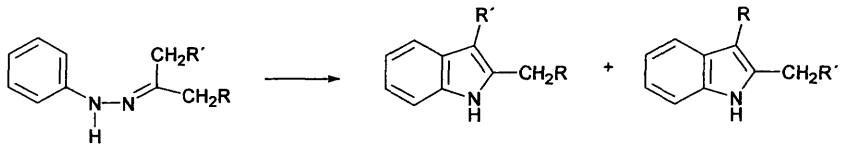
rearrangement. Acid treatment of the ene-hydrazine **266** gives the salt **268**: in this particular instance aromatization is prevented by the *ortho*-methyl groups.[74]



266 267 268, 30%

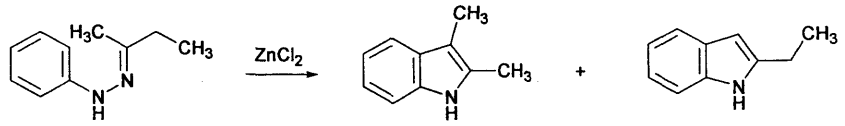
3.3.1e The direction of Cyclization of Unsymmetrical Phenylhydrazones.

The cyclisation of a phenylhydrazone of general structure **269** could proceed in either of two directions **270** and **271**.



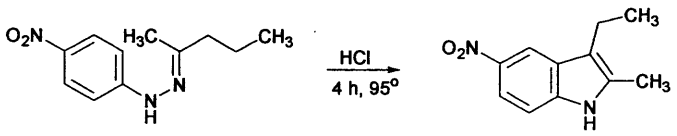
269 270 271

It has been demonstrated that in the case R = H, R′= alkyl or aryl, the cyclization proceeds to give **270**, R = H, i.e., cyclization tends to occur in a substituted chain in preference to a methyl group. The phenylhydrazone of methyl ethyl ketone **272** gives predominately 2,3-dimethylindole **273** with a selectivity of 4:1 with zinc chloride as catalyst.[75]



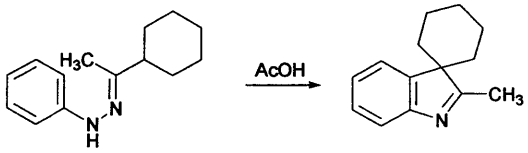
272 273 4 : 1 274

In contrast to this result, the nitrophenylhydrazone of methylpropylketone **275** gave 3-ethyl-2-methylindole **276** in 45% yield and no 2-propylindole was detected.[76]



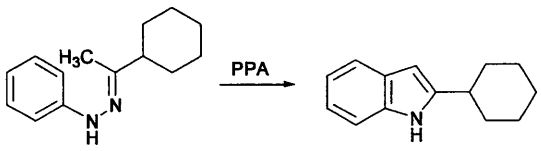
275 276

In 1938, cyclohexyl methyl ketone phenylhydrazone **277** was reported to undergo a simple conversion into the spiro-3H-indole **278** on heating with acetic acid.[77]



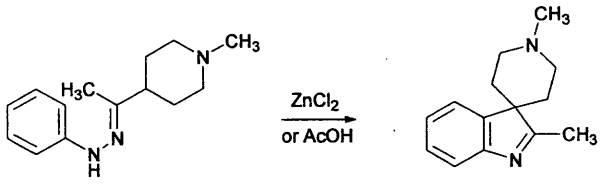
277 278

In 1941, the Fischer synthesis with **277** under specified conditions was reported to give a poor yield of 2-cyclohexylindole **279**. These results suggested that some further parameter than the degree of substitution must be important in determining the direction of the Fischer reaction with such compounds. The Fischer indole synthesis with cyclohexyl methyl **277** was investigated. The Fischer indole synthesis with **277** catalysed by polyphosphoric acid (PPA) gave primilarly the corresponding 2-substituted indole **279** contrary to what would have been predicted.[78]



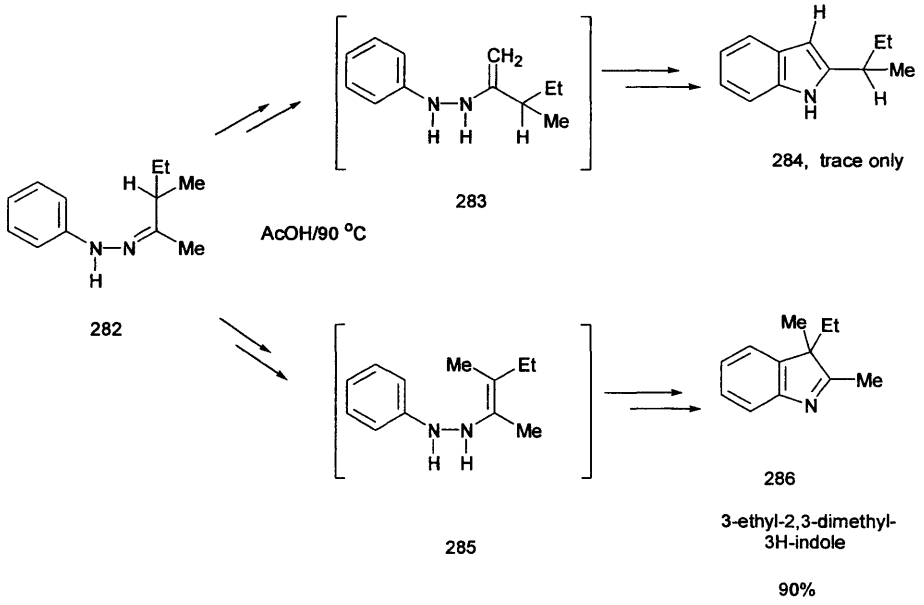
277 279

Using zinc chloride as the acidic catalyst the compound **280** gave product containing only 3H-indole **281**. Acetic acid appeared to cause reaction to give only 3H-indoles; however, the yield of **281** was not very large.

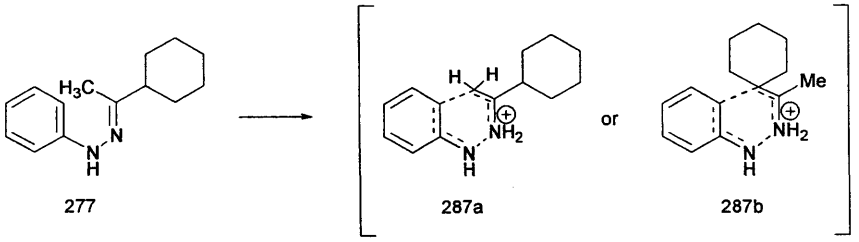


280 281

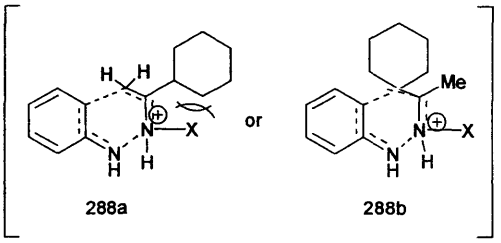
In the case of ketones with one branched and one straight alkyl chain, cyclization of the phenylhydrazone **282** can give a 2-substituted indole **284** or a 2,3,3-trisubstituted-3H-indole **286**. Indolenines (3H-indoles) **286** are frequently products of the Fischer reaction, the next example illustrates this.



The direction of the cyclization in a Fischer reaction may be highly dependent on the identity of the catalyst used and on the concentration of the catalyst. Lyle and Skarlos have put forward an explanation for the effect of the catalyst on the direction of cyclisation based on consideration of steric effects in the alternative transition states.[79] In the case of methyl cyclohexyl phenylhydrazone **277** the two vinylhydrazines must cyclize through transition states **287a** or **287b**. They also suggest that steric repulsion between the phenyl group and axial hydrogen of the cyclohexane ring in **287b** will make **287a** the more easily attained transition state.

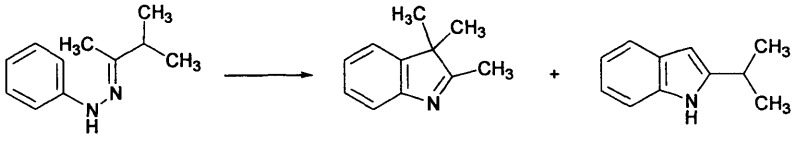


They suggest that catalysts sterically larger than the proton, for example coordinated metal atoms or acyl groups, will raise the energy of transition state in **288a** and lead to cyclization via **288b**.



288a 288b

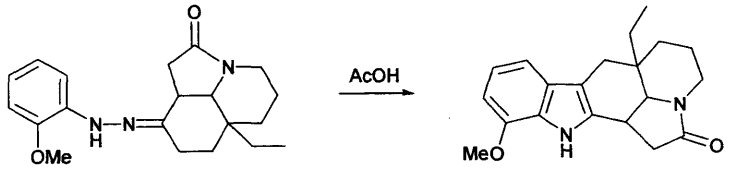
Illy and Funderbunk have demonstrated that concentration of the acid catalyst is important in determining the direction of cyclization of the phenyl hydrazone **289** of isopropylmethylketone.[80]



289 290 291

Acetic acid, bisulfate ion, aqueous phosphoric acid all give predominately 2,3,3-trimethyl-3H-indole **290**, the product of cyclization into the more branched chain of the ketone. Polyphosphoric acid and concentrated sulphuric acid in molar ratios of 5:1 over the hydrazone favour formation of 2-isopropylindole **291**, the product of cyclization into the methyl group.

An interesting ring strain-effect was noted by Stork and Dolfini when applying the Fischer cyclization to the synthesis of aspidospermine.[81] The *o*-methoxyphenylhydrazone **292** apparently cyclized to the indole **293**.



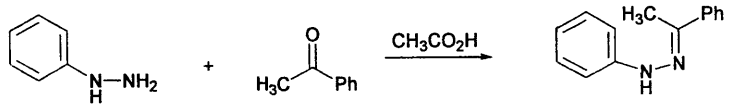
292 293

3.3.2 Results & Discussion.

In seeking for new applications of the choline chloride.2ZnCl$_2$ our attention was drawn by some recent publications on the synthesis and reactions of heterocyclic compounds in ionic liquids. We were particularly interested in carrying out the Fischer indole synthesis in an ionic liquid, there was one report of this reaction using 1-butylpyridinium chloride-AlCl$_3$ (*n*-BPC-AlCl$_3$) ionic liquid.[65] The Fischer indole reaction is a good candidate for ionic liquids as it is normally carried out in hot poly-phosphoric acid, product isolation is by addition to water and filtration of the product, disposal of the phosphoric acid residues can have a considerable environmental impact.

3.3.2a The Fischer Indole Synthesis in Choline Chloride.2 ZnCl$_2$ from Hydrazone with Product Isolation by Aqueous Work-up.

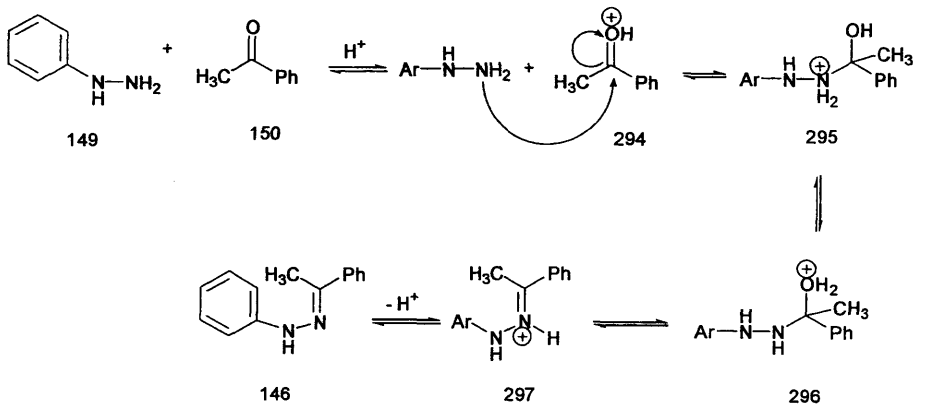
As a starting point for the project the reaction phenylhydrazine **149** and acetophenone **150** was carried out in acetic acid to give phenylhydrazone of acetophenone **146** as colourless crystals in 48% yield.



149 150 146

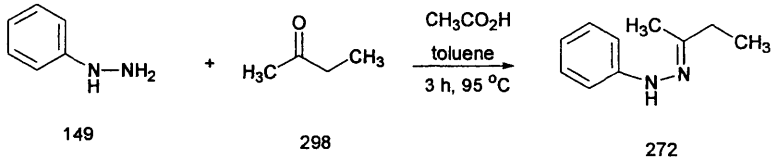
The mechanism of this reaction is shown in Scheme 6.

Nucleophilic attack of the phenylhydrazine **149** on the protonated ketone **294**, proton transfer and elimination of water gives the iminium cation **297**, which after deprotonation gives the phenylhydrazone **146**.

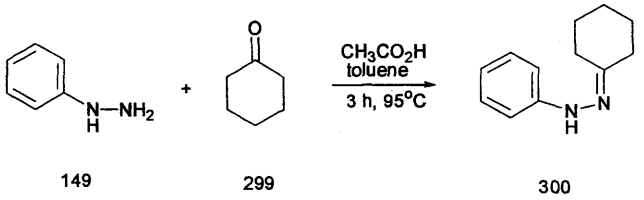


Scheme 6, Mechanism of synthesis of phenyl hydrazone of acetophenone.

Phenylhydrazine **149** was added to a solution of butanone **298** in acetic acid and toluene to give phenylhydrazone **272** as a brown solid in 80% yield. The mechanism is the same as described above in scheme 6.

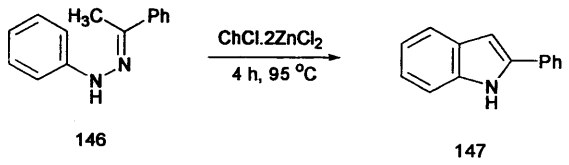


Similarly, phenylhydrazine **149** was added to a solution of cyclohexanone **299** in acetic acid and toluene to furnish phenylhydrazone of cyclohexanone **300** as a brown solid in 60% yield. The mechanism is as shown above in Scheme 6.



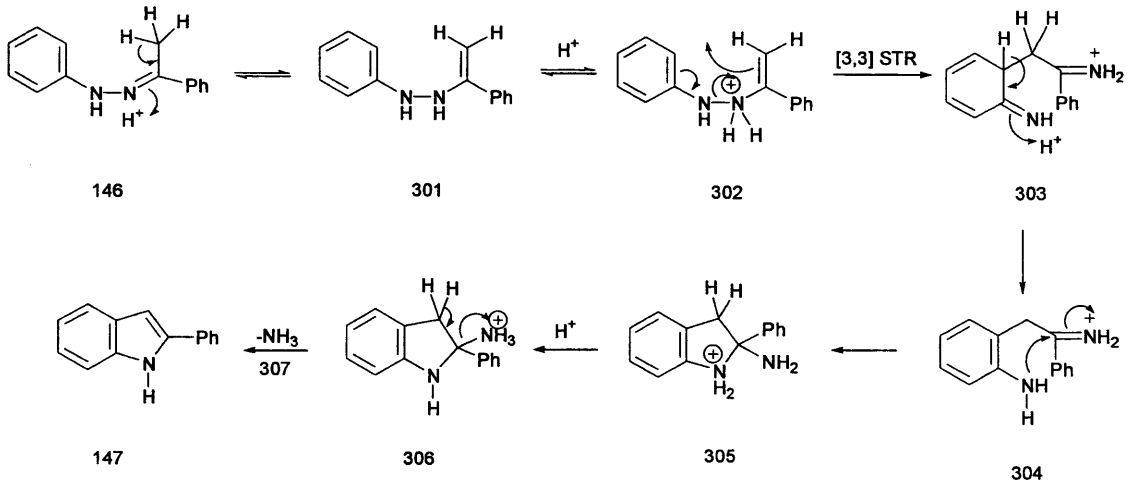
3.3.2b Synthesis of Indole from the Phenylhydrazone in ChCl.2ZnCl$_2$.

Phenylhydrazone of acetophenone **146** was heated with three equivalents of the choline chloride.2ZnCl$_2$ ionic liquid for 4 hours at 95 °C. Product isolation by addition of water and filtration gave 2-phenylindole **147** as a yellow crystals in 91% yield.



146 147

The mechanism of the reaction is shown in Scheme 7.

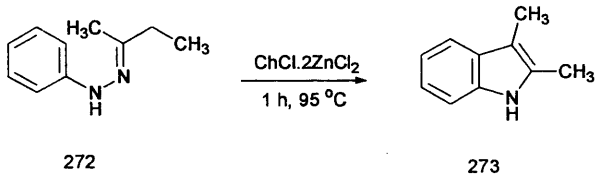


146 301 302 303 304 305 306 147

Scheme 7, Mechanism of the synthesis of 2-phenylindole from the hydrazone.

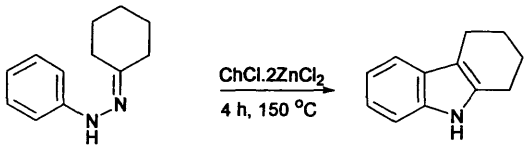
Phenylhydrazone of acetophenone **146** looses a proton to give the enamine **301**. Then a [3,3] sigmatropic rearrangement of **302** gives intermediate **303**. Rearomatization of **303** gives intermediate **304** and nucleophilic attack of the amine on the iminium cation undergoes intermediate **305**. Proton transfer to give **306** and loss of ammonia gives the final indole **147.**

To choline chloride.2ZnCl$_2$ ionic liquid was added phenylhydrazone **272**. Direct sublimation from the ionic liquid of the product gave 2,3-dimethylindole **273** as yellow crystals in 56% yield.



272 273

After 4 hours at 150 °C in 3 equivalents of choline chloride.2$ZnCl_2$ ionic liquid phenylhydrazone **300** gave 1,2,3,4-tetrahydrocarbazole **308** as a white crystals after direct sublimation of the product from the ionic liquid.



300 308

The isolated products of these reactions were finally purified by vacuum sublimation. It occurred to us that it might be possible to isolate the indole product directly from the ionic liquid by vacuum sublimation. Since an ionic liquid has 'little or no vapour pressure,'[82] then the vapour pressure of the solution of the indole product in the ionic liquid would be expected to be about the same as the vapour pressure of the indole itself. We were delighted to find that the idea did in fact work and a 91% yield of 2-phenylindole **147** could be obtained by direct vacuum sublimation from the ionic liquid reaction mixture.

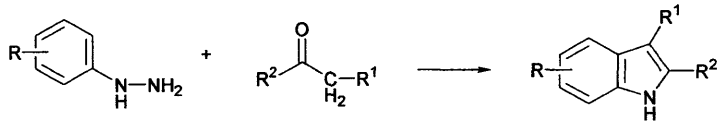
In the case of 2,3-dimethylindole **273** a 56% yield was obtained by the vacuum sublimation method. In the reaction with the phenylhydrazone **300**, the product 1,2,3,4-tetrahydrocarbazole **308** sublimed directly from the reaction without vacuum and could be isolated by scraping from the ionic liquid surface and from the glass of the reaction vessel. A key factor in determining the efficiency of the product sublimation is that we are going from a hydrazone which is basic to a product which is a weak base as the lone pair on the indole nitrogen is part of the aromatic system and not available for coordination to the $ZnCl_2$.

We further reasoned that it may be possible to carry out a series of reactions in the same ionic liquid. To this end when we had sublimed out the 2-phenylindole **147** in 91% yield from the ionic liquid, we added a further quantity of acetophenone hydrazone and carried out a second reaction. This time the yield was 72% and a third repetition gave a 34% yield. During the Fischer indole reaction, one equivalent of ammonia is produced which would be expected to coordinate to the $ZnCl_2$. In the repeated use of the choline chloride.2 $ZnCl_2$ for a series of reactions as shown by the mechanism in

scheme 7, NH_3 is produced in the Fischer indole reaction. Ammonia would be expected to accumulate and reduce the efficiency of the reaction as observed by the fall in yield.

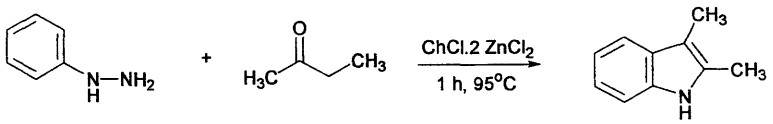
3.3.2c One Pot Reaction with 3 equivalents of ChCl.2ZnCl$_2$.

In seeking further improvements in the conditions of the Fischer indole synthesis we carried out a series of reactions of the hydrazine and the ketone in 3 equivalents of the ChCl.2ZnCl$_2$. The aim is to reduce the quantity of ChCl.2ZnCl$_2$ used and to avoid the isolation of unstable hydrazones.



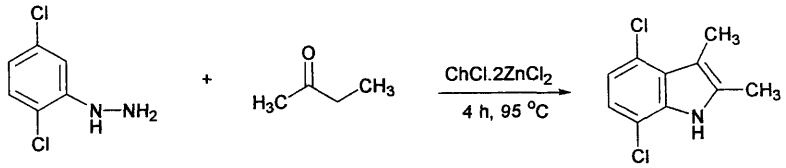
309 310 311

Butanone **298** and phenylhydrazine **149** reacted at room temperature in 3 equiv. of ChCl.2ZnCl$_2$, direct sublimation from the ionic liquid of the product gave 2,3-dimethylindole **273** as a yellow crystals in 80% yield.



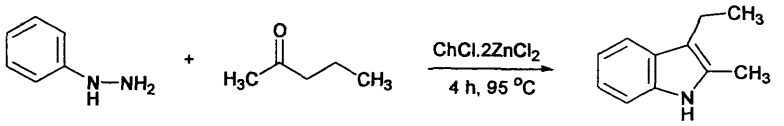
149 298 273

Similarly, butanone **298** and 2,5-dichlorophenylhydrazine **312** reacted in choline chloride.2ZnCl$_2$ ionic liquid to give 4,7-dichloro-2,3-dimethylindole **313** as white crystals in 72% yield.



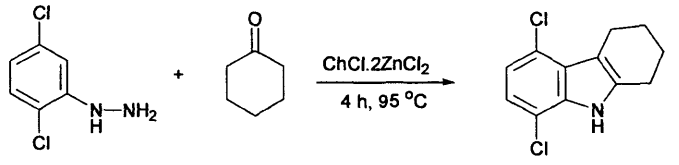
312 298 313

In the third example 2-pentanone **314** and phenylhydrazine **149** were added to ChCl.2ZnCl$_2$ ionic liquid at room temperature, direct sublimation from the ionic liquid of the product gave 3-ethyl-2-methylindole **315** as white crystals in 48% yield.



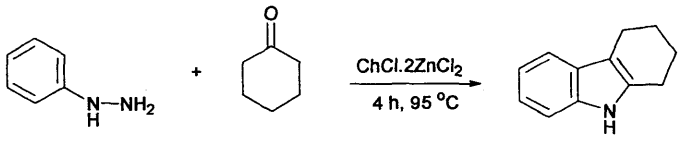
149 314 315

Similarly, cyclohexanone **299** and 2,5-dichlorophenylhydrazine **312** gave 5,8-dichloro-1,2,3,4-tetrahydrocarbazole **316** as yellow crystals with 59% yield.



312 299 316

Finally, to choline chloride.2ZnCl$_2$.ionic liquid were added cyclohexanone **299** and phenylhydrazine **149** at room temperature, direct sublimation from the ionic liquid of the product gave 1,2,3,4-tetrahydrocarbazole **308** as white crystals in 55% yield. Then work up of the ionic liquid with water gave white solid which was filtered off in a Buchner funnel. Sublimation of the white solid gave again 1,2,3,4-tetrahydrocarbazole **309** as white crystals in 27%. The total yield was 82%.

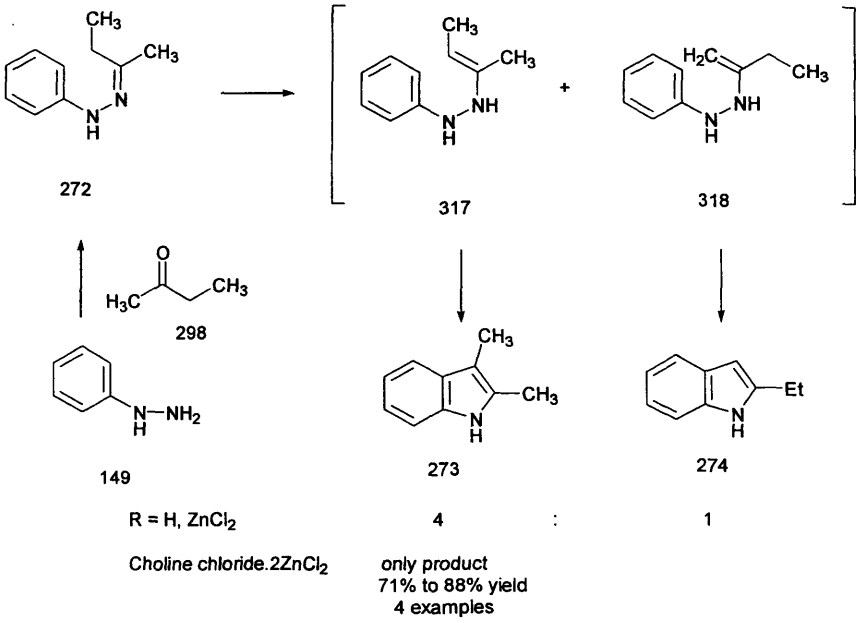


149 299 308

In this case, vacuum sublimation direct from the ionic liquid was incomplete, the unsublimed product was isolated by aqueous work-up and sublimation of the isolated product. Yields quoted and based on the total weight of isolated product.

3.3.3d Regiospecific Formation with Unsymmetrical Dialkyl Ketones.

An important issue in the Fischer indole synthesis is the selectivity when an unsymmetrical dialkyl ketone is used. In previous studies on the Fischer indole synthesis [83.a-c] on the phenylhydrazone of butanone a 4:1 mixture of 2,3-dimethylindole **273** and 2-ethylindole **274** was obtained (Scheme 8).



Scheme 8, Regiospecific formation of 2,3-dimethylindole.

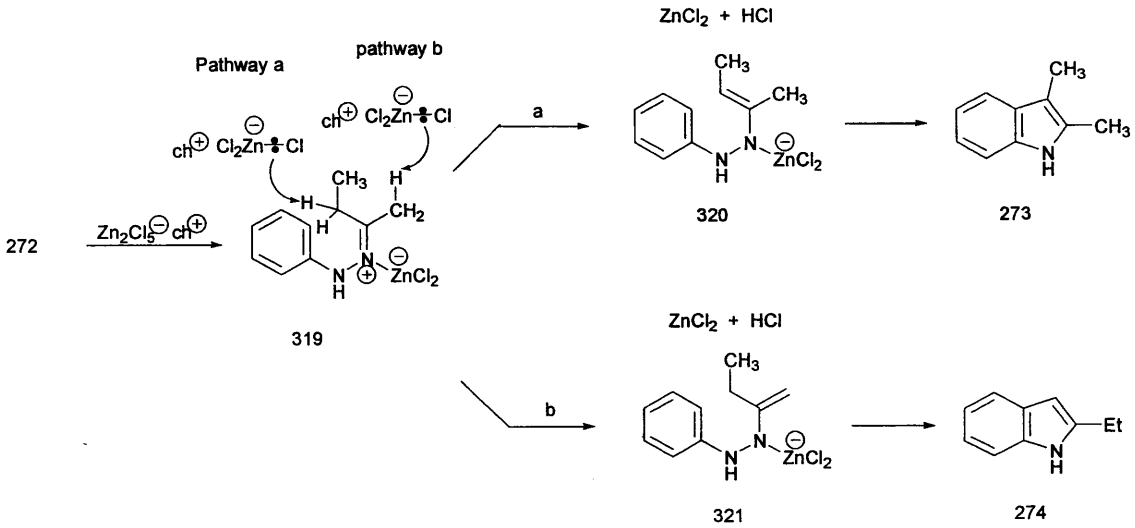
In order to explain this selectivity we first have to consider the actual species present in the ionic liquid choline chloride zinc chloride. The FAB mass spectrum of choline chloride.2 zinc chloride shows the presence of $[ZnCl_3]^-$ (m/z, 171), $[Zn_2Cl_5]^-$ (m/z, 307) and $[Zn_3Cl_7]^-$ (m/z, 443).[58] We believe that these species are arising from the following equilibria where Ch^+Cl^- is choline chloride .[84]

$$2ZnCl_2 + Ch^+Cl^- \rightleftharpoons Zn_2Cl_5^- + Ch^+ \qquad \text{equation} \quad (1)$$

$$2Zn_2Cl_5^- \rightleftharpoons ZnCl_3^- + Zn_3Cl_7^- \qquad \text{equation} \quad (2)$$

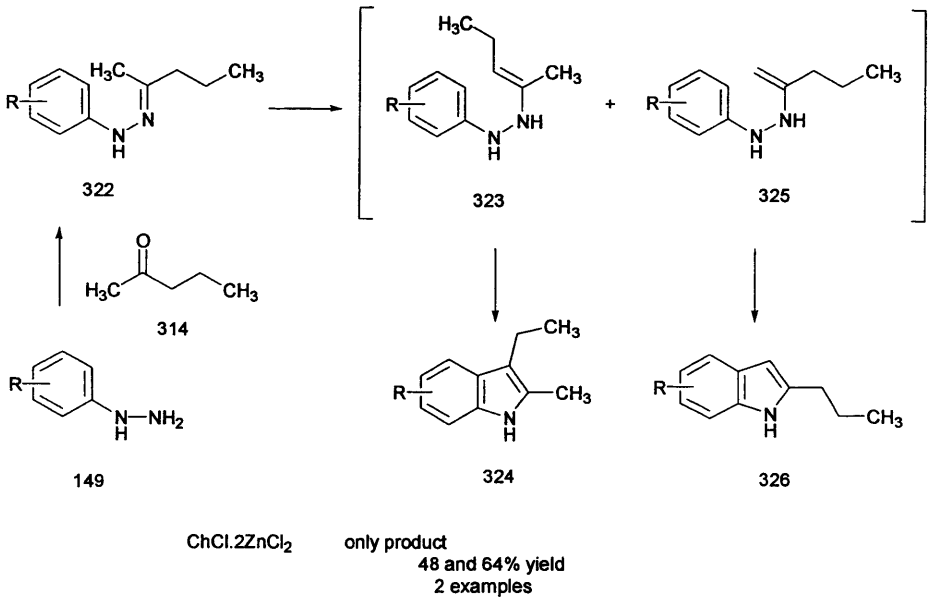
$$Zn_2Cl_5^- \rightleftharpoons ZnCl_2 + ZnCl_3^- \qquad \text{equation} \quad (3)$$

If we consider equation (3), the effect of reacting the hydrazone **272** as a Lewis base with $Zn_2Cl_5^-$ will produce iminium cation **319** and $ZnCl_3^-$, as shown in Scheme 9. $ZnCl_3^-$ can now act as a base and remove a proton in one of two ways. In pathway a, the proton is removed by $ZnCl_3^-$ to produce the zinc enamine **320**, which is the thermodynamic product, $ZnCl_2$ and HCl. Under the published reaction conditions[84a-c] pathway b is also observed in which a proton is lost from the methyl group to give the less substituted zinc enamine **322**, which is the kinetic product. The reaction here is under kinetic control as there is no special stability of the iminium cation **319** and pathways a and b are irreversible processes leading to two products **273** and **274**. We propose that in the ionic liquid choline chloride.2ZnCl$_2$ the iminium cation is stabilised and pathway b becomes a reversible reaction hence the less substituted zinc enamine **321** can reprotonate, return to the iminium cation **319** and follow pathway a to the more stable zinc enamine **320** and hence form exclusively the 2,3-dimethylindole **273**. This explanation is supported by four examples using butanone and two using pentanone, in all cases a single indole arising from the more substituted enamine intermediate is observed.



Scheme 9, Selectivity of phenylhydrazone of butanone **272** in ChCl.2ZnCl$_2$ ionic liquid.

In the case of phenyl hydrazine **149** and pentanone **314** as starting materials, our explanations were confirmed due to only thermodynamic product **324** was obtained (Scheme 10).



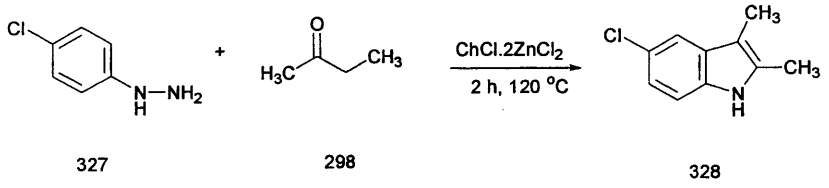
Scheme 10, Regiospecific formation with unsymmetrical dialkyl ketone.

3.3.3e One Pot Reaction with 1 equivalent of ChCl.2ZnCl$_2$.

Finally we reduced the amount of ionic liquid used in the reaction to one equivalent to obtain between 64 and 88% of directly sublimed product for the synthesis of 5-chloro-2,3-dimethylindole **328** and 2,3,7-trimethylindole **332**, 5-chloro-3-ethyl-2-methylindole **329**, and 6-chloro and 8-methyl-1,2,3,4-tetrahydrocarbazole **330** and **333**.

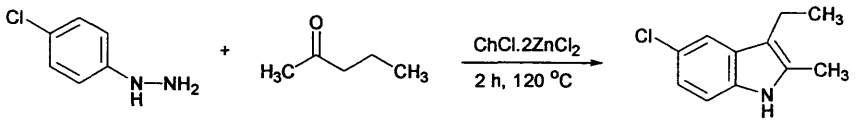
One pot reaction using 4-chloro-phenylhydrazine as starting material.

Ethylmethylketone **298** and 4-chlorophenylhydrazine hydrochloride **327** reacted at room temperature in 1 equivalent of ChCl.2ZnCl$_2$ ionic liquid, direct sublimation from the ionic liquid of the product gave 5-chloro-2,3-dimethylindole **328** as white crystals in 88% yield.



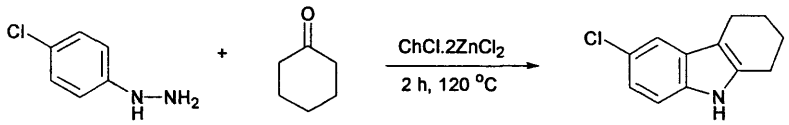
327 298 328

Similarly, 2-pentanone **314** and 4-chlorophenylhydrazine hydrochloride **327** gave 5-chloro-3-ethyl-2-methylindole **329** as white crystals in 64% yield.



327 314 329

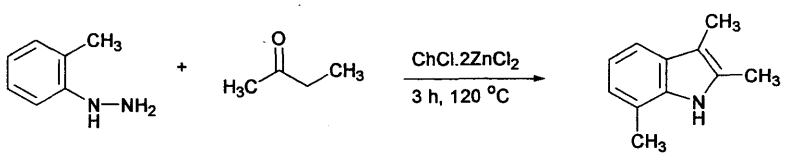
Finally, 4-chlorophenylhydrazine hydrochloride **327** and cyclohexanone **299** were added to choline chloride.2ZnCl$_2$ ionic liquid at room temperature, direct sublimation from the ionic liquid of the product gave 6-chloro-1,2,3,4-tetrahydrocarbazole **330** as white crystals in 84% yield.



327 299 330

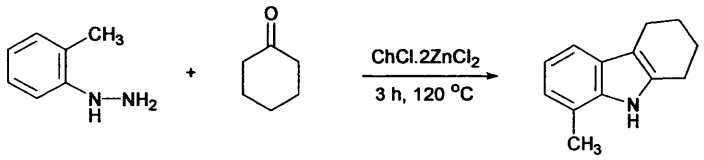
One pot reaction using *o*-methylphenylhydrazine as starting material.

Ethylmethylketone **298** and *o*-tolylhydrazine hydrochloride **331** were added to ChCl.2ZnCl$_2$ to give 2,3,7-trimethylindole **332** as yellow crystals in 71% yield; 53% after direct sublimation and 18% after work-up with water and direct sublimation.



331 298 332

Finally, cyclohexanone **299** and *o*-tolylhydrazine hydrochloride **331** gave 8-methyl-1,2,3,4-tetrahydrocarbazole **333** as yellow crystals in 76% yield; 51% after direct sublimation and 25% after work-up with water and sublimation.



331 299 333

In conclusion we have carried out the Fischer indole synthesis using one equivalent of the ionic liquid choline chloride.2$ZnCl_2$ with direct product isolation by vacuum sublimation. In unsymmetrical cases regiospecific formation of a single product arising from the formation of the more substituted enamine intermediate is observed.

The novel aspects of this research have been:

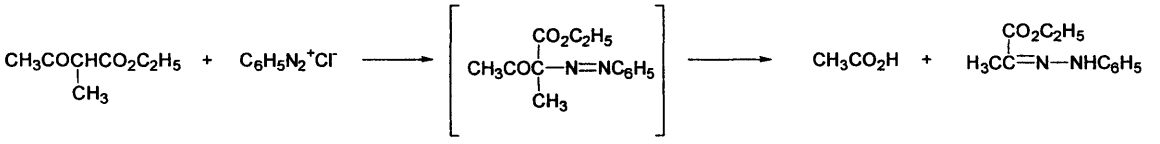
1. To get the indole product from the hydrazine in one pot ionic liquid reaction.
2. To isolate the product by sublimation.
3. To use the same ionic liquid for the same reaction.

Chapter 4
Additional Methods
for the Synthesis of Indoles

4.1. Introduction.

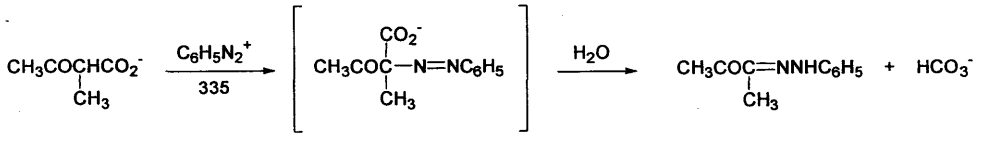
4.1.1 The Japp-Klingemann Reaction.

The Japp-Klingemann reaction is an important extension to the scope of the Fischer indole synthesis, which involves the electrophilic substitution of electron-rich carbon-carbon multiple bonds by aryl diazonium salts.[85] The reaction was discovered by Japp and Klingemann[86] by an attempt to prepare the azo ester **336** by coupling benzenediazoniun chloride **335** with ethyl 2-methylacetoacetate **334**, the phenylhydrazone of ethyl pyruvate **338** was obtained as the product.



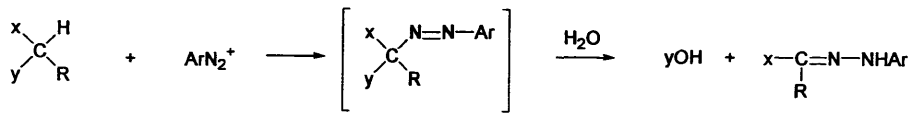
334 335 336 337 338

It appeared that the acetyl group is displaced during this process; actually the coupling product **336** was unstable under the conditions of its formation, undergoing hydrolytic cleavage of the acetyl group and rearrangement of the azo structure. A year later the same authors discovered that, if the substituted acetoacetic ester was hydrolysed and the coupling carried out on the sodium salt, the carboxylate function, rather than the acetyl group, was lost and the product isolated was the phenylhydrazone of biacetyl **341**.[87]



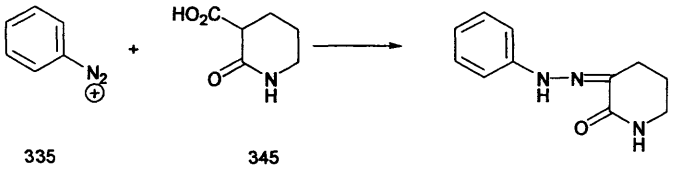
339 340 341

In later years the reaction has been extended to other systems containing activated methinyl groups. The process can be generalized as shown in the following equation, in which **x** and **y** are electron-withdrawing groups.

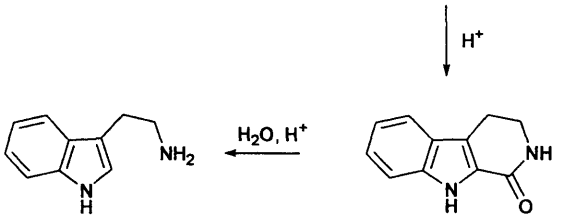


342 343 344

The first stage of the Abramovitch tryptamine **348** synthesis will be recognized as a Japp-Klingemann reaction of the latter type.[88]

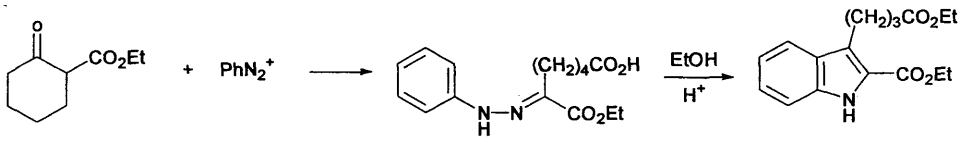


335 345 346



348 347

Cyclic β-keto ester **349** undergoes ring opening under the conditions of the Japp-Klingemann reaction. Fischer cyclization of the resulting hydrazone **350** then gives indole-2-carboxylic acid derivatives **351** having an alkanoic acid side chain at the 3-position.[89]

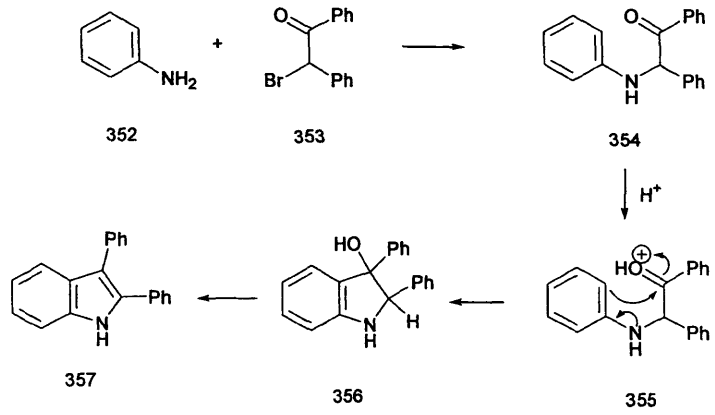


349 335 350 351, 80%

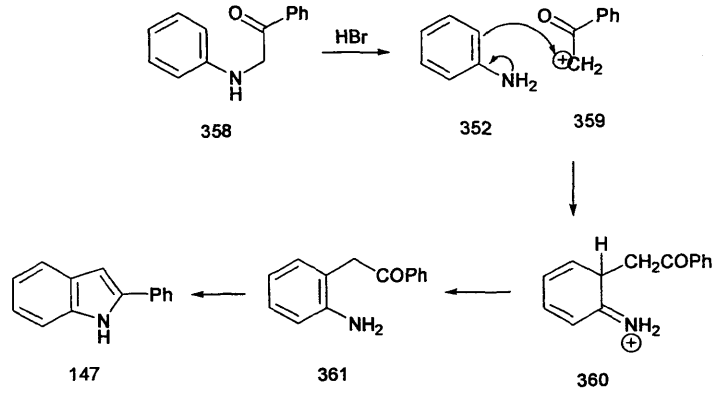
4.1.2 The Bischler Reaction.

The reaction of arylamine and α-halogenated ketone to form α-arylaminoketone followed by acid or zinc chloride catalysed dehydrative cyclization to give indole is known as the Bischler reaction. For example, reaction of aniline **352** with the α-

bromoketone **353** to give α-arylaminoketone **354** followed by acid catalysed cyclization leads to 2,3-diphenylindole **357** in 80% yield.[90] The simple mechanism for the cyclization involves protonation of the carbonyl oxygen of α-arylaminoketone **354** followed by dehydratation to give the indole 2,3-diphenylindole **357**.



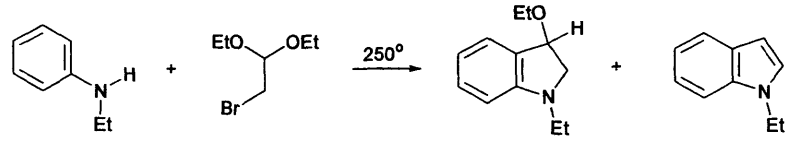
In the case of the α-arylamino-ketone **358**, the product obtained was 2-phenylindole **147** and not the expected 3-substituted product. Several mechanisms have been proposed to explain this rearrangement.[91] One example is shown by the sequence **358-147** which is known as the "ortho shift" hypothesis.[91] Acid catalysed cleavage of the α-arylaminoketone **358** to give aniline **352** and the carbonium ion **359** is followed by the recombination of these two species forming the ortho substituted aniline **361**, which then undergoes cyclization to 2-phenylindole **147**.



Both mechanisms involve activation of a benzene ring by the nitrogen lone pair in reactions **354-355** and **352-360**, even though an acid catalyst is used. Clearly an

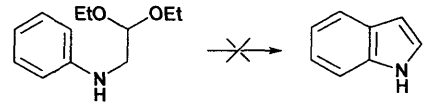
equilibrium protonated and unprotonated nitrogen is present, and only the form unprotonated on nitrogen **361** leads to cyclization.

An extension of the Bischler reaction which has received attention in recent years is the cyclization of α-arylamino-acetaldehydedialkylacetals. It has been reported,[92] that a 2:1 mixture of *N*-ethylaniline **362** and bromoacetaldehyde diethyl-acetal **363,** heated to 250 °C gave 1-ethylindole **365** in 36% yield and a small amount of the expected intermediate **364.**



362 363 364 365

The reaction was found to be successful with secondary but not with primary amines. *N*-Phenylaminoacetaldehydediethylacetal **366** was treated with 10% hydrochloric and 70% sulphuric acid, but no indole **231** formation occurred.[93]

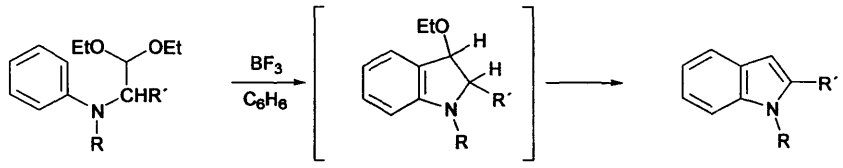


366 231

Similarly, attempts to cyclise **366** using arylamine hydrochloride, zinc chloride and cuprous chloride[94] catalysts which are known to promote the Bischler reaction, gave resins only.

An extensive study of the cyclisation of α-arylaminoaldehydedialkylacetals **367** has been published,[95] in which it was shown such acetals could be cyclised to indoles under certain conditions. Treatment of acetals of general formula **367** with BF_3 gave cyclization to indoles **369** only if an alkyl substituent was attached to the aldehyde moiety i.e., R′ = alkyl. The failure of primary or secondary arylaminoaldehydedialkylacetals to cyclise to indoles when treated with acid, was found to be due to the much faster reaction of the methylene group of the aldehyde with the liberated carbonyl group, to form polymeric products. However, if one of the α-

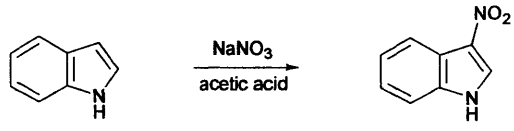
hydrogens in **367** is replaced by an alkyl substituent, and the arylamine group is either primary or secondary (**367**, R = H or alkyl, R′ = methyl or ethyl), then in dry benzene solution and in the presence of boron trifluoride, polymerisation was minimised and a 29-53% yield of the corresponding indole **369** was obtained. The expected intermediate **368** could not be isolated. The reaction has been successfully accomplished with a methyl substituent in the *o*-, *m*-, or *p*-position with respect to the amino group.



367 368 369

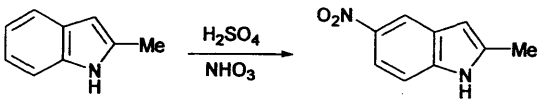
4.1.3 Nitration in Indoles.

The course of nitration of simple derivatives of indole has received considerable recent attention, principally from Noland and co-workers.[96] The 3-position of the indole ring is normally the most reactive toward electrophilic substitution. Indole **231** in acetic acid was reacted with $NaNO_3$ to give 3-nitroindole **370** in 78% yield.[97]

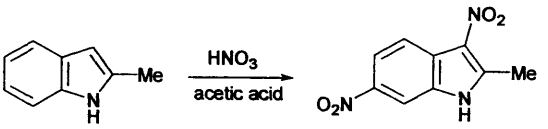


231 370

The orientation in simple 2-substituted indoles depends upon the reaction media. Nitration of 2-methylindole **219** in concentrated sulphuric acid gives high yields of 5-nitro derivatives **371**, but nitration in nitric acid or nitric acid-acetic acid mixtures gives lower yields of 3,6-dinitro derivatives **372**.[98]

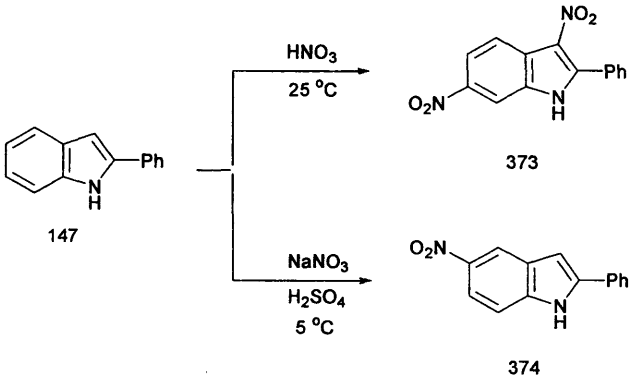


219 371



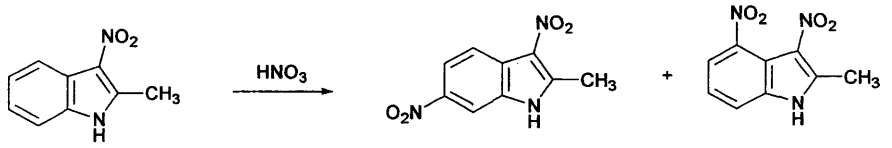
219 372

2-Phenylindole **147** under concentrated nitric acid gives 3,6-dinitro-2-phenylindole **373** in 40% yield and nitration of 2-phenylindole **147** in concentrated sulphuric acid gives 5-nitro-2-phenylindole **374** in 87% yield.[98]



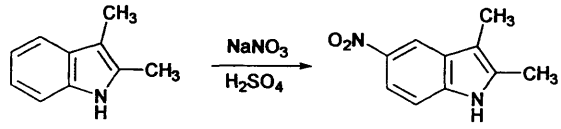
147 373 374

Nitration of 2-methyl-3-nitroindole **375** to 3,6-dinitro-2-methylindole **373** has been shown to be an efficient process in concentrated nitric acid in 67% yield.[99]



375 373 67% 376 3%

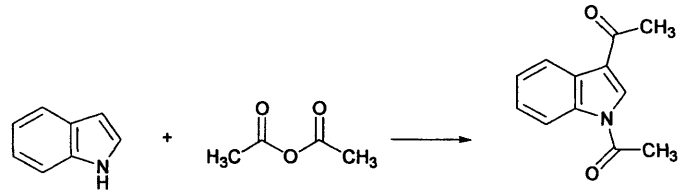
2,3-Dimethylindole **273** was reacted with sodium nitrate in concentrated sulphuric acid at 5 °C to yield 2,3-dimethyl-5-nitroindole **377** in 66% yield.[100]



273 377

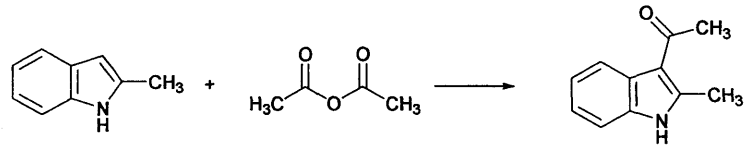
4.1.4 Acylation in Indoles.

The acylation of indoles has been a widely used synthetic procedure for some time. The 3-position is the normal site of attack although acylation may also take place on the nitrogen atom. Indole **231** and 2-methyl-indole **219** are acetylated by heating with acetic anhydride **378**. When indole **231** and acetic anhydride **378** are refluxed for 24 hours, 1,3-diacetylindole **379** is formed in 75% yield.[101] *N*-Acyl group can be removed by alkaline hydrolysis.



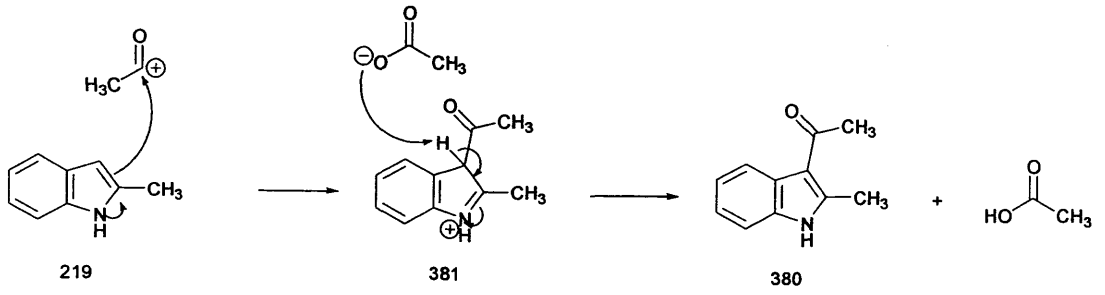
231 378 379

The 3-acetyl-derivative **380** is formed from the reaction of 2-methylindole **219** with acetic anhydride **378** in 40% yield.[102]



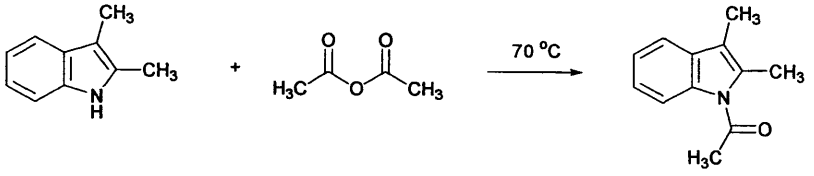
219 378 380

Acylations of indole are mechanistically viewed as Friedel-Crafts acylations of a reactive aromatic ring. It is an electrophilic aromatic substitution that forms carbon-carbon bonds. This reaction proceeds through an acyliminium cation.



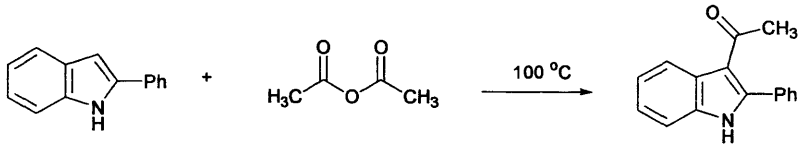
219 381 380

2,3-Dimethylindole **273** was reacted with acetic anhydride **378** to give *N*-acetyl-2,3-dimethylindole **382** in 80% yield.[103]



273 378 382

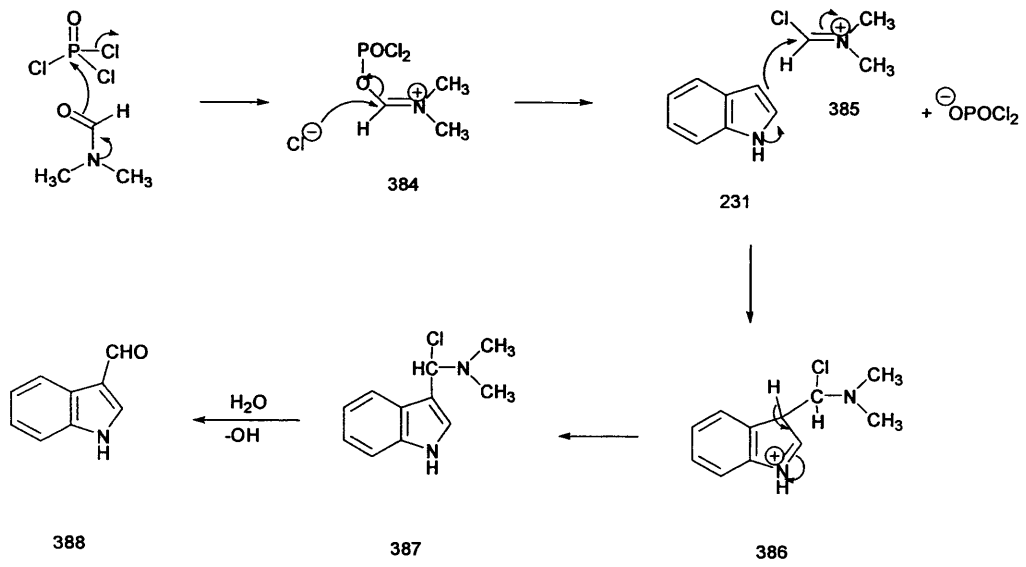
The 3-acetyl-2-phenylindole **383** is formed from the reaction of 2-phenylindole **147** with acetic anhydride **378** in 60% yield.[102]



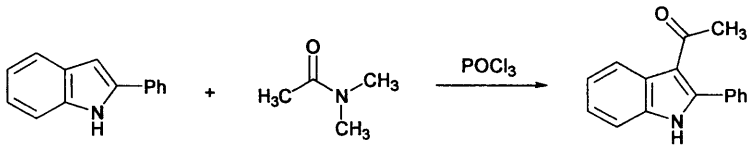
147 378 383

Another useful method is the Vilsmeier-Haack acylation employing DMF and phosphoryltrichloride.[104] Indole **231** gives the 3-formyl derivative **388** in 95% yield.[104]

DMF reacts with phosphoryltrichloride to produce the iminium cation **384**. An alternative iminium cation is form by attack of chloride anion to furnish the chloro-iminium cation known as the Vilsmeier reagent **385** and the phosphorus anion. Electrophilic attack of indole **231** on the reagent **385** gives the intermediate **386**. Final hydrolysis of intermediate **387** furnishes indole **388**.



2-Phenylindole **147** reacts with *N,N*-dimethylformamide to give 3-acetyl-2-phenylindole **379** in 70% yield at 90 °C.[105]

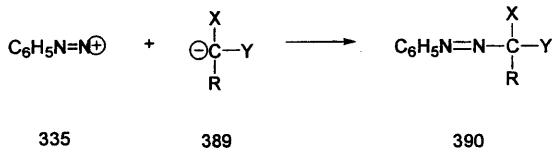


4.2 Results & Discussion.

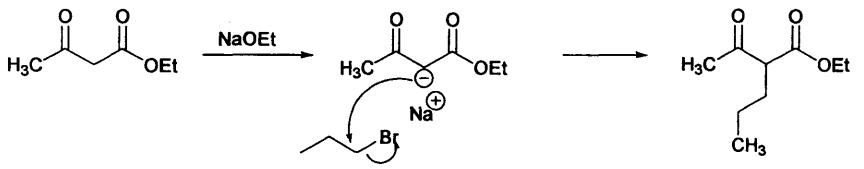
After a successful study of the Fischer indole reaction we decided next to turn our attention to study of other indole synthesis in $ChCl.2ZnCl_2$.

4.2.1 The Japp-Klingemann Reaction.

The Japp-Klingemann reaction is a special case of the coupling of diazonium salts **335** with aliphatic compounds. The key step in this process is the reaction of a diazonium cation **335** with a stabilised carbanion **389** to produce the azo compound **390**.

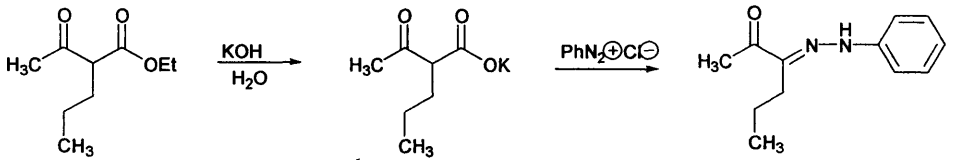


Our study of this reaction starts with the alkylation of ethyl acetoacetate **391**. Sodium ethoxide in ethanol was used to produce resonance stabilised enolate **392,** which underwent reaction with bromopropane in a S_N2 reaction to give the alkylated compound **393** in 55% yield.



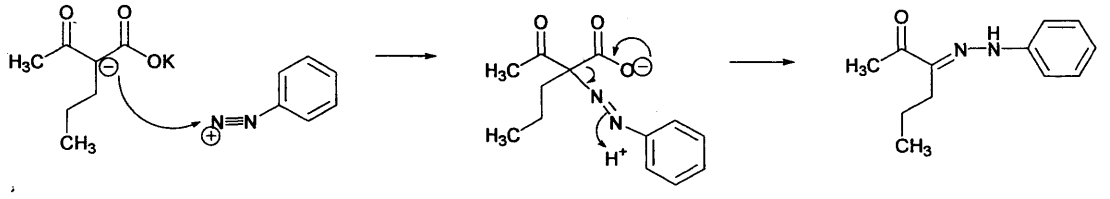
391 392 393

The ester group in **393** was hydrolysed with potasium hydroxide to the potasium salt **394,** which reacted with phenyldiazonium chloride to produce the hydrazone **395** in 2% yield.



393 394 395

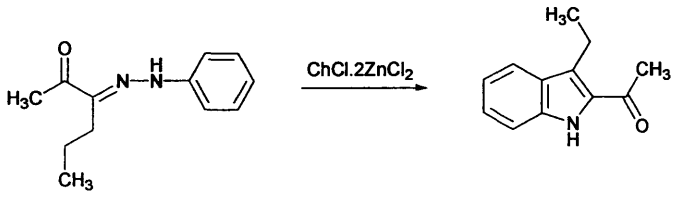
The mechanism of this reaction[86] involves the reaction of enolate **396** with the diazonium cation to furnish the intermediate azo compound **397** which undergoes decarboxylation to generate the hydrazone **395.**



396 335 397 395

To $ChCl.2ZnCl_2$ ionic liquid was added 3-(phenylhydrazone)hexan-2-one **395** and the mixture was heated at 95 °C for 3 hours. Direct sublimation of the indole did not occur. Aqueous work-up gave no identifiable products. The yield of hydrazone **395** was very low, consequently, we were only able to carry out the Fischer indole reaction

on 8 mg of hydrazone **395** in $ChCl.2ZnCl_2$. The expected indole is 2-acetyl-3-ethylindole **398**, however, was not observed. Clearly more work is needed to improve the yield of hydrazone **395** so that the Fischer indole reaction can be carried out on a large scale.

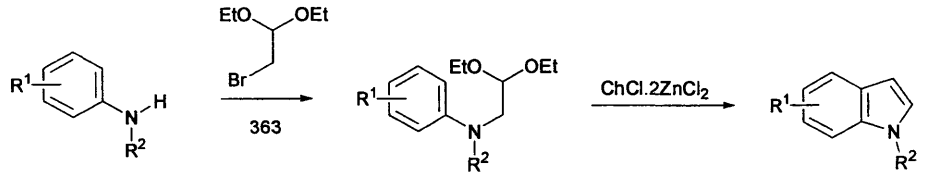


395 398

4.2.2 The Bischler Reaction.

The aim of this part of the project is to carry out the synthesis of indoles using the Bischler method in $ChCl.2ZnCl_2$ as shown by conversion of **400** into **401** in Scheme 11.

Aniline **399** reacted with bromoacetaldehyde diethylacetal **363** to give α-arylaminoacetaldehyde dialkylacetal **400**.

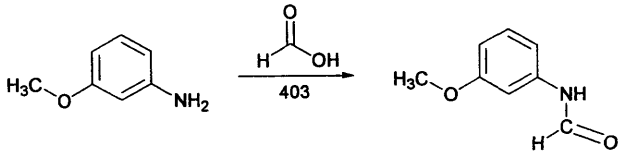


399 363 400 401

scheme 11

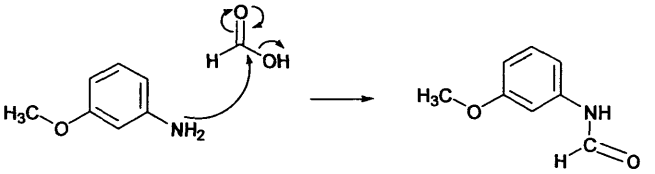
Our first example is where $R^2 = CH_3$ and this is prepared by first converting the aniline into the formamide and then reducing to an *N*-methyl using $LiAlH_4$.

3-Methoxyaniline **402** was reacted with formic acid **403** to produce formamide **404** in 85% yield.[106]



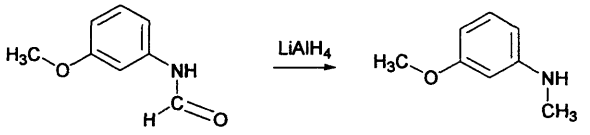
402 403 404

N-Formyl-3-methoxyaniline **404** is obtained by nucleophilic attack of 3-methoxy-aniline **402** on the formic acid.



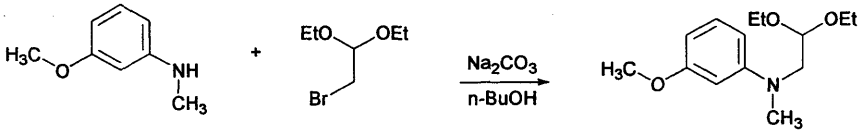
402 404

N-Formyl-3-methoxyaniline **404** was reacted with $LiAlH_4$ in excess. Reduction of the formamide group is achieved and *N*-methyl-3-methoxyaniline **405** is obtained in 51% yield.[106]



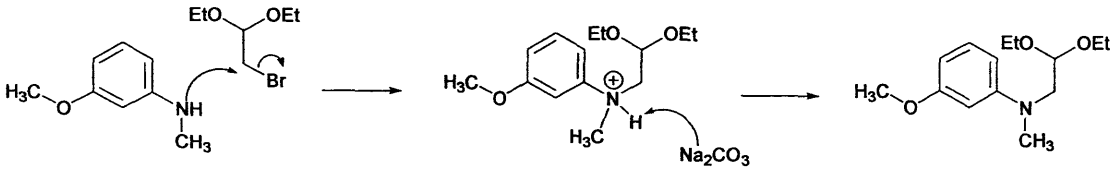
404 405

N-Methyl-3-methoxyaniline **405** was reacted with bromoacetaldehyde diethylacetal **363** to produce (2,2-diethoxyethyl)-(3-methoxyphenyl)methylamine **406** in 79% yield.[106]



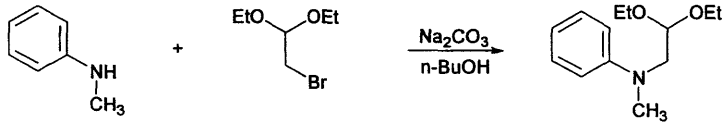
405 363 406

This mechanism goes through nucleophilic attack of the nitrogen lone pair on the bromoacetaldehydediethylacetal **363** to produce intermediate **407,** then sodium carbonate takes a proton the ammonium in intermediate **407** to produce (2,2-diethoxyethyl)-(3-methoxyphenyl)methylamine **406.**



405 407 406

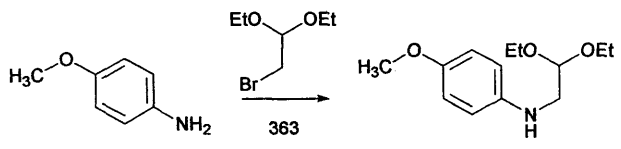
Using the same method for the synthesis of (2,2-diethoxyethyl)-(3-methoxyphenyl)methylamine **406**, commercially available *N*-methylaniline **408** was reacted with bromoacetaldehydediethylacetal **363** to produce (2,2-diethoxyethyl)-methylphenylamine **409** in 71% yield.



408 363 409

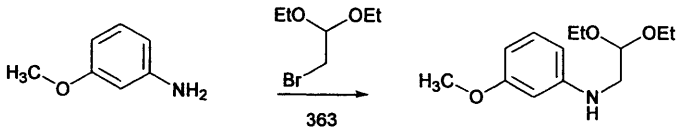
Our next example is where R^2 = H in structure **399** and this is prepared by converting the aniline into the α-arylaminoacetaldehyde dialkylacetals **400**. Three different substrates were synthesised. Aniline **399** was reacted with bromoacetaldehyde diethylacetal **363** to produce α-arylaminoacetaldehyde dialkylacetal **400.**

4-Methoxyaniline **402** was reacted with bromoacetaldehyde diethylacetal **363** to produce (2,2-diethoxyethyl)-(4-methoxyphenyl)amine **410** in 63% yield. ^{1}H NMR shows one signal at 3.2 ppm as a doublet which corresponds to the CH_2 next to the nitrogen and another signal at 4.68 ppm as a triplet which corresponds to the CH next to the OEt groups. Both signals are coupled with a *J* of 5.5 Hz. This was confirmed by the ^{13}C NMR which showed a signal at 47.8 ppm corresponding to the CH_2 and 101.4 ppm from the CH between the two ethoxy groups. Accurate mass indicates a molecular formula of $C_{13}H_{21}NO_3$.



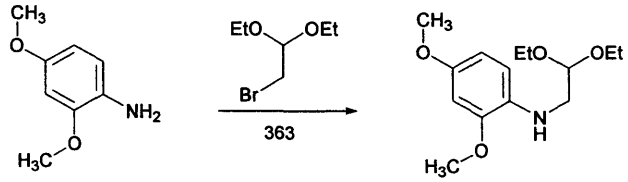
402 410

3-Methoxy-aniline **411** was reacted with bromoacetaldehyde diethylacetal **362** to produce (2,2-diethoxyethyl)-(3-methoxyphenyl)amine **412** in 79%.[107]



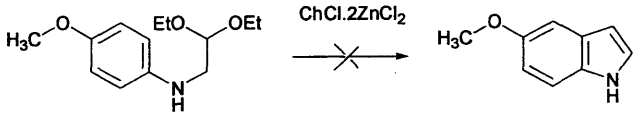
411 412

Similarly, 2,4-dimethoxyaniline **413** reacted with bromoacetaldehyde diethylacetal **363** to produce (2,2-diethoxyethyl)-(2,4-dimethoxyphenyl)amine **414** in 79%. Satisfactory spectroscopic data was obtained for **414** which is similar to that obtained for compound **412**, accurate mass spectrum indicates a molecular formula of $C_{14}H_{23}NO_4$.



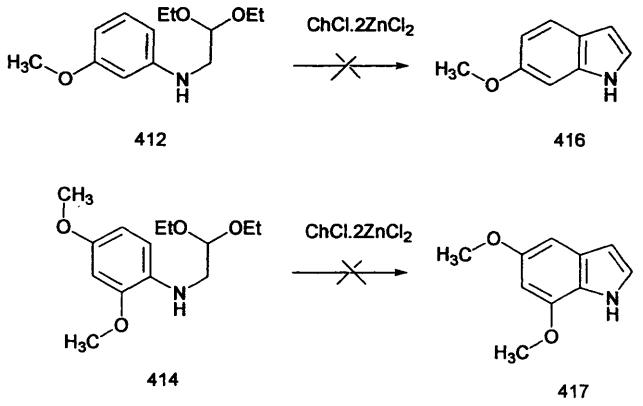
413 414

(2,2-Diethoxyethyl)-(4-methoxyphenyl)amine **410** was added to $ChCl.2ZnCl_2$, none of the expected product 5-methoxyindole **415** was isolated from the reaction either by sublimation or aqueous work-up.

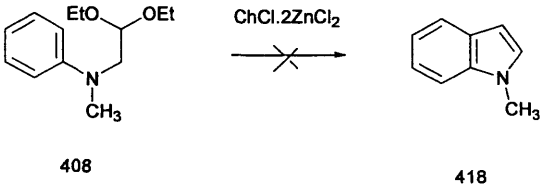


410 415

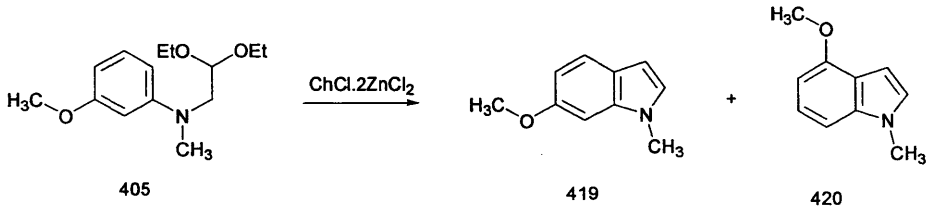
Similar negative results were obtained with both (2,2-diethoxyethyl)-(3-methoxyphenyl)amine **412**, and (2,2-diethoxyethyl)-(2,4-dimethoxyphenyl)amine **414** which did not undergo conversion to 6-methoxyindole **416** and 5,7-dimethoxyindole **417** respectively.



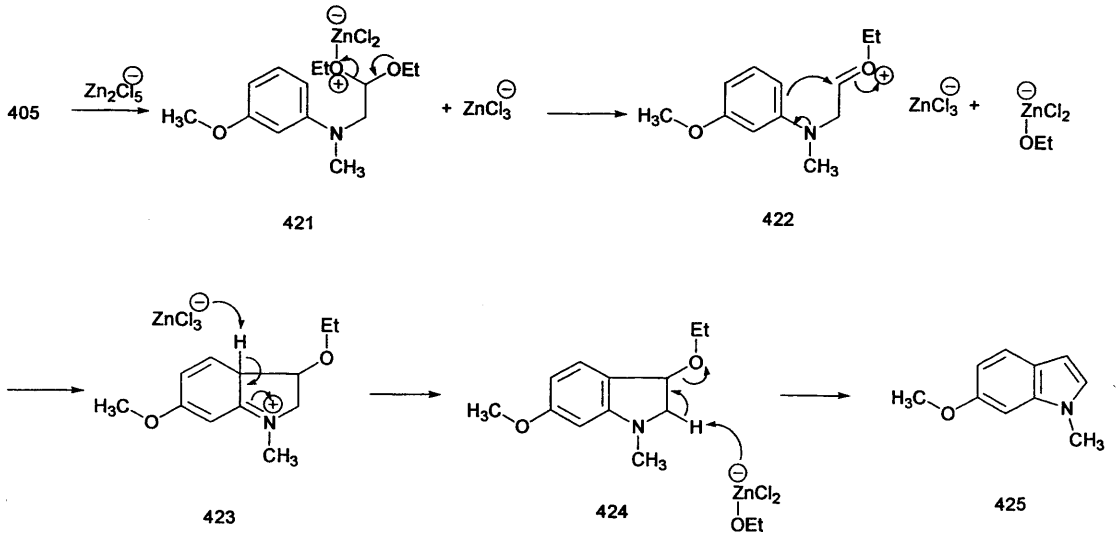
The reaction of (2,2-diethoxyethyl)methylphenylamine **408** did not give the indole **418**. Neither sublimation nor aqueous work-up worked, product isolation was not possible.



Finally, to $ChCl.2ZnCl_2$ ionic liquid was added (2,2-diethoxyethyl)-(3-methoxyphenyl)methylamine **405**. 6-Methoxy-1-methylindole **419** and 4-methoxy-1-methylindole **420** were obtained in 11% and 13% yield respectively.



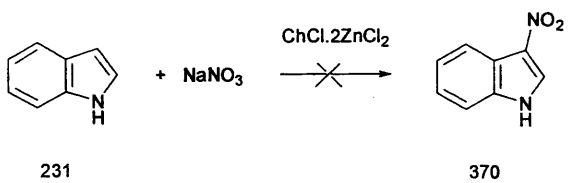
As described for the mechanism of the Fischer indole reaction acetal **405** reacts with $Zn_2Cl_5^-$, one of the major species present in the ionic liquid $ChCl.2ZnCl_2$, to give intermediate **421**. Loose of $OEtZnCl_2^-$ leads to the oxonium ion **422** which acts as an electrophile on the benzene ring to furnish intermediate cation **423**. Rearomatization produces the indoline **424** and finally elimination of ethanol gives 6-methoxy-1-methylindole **425**.



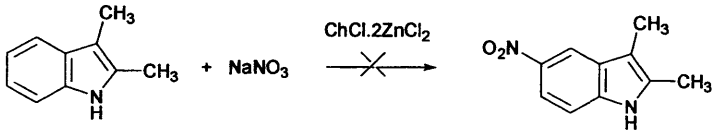
Eventually we did achieve a Bischler cyclisation with substrate **405**. However, in the light of the low yields obtained in this reaction we decided to move to a different topic.

4.2.3 Nitration in Indoles.

Having studied the Fischer indole synthesis in $ChCl.2ZnCl_2$ we next turned our attention to the electrophilic aromatic substitution of indoles in this ionic liquid. Three different indoles were used as starting material for nitration, indole itself **231**, 2,3-dimethylindole **273** and 2-phenylindole **147.** To $ChCl.2ZnCl_2$ was added indole **231** and sodium nitrate at room temperature and the mixture was heated for 2 hour at 95 °C, direct sublimation of the product was not possible, however, work-up with water gave a brown solid, direct sublimation of this brown solid was unsuccessful. The brown solid was used to run a NMR and GC/MS and the results were unsuccessful. 3-Substitution on the indole itself should have been obtained. As it was explained the 3-position of the indole ring is normally the most reactive toward electrophilic substitution, but 3-nitroindole **370** was not obtained.

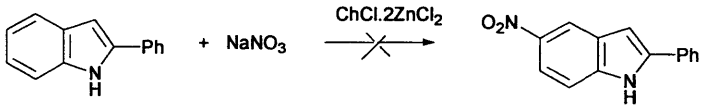


Nitration on 2,3-dimethylindole **273** using sodium nitrate was unsuccessful. Crystals from sublimation were found in the walls of the sample tube but the ^{1}H NMR confirmed that the white solid was only starting material.



273 377

As explained in the introduction, the position of nitration in simple 2-substituted indoles depends on the reaction medium.[96] The same reaction was set up with 2-phenylindole **147** and it was also unsuccessful. The reaction mixture in $ChCl.2ZnCl_2$ was worked up with water and a black solid was obtained. ^{1}H NMR and GC/MS of the black solid was run and the results were not clear. Then a TLC of the crude was made and it was confirmed that the impure starting material was isolated as a black solid which was poorly soluble in $CDCl_3$.



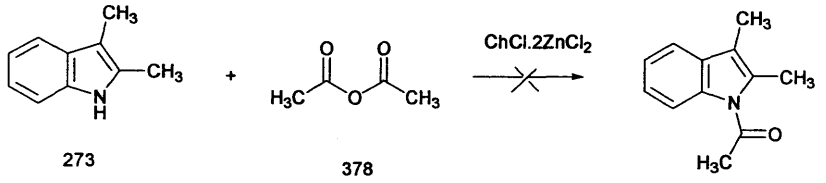
147 374

In conclusion, nitration of indole rings in $ChCl.2ZnCl_2$ ionic liquid was unsuccessful, one of the main problems was carrying out the reaction in ionic liquid because a sticky solid is always obtained.

4.2.4. Acylation in Indoles.

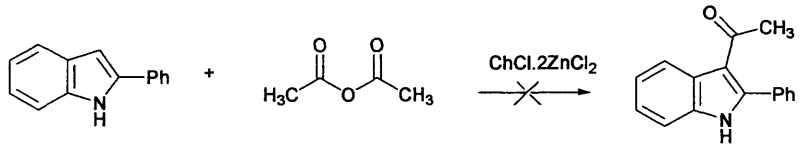
Acylation of indoles goes with 3-subtitution although it may also take place on the nitrogen atom. There are examples of acylation at C-2 when the 3-position is already substituted. The Friedel-Crafts method was the first method used for acylation of 2,3-dimethylindole **273** and 2-phenylindole **147**.[102, 103] 2,3-Dimethylindole **273** and acetic anhydride were reacted in $ChCl.2ZnCl_2$ ionic liquid. After reaction was completed crystals appeared due to sublimation on the walls of the test tube. The ^{1}H NMR and

GC/MS of the crystals showed that only starting material was obtained and *N*-acyl-2,3-dimethylindole **382** was not obtained as a final product.



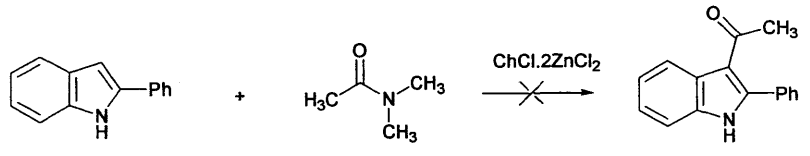
273 378 382

Similarly, 2-phenylindole **147** did not give the final product of 3-acyl-2-phenylindole **383**. Again crystals were found on the walls. The black mixture reaction was worked up with water and the ^{1}H NMR and GC/MS results showed starting material. A TLC was made and the result showed that the reaction did not take place and 3-acyl-2-phenylindole **383** was not obtained.



147 378 383

A second method for acylation of indoles was the Vilsmeier acetylation. The conditions and the results of the experiment were exactly the same as the Friedel-Crafts acetylation. The indole used as starting material was 2-phenylindole **147** but 3-acyl-2-phenylindole **383** as a final product was not obtained.



147 383

CHAPTER 5
THE 1,3 ARENE-OLEFIN CYCLOADDITION REACTION

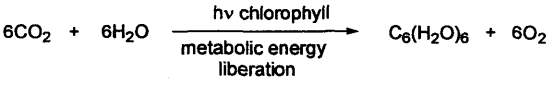
5.1 Introduction.

5.1.1 Aim of the chapter.

The basis of this project is to study the arene olefin photoannulation reaction to obtain natural products with complicated ring systems. A second objective will be to control the regioselectivity and stereoselectivy of the process.

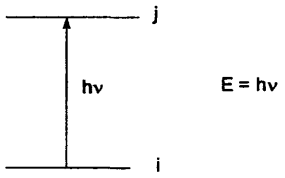
5.1.2 Photochemistry.

A long time ago it is known that the photochemical processes are the greatest important for life. Photosynthesis is a good example how light gets involved in chemical change. In this process, sunlight is absorbed by the chlorophyll in the leaves of a plant and the acquired photochemical energy is used to change carbon dioxide, water and oxygen into carbohydrates. In green plants, the product of photosynthesis is glucose.



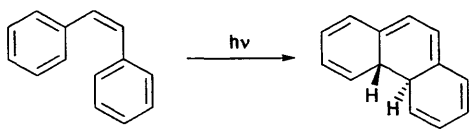
The interaction of the light with organic compounds has not been exploited until the last half of twentieth century due to the lack of appropriate technology to carry out this kind of chemistry. Also, until the discovery of the principle of conservation of orbital symmetry to concerted reactions, developed by Woodward and Hoffman,[107] it was not possible to understand many of the photochemical processes.

The absorbtion of light by a substance leads to excitation from the ground state to an excited state where photochemical reactions can occur. Only light with the appropriate energy can be absorbed by the molecule. This happens because the difference of energy between the electronic levels of the reactant is exactly the same as the energy of the associated photon. In general:



Where hν is the quantum of energy required to go from i to j. After this, the molecule in the excited state can exhibit new chemistry compared with the reactions in ground state. It must be remembered that a photochemical reaction is just another means of using the energy absorbed. For example, luminescence, ionization, physical quenching, intra or intermolecular energy transfer can be other ways to lose the energy from the excited state. Photochemical reactions enable us to get molecules to overcome the energy of activation required for reaction. This energy is not provided by thermal methods due to the separations between electronic levels is higher and only light with a suitable wavelength can provide it. For organic molecules the range of light used in photochemical reactions is from the visible to the ultraviolet regions of the electromagnetic spectrum. This range depends on the structure, i. e. where the chromophor in the molecule absorbs light. Thus, each molecule has different gaps in the levels of energy of the molecular orbitals.

Aromatic compounds often cyclise to give polycyclic non-aromatic products, as exemplified by the photocyclisation of cis-stilbene **426** to dihydrophenantrene **427**.[108] This is a pericyclic reaction where the starting material has 14 π electrons to give a product with 12 π electron in a conrotatory way according to Woodward and Hoffman rules. This process occurs together with a cis- and trans- isomerisation.

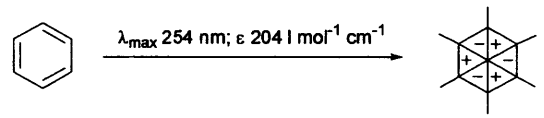


426 427

5.1.3 Photochemistry of Benzene.

The UV spectra of benzene consists of three bands:

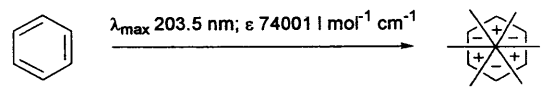
1) λ_{max} 254 nm; ε 204 l mol^{-1} cm^{-1}. The first band is the S_0 to S_1 transition from the totally symmetric ground state ($^1A_{1g}$) to the S_1 state ($^1B_{2u}$) which is antisymmetric to a plane perpendicular to the molecular plane and passing through an opposite pair of carbon atoms.



S_0 ($^1A_{1g}$) S_1 ($^1B_{2u}$)

This is formally a forbidden transition and therefore it has a low intensity. However, it is a transition most commonly involve in the photochemistry of benzene. It occurs through deformation of the ring which changes it symmetry. Intersystem crossing to T_1 can occur but benzene has triplet energy 355.64 KJ $mole^{-1}$. The T_1 of benzene is involved in few of its photoreactions.

2) λ_{max} 203.5 nm; ε 7400l mol^{-1} cm^{-1}. This is also a formally forbidden transition from S_0 ($^1A_{1g}$) to S_2 ($^1B_{1u}$). S_2 in benzene is antisymmetric about a plane perpendicular to the molecular plane which bisects an opposite pair of the bonds.



S_0 ($^1A_{1g}$) S_2 ($^1B_{1u}$)

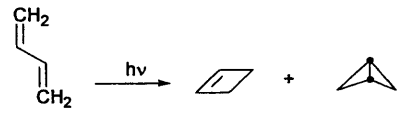
3) λ_{max} 180 nm; ε 60000 l mol^{-1} cm^{-1}. The third transition is from S_0 ($^1A_{1g}$) to S_3 (E_{1u}). It is formally allowed but is near the wavelength at which quartz absorbs light, this transition is not important in benzene photochemistry.

5.1.4 Cycloaddition Reactions of Benzene.

In contrast with its thermal chemistry, the photochemistry of benzene has only recently been systematically studied.[109, 110] Isomerisation and the formation of addition products with alkenes are the best known reactions. Isomerisation of benzene **155** itself produces the highly reactive species benzvalene **428** and, with more energetic light, bicyclohexadiene **429** and fulvene **430** are formed. Other photoisomers can be produced by direct irradiation of benzvalene **428** as Dewar benzenes **429** and prismanes **431**.

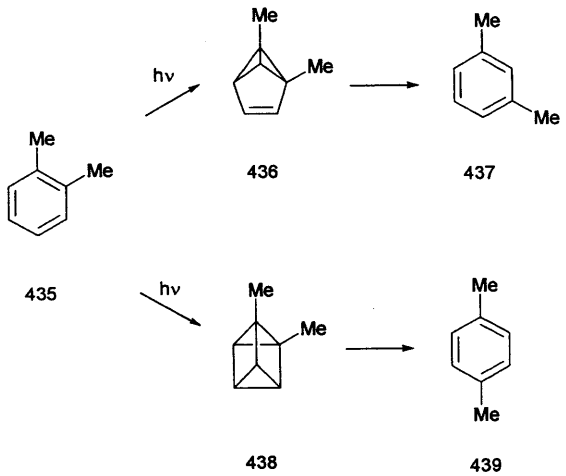
428 benzvalene | 429 Dewar benzene | 430 fulvene | 431 prismane

The formation of benzvalene **428** is formally analogous to the formation of bicyclo[1,1,0]butane **434** from transoid butadiene **432**, an allowed photochemical process.



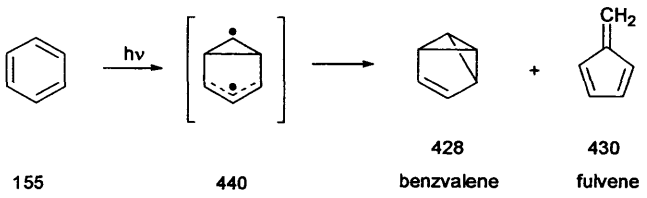
432 | 433 | 434

The intramolecular photointerconversion of xylene **435** probably involves either a benzvalene intermediate **436** or prismane intermediate **438**.



435 | 436 | 437 | 438 | 439

Liquid benzene undergoes photoisomerisation to fulvene **430** at 55°C, and while benzvalene **428** is also formed, it slowly reverts to benzene **155** at room temperature. Prefulvene **440** is though to be an intermediate to both isomers.[111]



The state symmetries shown in S_1 benzene ($^1B_{2u}$) and S_2 ($^1B_{1u}$) were first used by Bryce-Smith and Longuet-Higgins[111a] to provide theoretical analyses of photoreactions of benzene, and subsequently by Hoffmann and Woodward[112] and Haller.[113] For example, the non planar diradical **440** termed "prefulvene",[111a] which would be formed by *meta* bonding in benzene, has in its ground state an electronic configuration which is antisymmetric about its molecular symmetry plane similar to the S_1 of benzene. Following the correlation principle first enunciated by Longuet-Hinggins and Abrahamson,[114] it is to be expected that S_1 benzene should be potentially meta-bonding and capable in principle of undergoing an adiabatic transformation into the ground state of the prefulvene diradical **440**: this diradical in turn is readily conceived as a precursor of both benzvalene **428** and fulvene **430**. By such reasoning, one is led to conclude that if fulvene and benzvalene arise by processes which initially involve the formation of a *meta* bond in benzene, these isomers may be derived from S_1 benzene, as is indeed found experimentally.[115] We shall later see that benzvalene can be formed from S_2 benzene by a fully concerted process not involving prefulvene as an intermediate.

The orbital symmetries of benzene are drawn in Figure 5.

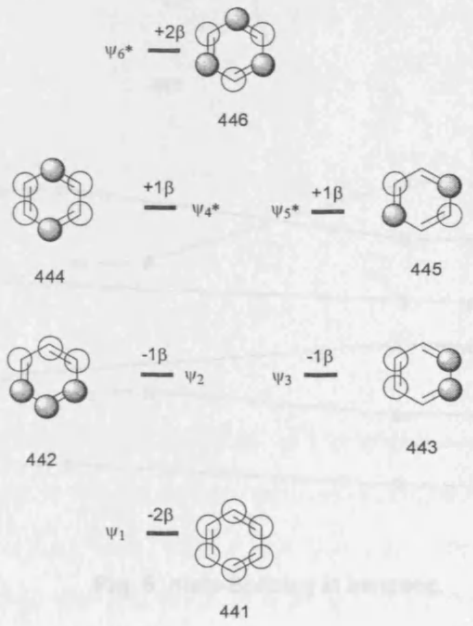
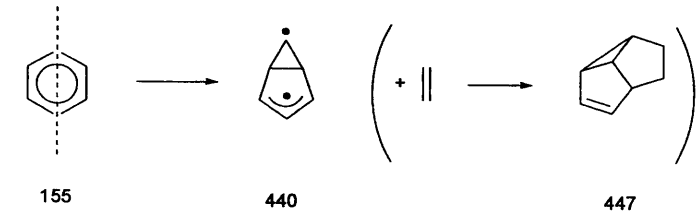


Fig. 5, π-Molecular orbitals of benzene.

Let us first consider S_1 benzene. This state, of symmetry $^1B_{2u}$ has two components in its wave-function, one corresponding to the excitation of an electron from ψ_3 to ψ_5, and the other to excitation of an electron from ψ_2 to ψ_4 (it will be noted that combination of the *orbital* symmetries of ψ_3 and ψ_5, and ψ_2 and ψ_4, gives the S_1 *state* symmetry). The S_1 (B_{2u}) state is represented as $\psi_3\psi_5-\psi_2\psi_4$. Likewise, the S_2 or T_1 states of symmetry B_{1u} are represented as $\psi_3\psi_4+\psi_2\psi_5$. Although the S_1 and S_2 states each involve partial occupancy of the degenerate orbital pairs ψ_2, ψ_3 and ψ_4, ψ_5, the energy of the S_2 state lies well above that of the S_1 state.

We may now construct and orbital correlation diagram for the *meta*-bonding in benzene: this is shown in Fig. 6.



155 440 447

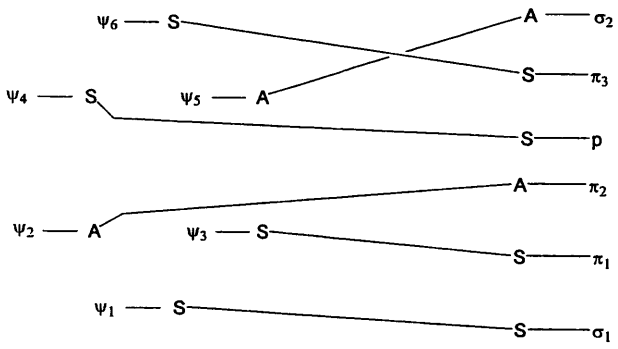
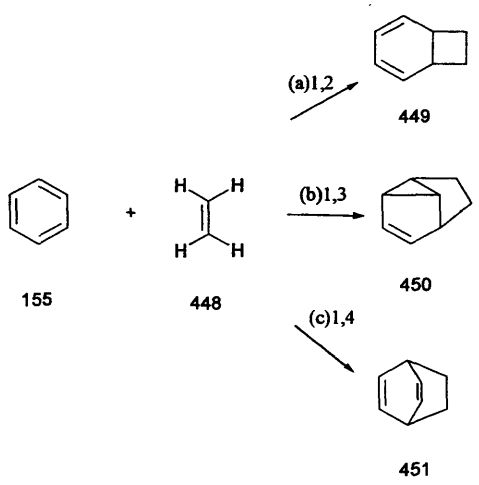


Fig. 6, *meta*-Bonding in benzene.

The correlation diagram is constructed in the normal manner, expressing the orbitals as symmetrical (S) or antisymmetrical (A) with respect to the molecular symmetry plane, and avoiding forbidden crossings of correlations between orbitals of like symmetry. It is readily seen that the ground state of the prefulvene diradical **440** (π_2 and p each singly occupied) correlates uniquely with the S_1 state of benzene through the $\psi_2\psi_4$ component of the latter. Since $\psi_2\psi_4$ and $\psi_3\psi_5$ are equally part of the wave function of S_1 benzene, either can serve to stablish a valid correlation with orbitals in the non-aromatic product. Thus we have reached the same conclusion as that reached previously by consideration of state symmetries, namely that *meta*-bonding in benzene is a property associated with the S_1 state, of symmetry $^1B_{2u}$. However, it is a property of S_1 benzene that carbon atoms C_1 and C_3 are non bonding in the equilibrium molecular conformation a planar regular hexagon, of side slightly larger than S_0 benzene,[116] but tend to become bonding when brought closer together by an appropriate disrotatory distorsion of the ring structure.[115] Thus both electronic and vibrational factors must be involved in *meta*-bonding.

5.1.5 Addition of an Alquene to Benzene.

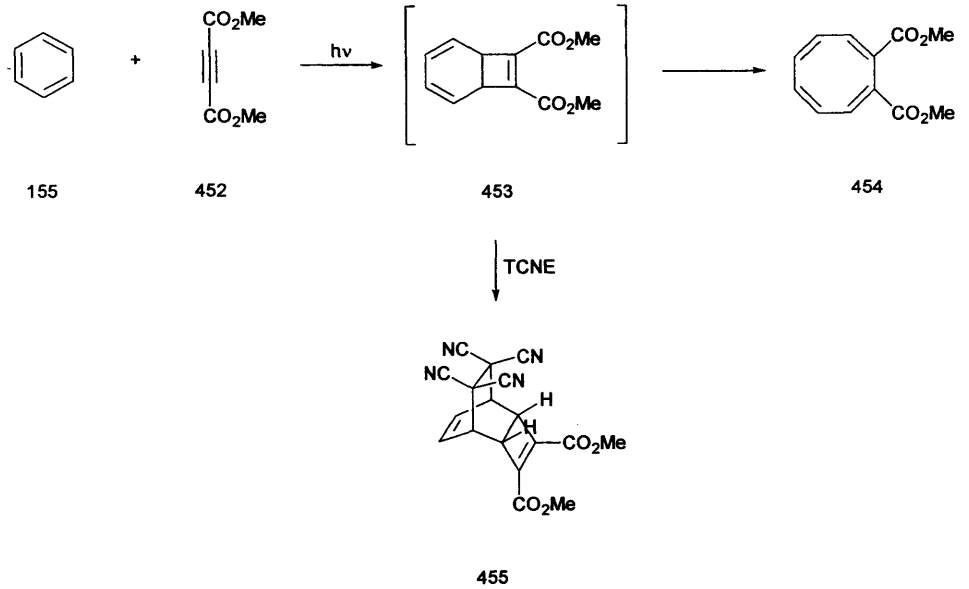
Addition of an alkene **448** to benzene **155** can occur in three different ways:



Path (a) shows ortho addition of benzene **155** reacting as a simple olefin. Only 2 π electrons of the benzene are involved in the reaction with the olefin which results in the formation of a cyclobutane ring **449**. Path (b) is the less common addition because the final product is non-aromatic and the product has three fusioned cycles **450**. Path (c) is the Diels-Alder reaction. Here benzene **155** acts as a diene and olefin **448** is the dienophile obtaining a bicycle **451**.

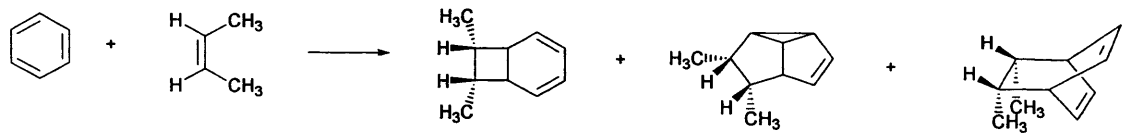
Examples of 1,2 Cycloaddition.

Benzene **155** reacts with acetylene **452** to give the cyclo-octatetraene **454**. The reaction goes through dimethyl-acetylenedicarboxylate intermediate **453** which was trapped with tetracyanoethylene (TCNE).[117]



Examples of 1,4 Cycloaddition.

Benzene **155** and *cis*-2-butene **456** react in a photoaddition reaction to give bicyclo[4.2.0]octa-2,4-diene **457**, tricycle[3.3.0.$0^{2,8}$]oct-3-ene **458** and bicycle[2.2.2]octa-2,5-diene **459** in a 6:40:1 ratio respectively.[118]

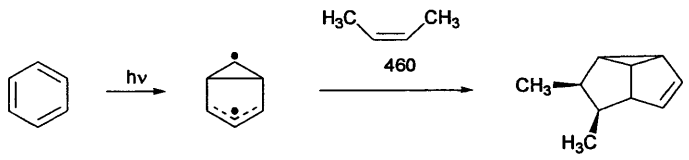


155 456 457 458 459

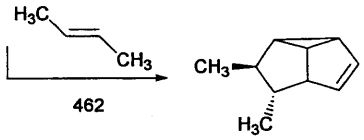
1,2-addition 1,3-addition 1,4-addition

Examples of 1,3 Cycloaddition.

1,3-Addition to benzene **155** results when prefulvene **440** is trapped by an olefin or by a diene. The addition is thought to involve the initial excitation of benzene from the ground state (S_0) to a high vibrational level of the first excited singlet (S_1) from which prefulvene **440** is formed.

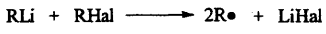


155 440 460 461

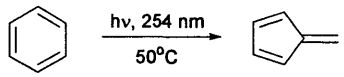


462 463

Bryce-Smith and Gilbert[119] were studying a reaction where isopropylbenzene was used as a trap of radicals produced by the reaction:

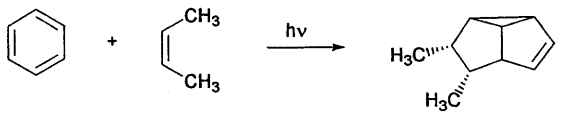


Another independent low temperature source of free radicals in solution was required for comparison. RI, R_2Hg and R_4Pb were irradiated with UV light in isopropylbenzene. In a control experiment isopropyl benzene was irradiated alone and gave traces of a product which could not be isolated but, apparently an isomer highly unsaturated. One year after it was founded that benzene **155** photoisomerise to fulvene **430** in an unusual process.[120]



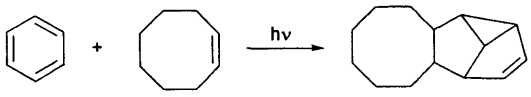
155 430

The intermolecular 1,3-cycloadditions to benzene with alkenes was discovered by two different groups.[121, 122] Wilzbach reported that the room temperature irradiation of a solution of *cis*-but-2-ene **460** in benzene produced substituted tricyclo[5.1.0]oct-2-ene **461.** This reaction corresponds to addition of the olefin across the cyclopropane ring of benzvalene **428**.



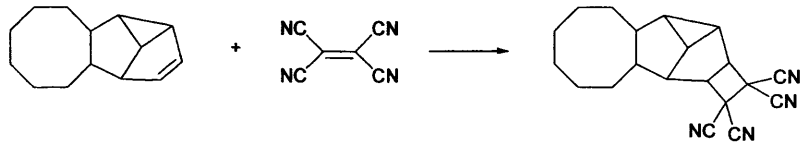
155 460 461

In the same year Bryce-Smith published results with several olefins like cyclo-octene **464**, but-1-ene, oct-1-ene and cycloocta-1,5-diene to obtain analogous of product **465**. The case of cyclo-octene **464** was investigated in the greatest details. Irradiation at room temperature of an equimolar mixture of benzene **155** and *cis*-cyclo-octene **464** with ultraviolet radiation gave adduct assigned as structure **465**.



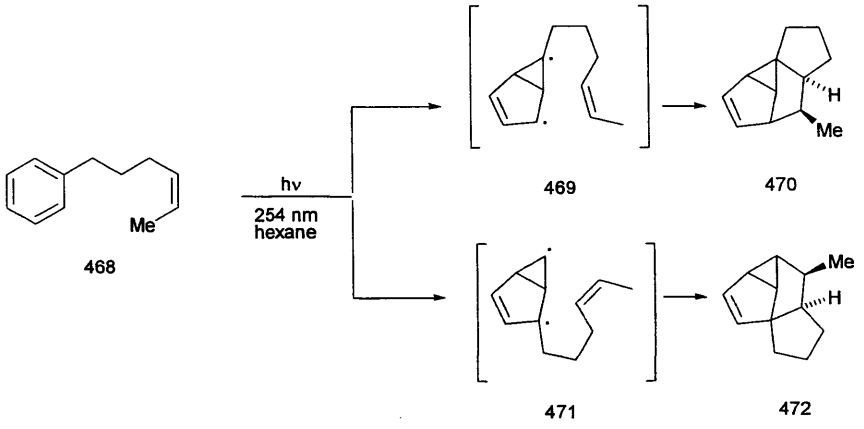
155 464 465

To confirm structure **465**, it was reacted with dimethyl acetylenedicarboxylate under the usual conditions of Diels-Alder, but not possible reaction was carried out. Crystalline adduct **467** was formed with tetracyanoethylene **466**.



465 466 467

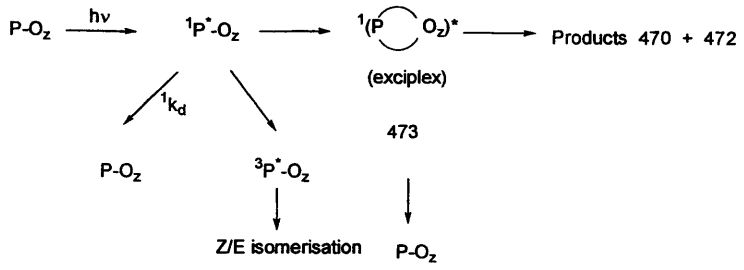
The first intramolecular example of 1,3-cycloadditions was reported by Morrison,[123] who suggests that the reaction goes through an intramolecular singlet exciplex. The photochemistry of (Z)-6-phenyl-2-hexene **468** was the first intramolecular example reported. 1,3 Cycloaddition proceeds with retention of the cisoid relationship in **470** and **472.**



468 469 470 471 472

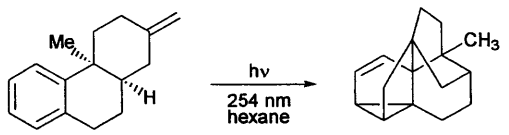
5.1.6 Physical Chemistry of Benzene Photochemistry.

After using spectroscopic techniques it could be determined aryl excited singlet state is efficiently trapped by the olefin. The routes proposed are shown in Scheme 11 in which P = phenyl and O = olefin.



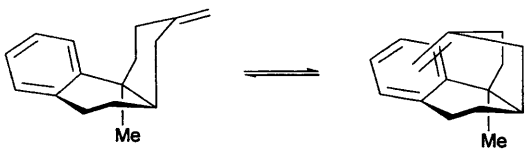
Scheme 11

The species that leads to the desired compounds is an exciplex which has suffered a conformational reorientation. The formation of an excited complex ("exciplex") **473** involves ground state olefin and the aryl excited singlet. This exciplex may undergo radiationless decay to the ground state or undergo cycloaddition to products **470** and **472**. Another analogous example is the *cis*-decalin **474** undergoing intramolecular 1,3-cycloaddition to give product **475**. The analogous reaction does not occur in the *trans*-decalin because it is more rigid and the aromatic ring and the olefin functionalities cannot approach the coplanar relationship.



474 475

Calculations made by Morrison[124] show that the energy implied in the requisite conformational necessary for the reaction is similar to the equilibrium chair-boat in methylenecyclohexane. For the *cis*-decalin **474**, the rate-controlling conformational reorientation involves the conversion of the half-chair / chair conformer **474a** into the half-chair / boat conformer **474b**.

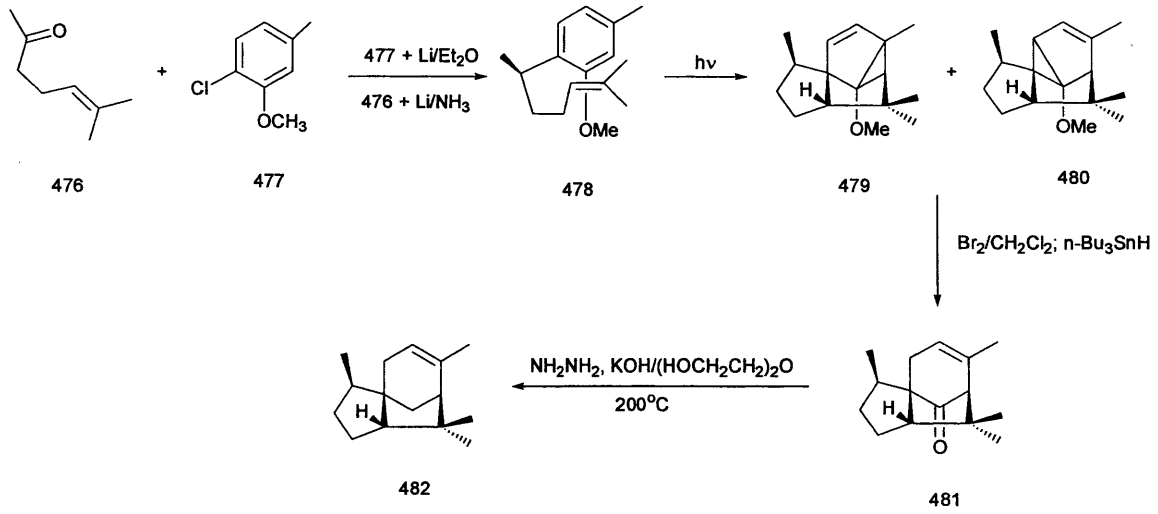


474a
non reactive conformation

474b
reactive conformation

5.1.7 Total Synthesis of (±)-α-Cedrene 482.

One of the most important examples of this could be the total synthesis of (±)-α-Cedrene **482** (Scheme 13) carried out by Wender and Howbert.[125] This example serves to define those features of the intramolecular cycloaddition.

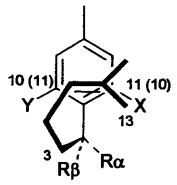


Scheme 13, Total synthesis of (±)-α-Cedrene **482.**

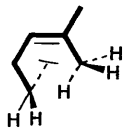
In this total synthesis is very important to make clear the mode of selectivity, regioselectivity, endo/exo selectivity, and degree of stereoinduction. The authors claim that there are 36 possible products in the photoannulation of **478**. However, they observe only two, **479** and **480**.

Selectivity is determined by olefin and arene substitution. In the case of arenealkene **478**, generally correlates with a preference for *meta* cycloaddition over *ortho* and *para* modes. Within the *meta* possibilities, addition to centers C1, C7 was considered to be more favourable than C10, C11 addition due to the unfavourable steric interactions.

Meta (10,11 / 11,10) Exciplexes

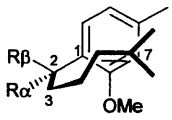


483

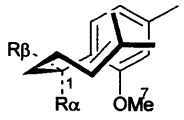


484

Meta (1,7) Exciplexes



485
EXO

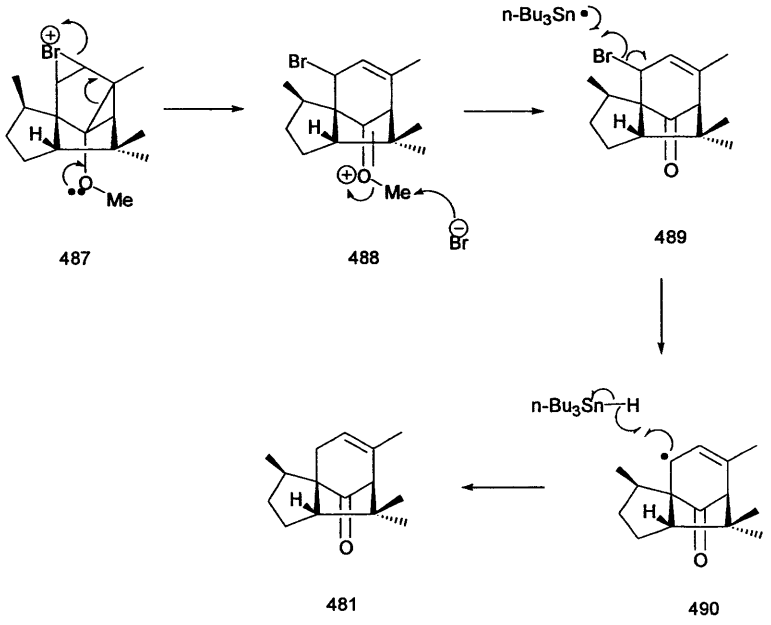


486
ENDO

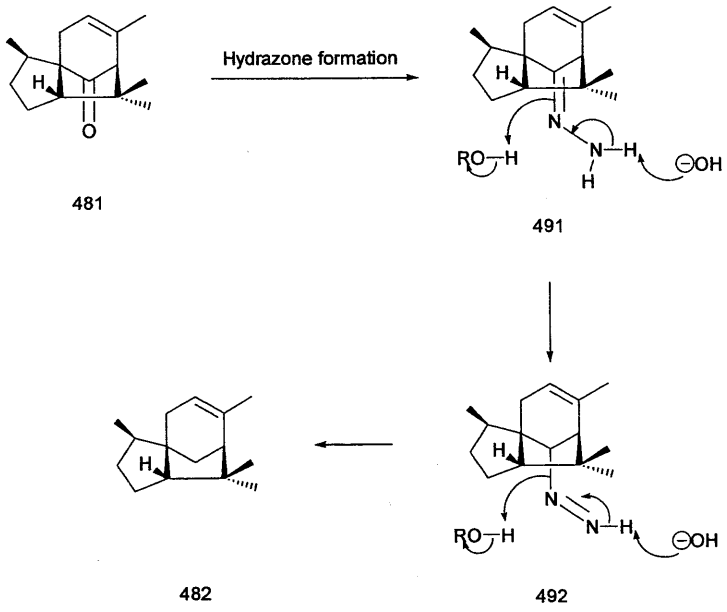
For the remaining C1, C7 meta addition, the *endo/ exo* selectivity issue was expected to be resolved in favour of the of the *exo* orientation due to the better alignment of the *exo* exciplex **485**.

In one operation, 2-chloro-5-methylanisole **477** was converted to its lithio derivative which was treated with 6-methylhept-5-en-2-one **476**; condensation of ammonia into the resulting mixture and addition of excess lithium provided the starting material for the photolysis. Irradiation of **478** in pentane at room temperature provides cycloadducts **479** and **480**.

Treatment of this mixture **(479** and **480)** with bromine in CH_2Cl_2 by electrophilic attack on the double bond induced cleavage of the cyclopropane ring and resulted in the formation of only 10α- and 10β-bromocedren-11-one **489**. The bromides were treated with tri-n-butyltin hydride to give **481** in 59% overall yield.



Wolff-Kishner reduction of **481** provided (±)-α-Cedrene **482** free of any isomeric product.

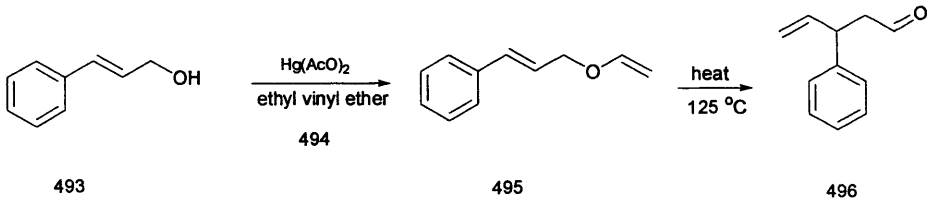


5.2 Results & Discussion.

During the course of a project on cyclobutanation an intramolecular photochemical reaction of an arene with an olefin was observed. The aim of this project is to investigate the stereochemistry of this reaction. The starting point was the synthesis of a versatile aldehyde to construct a range of substrates for the arene olefin photocycloaddition reaction.

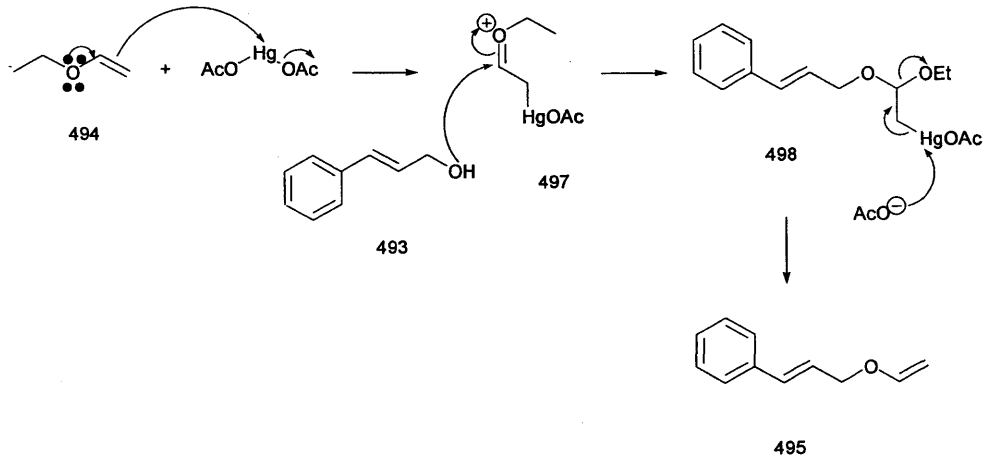
5.2.1. Aldehyde synthesis.

Cinammyl alcohol **493** was reacted with ethyl vinyl ether **494** and mercuric acetate to give ether **495**.



493 495 496

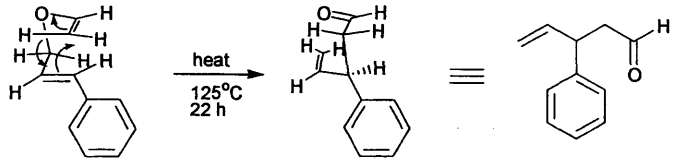
The mechanism of this reaction involves electrophilic attack of the mercuric acetate on the vinyl ether **494** to produce the oxonium ion **497.** A second nucleophilic attack of cinnamyl alcohol **493** on the oxonium ion **497** gives intermediate **498** which after elimination furnishes 3-phenyl-2-propenyl vinyl ether **495** in 35% yield.[126]



494 497 498 493 495

Ethyl vinyl ether was used as a solvent in the reaction and it was distilled at the end followed by distillation of the product **495** which was obtained in 35% yield.

In the second step a Claisen rearrangement is carried out on vinyl ether **495** to get the 3-phenyl-4-pentenal **496** in 58% yield.[127] The driving force for this [3,3] sigmatropic rearrangement is the formation of the carbonyl group of the aldehyde.



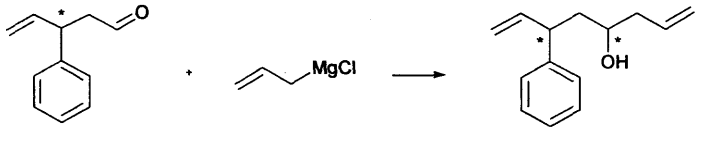
495 496

This is the key intermediate because from here we are able to prepare several alcohols depending on the Grignard reagent used.

5.2.2 Additions to Aldehyde 496.

5.2.2a Addition of allylmagnesium chloride to Aldehyde 496 and Photochemistry of the Product.

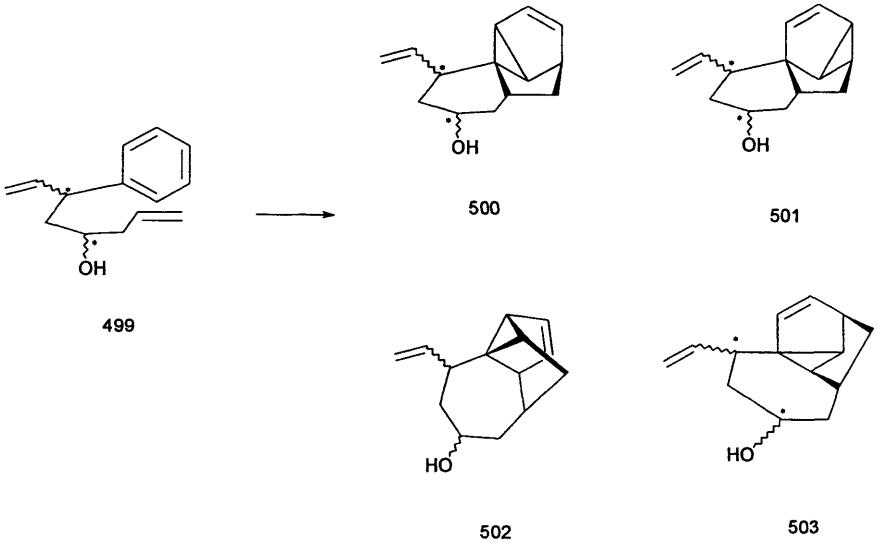
Allylmagnesium chloride was added to aldehyde **496** and 6-phenyl-1,7-octadien-4-ol **499** was obtained in 87% yield. The GC/MS shows two peaks from the two diastereoisomers of **499**.



496 499

6-Phenyl-1,7-octadien-4-ol **499** as a mixture of diastereoisomers was irradiated with ultraviolet light for 48 hours. Purification by column chromatography of the crude gave a mixture of products with some starting material. The NMR spectrum showed that complete separation was not achieved. There was some starting material indicated

by the presence of two signals of benzylic proton at 3.45 and 3.71 ppm corresponding to the mixture of two diastereoisomers. Also there was a group of signals at 7 ppm with a small integral compared to the integral of signals between 1 and 2 ppm corresponding to the alkyl hydrogens of the expected photochemical products **(500-503)**. Although the structure of the product cannot be elucidated, this experiment suggests that photochemical reaction would be better carried out with one diastereoisomer of 6-phenyl-1,7-octadien-4-ol **499** with the aim of obtaining one photochemical product.



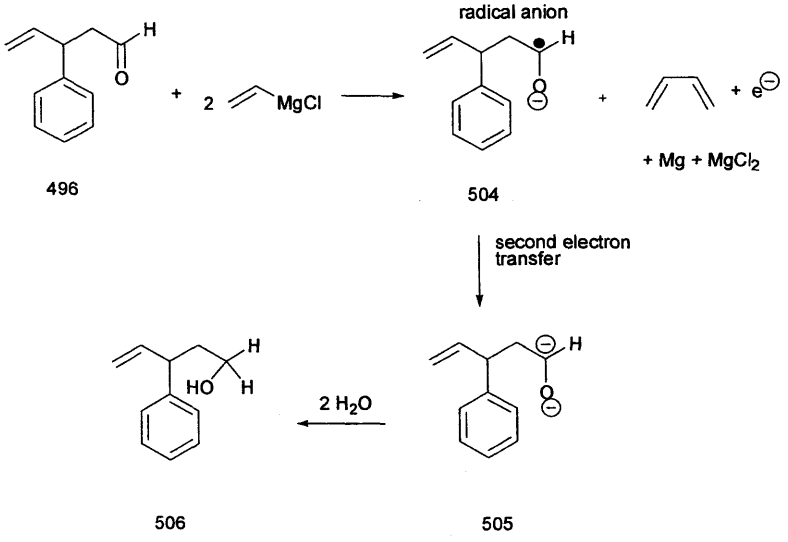
Separation of the diastereoisomers of 6-phenyl-1,7-octadien-4-ol **499** by flash chromatography and chromatotron was not achieved and photochemical reaction with only one diastereoisomer was not possible. We turned our attention to the addition of another Grignard reagent to aldehyde **496**.

5.2.2b Addition of Vinyl Grignard Reagents to Aldehyde 496.

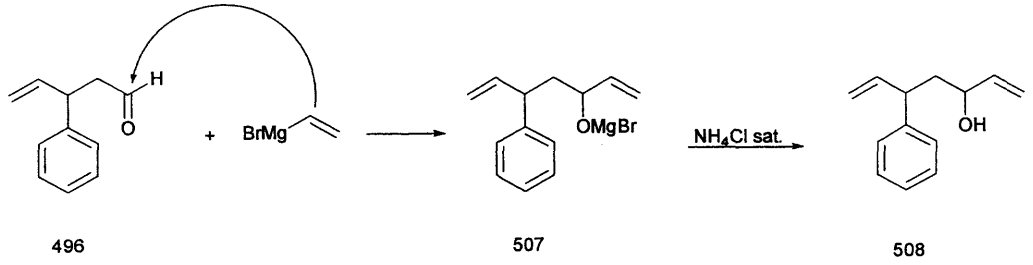
The reaction of 3-phenyl-4-pentenal **496** with vinylmagnesium chloride in THF gave the alcohol **506** in 51% yield. The NMR of the product showed the 3 vinylic protons at 4.85 ppm (CH_2) and 5.75 ppm (=CHR) compared with the 5 phenyl protons at 7.05 ppm. The expected product has two vinyl groups present and so we would expect to see 6 olefinic protons compared to the 5 aromatic signals. The product obtained also showed a signal at 3.58 ppm for a CH_2OH. This data was consistent with a reduction of the aldehyde to an alcohol. This idea was supported by the MS as the

product showed a molecular ion at 162, which is the molecular weight of the alcohol. To confirm the structure we reduced the 3-phenyl-4-pentenal **496** with $NaBH_4$ in MeOH to produce the alcohol **506** which showed exactly the same NMR as the product from the Grignard reaction.

We need to explain how vinylmagnesium chloride can reduce aldehyde **496**. Since no H^- is present the mechanism must be an electron transfer process. We must get an electron from the Grignard to make a radical anion **504.** When two molecules of vinyl Grignard combine to form butadiene two electrons are produced. If these are sequentially transferred to aldehyde **496** the radical anion **504** is produced followed by the dianion **505**. Protonation then leads to the alcohol **506**.



The reaction was carried out again but with a new bottle of vinylmagnesium bromine 1.0 M in THF. Nucleophilic attack of vinylmagesium bromide on the carbonyl carbon of the aldehyde **496** produced the intermediate **507** which is protonated after adding saturated solution of ammonia chloride to get 5-phenyl-1,6-heptadien-3-ol **508** in 73% yield.



This mechanism goes by non-stereoselective attack of the Grignard reagent ("CH_2=CH^-") on the carbonyl carbon to yield 5-phenyl-1,6-heptadien-3-ol **508**. ^1H NMR shows two signals at 4 ppm which correspond to the two possible diastereoisomers of alcohol **508** (Figure 7). GC/MS also showed two peaks at 12.46 and 12.66 minutes in the scan EI+ with *m/z* of 170 for both diastereoisomers.

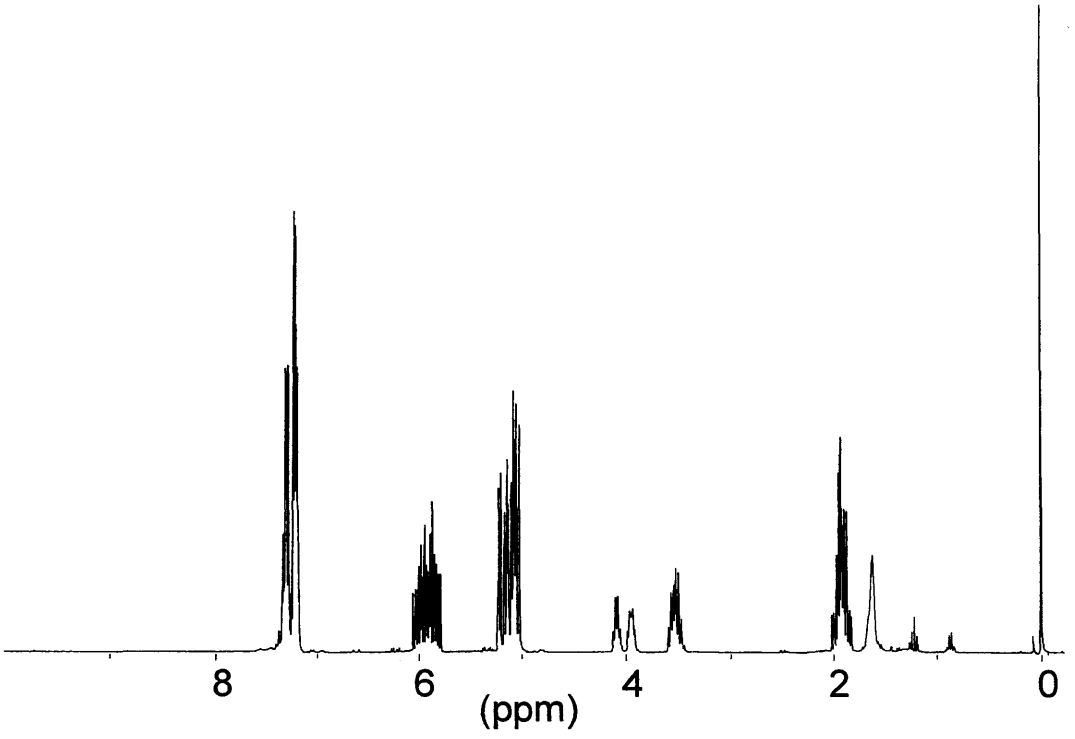


Fig. 7, ^1H NMR of the two diastereoisomers of alcohol **508**.

5.2.3 Photochemical Reaction of 5-Phenyl-1,6-heptadien-3-ol 508.

A benzene solution of (SS, RR, RS, SR)-5-phenyl-1,6-heptadien-3-ol **508** was irradiated at 254 nm in a water cooled quartz reaction tube to give a product in which the aromatic ring was absent. It was difficult to be clear about the structure of this product as it was obtained as a mixture of diastereoisomers.

In order to study the photochemistry on single diastereoisomers, the two diastereoisomers of alcohol **508** were separated using chromatotron using petrol/ether (10:1) as eluent. After collecting different fractions and analyzing by GC/MS, 100 mg

of one diastereoisomer was isolated. ^{1}H NMR shows only one peak at 3.96 ppm corresponding to the proton on the hydroxile carbon (Figure 8).

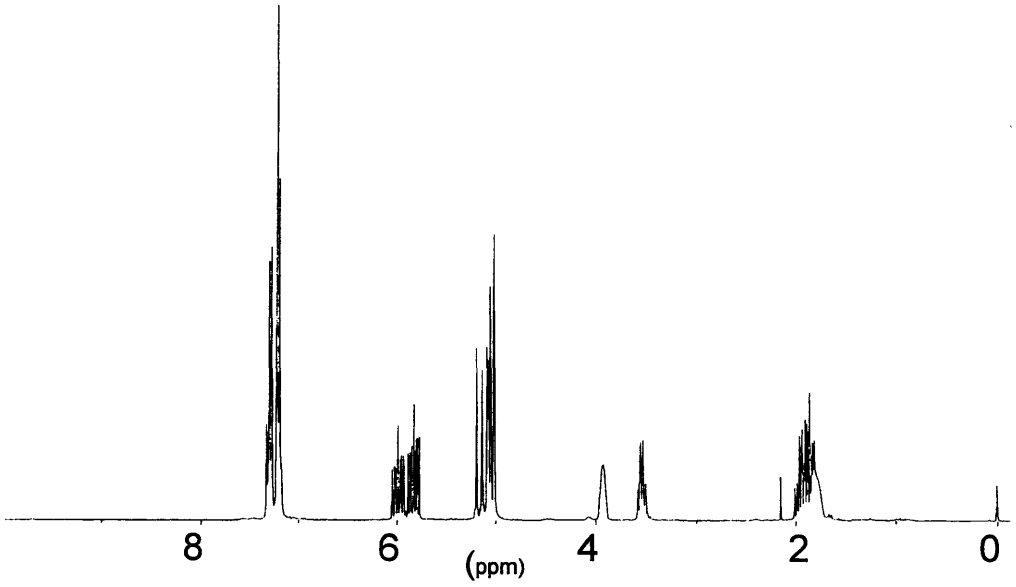


Fig. 8. Single diastereoisomer of 5-phenyl-1,6-heptadien-3-ol **508**.

Photochemical reaction with the single diastereoisomer of 5-phenyl-1,6-heptadien-3-ol (508).

The single diastereoisomer of 5-phenyl-1,6-heptadien-3-ol **508** was dissolved in dry ether and irradiated at 254 nm in a water cooled quartz tube for 48 hours. After work-up and purification of the crude a single diastereoisomer product was obtained in 30% yield. Table 1 shows the chemical shifts of the ^{1}H NMR of the irradiation photochemical product from alcohol **508.**

Peak number	Chemical shift (ppm)	Number of hydrogens	multiplicity	Couplings in Hz
1	0.83	1 H	ddd	3.2, 6.7, 6.7
2	1.45	1 H	broad, OH	
3	1.6	2 H	multiplet	
4	1.82	1 H	dt	2.05, 14.6

5	2.22	1 H	ddd	5.2, 7, 14.6
6	2.4	1 H	multiplet	
7	2.56	1 H	multiplet	
8	2.64	1 H	multiplet	
9	3.03	1 H	broad singlet	
10	4.03	1 H	broad quintet	2.3
11	5.06	1 H	dt	2.05, 10.3
12	5.12	1 H	dt	2.05, 17.2
13	5.55	1 H	dd	2.6, 5.9
14	5.75	1 H	dd	2.7, 5.5
15	6.14	1 H	ddd	5.5, 10.5, 17.2

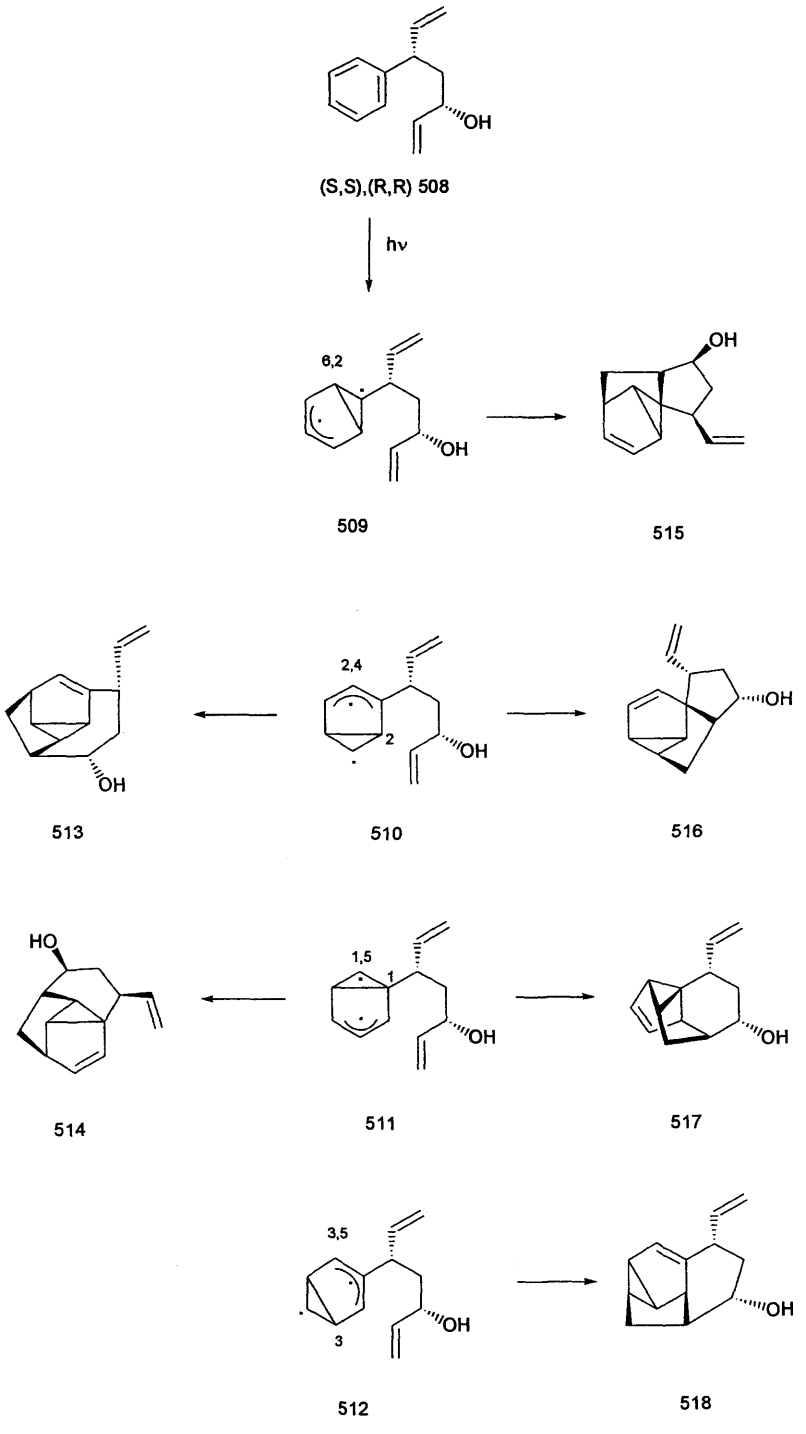
Table 1. ^{1}H NMR assignment of the irradiation product of alcohol **508.**

^{1}H NMR of signals at 5.06, 5.12 and 6.14 ppm correspond to the vinylic group so both 5.55 and 5.75 ppm signals correspond to the olefinic protons.

5-Phenyl-1,6-heptadien-3-ol **508** exists as two diastereoisomers. As drawn, the vinyl group and OH group can be on the same side *(S,S), (R,R)* or on the opposite side (R,S), (S,R). The less polar diastereoisomer was separated by chromatotron and it was not possible to separate of the most polar diastereoisomer. To make the discussion of the photochemistry of these isomers simpler, we make the assumption that the single isomer of **508** has the vinyl group and OH groups with *(R,R),(S,S)* configuration. When this compound was irradiated in dry ether, a single product was obtained.

Scheme 14 shows the complete reaction manifold for the arene-olefin reaction of the *(S,S),(R,R)* alcohol **508**. Four possible "pre-fulvene" diradicals[111a] are possible in the reaction (**509-512**). The radical on the cyclopropane is fixed at a particular carbon but the allyl radical can react at either end of the allylic system. The products are produced when the di-radical undergoes cycloaddition across the double bond. Hence we can obtain two possible products from each **510** and **511** "pre-fulvene" diradicals eg.

510 gives **513** or **516**, and only one possible product in **509** and **512** "pre-fulvene" diradicals.



Scheme 14. Intramolecular arene-olefin photoaddition of ***(S,S),(R,R)* 508**

We have now to distinguish between the different possible products **513-518**. To identify the structure of the single product obtained, the first indication was that we observed a doublet times doublet for each of the olefinic protons at 5.55 ppm (J = 2.6 and 5.9) and 5.75 ppm (J = 2.7 and 5.5) respectively (Figure 9). From the product structure **513-518** we can immediately see that only **515** and **517** have a proton adjacent to two olefinic hydrogens. For compounds **513, 514, 516**, and **518** one of the olefinic hydrogen is next to a quaternary center in which is not possible to get coupling.

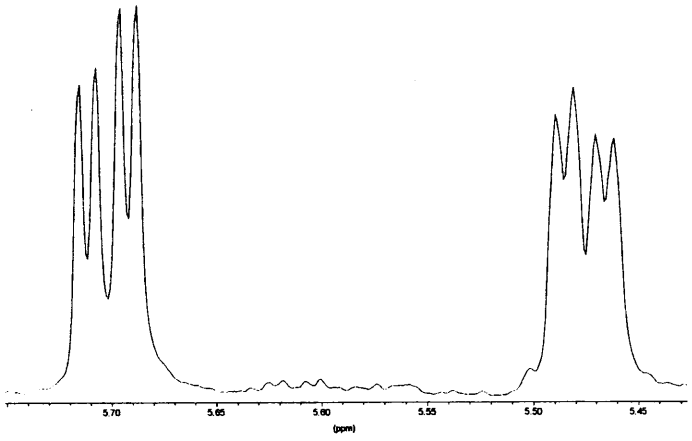
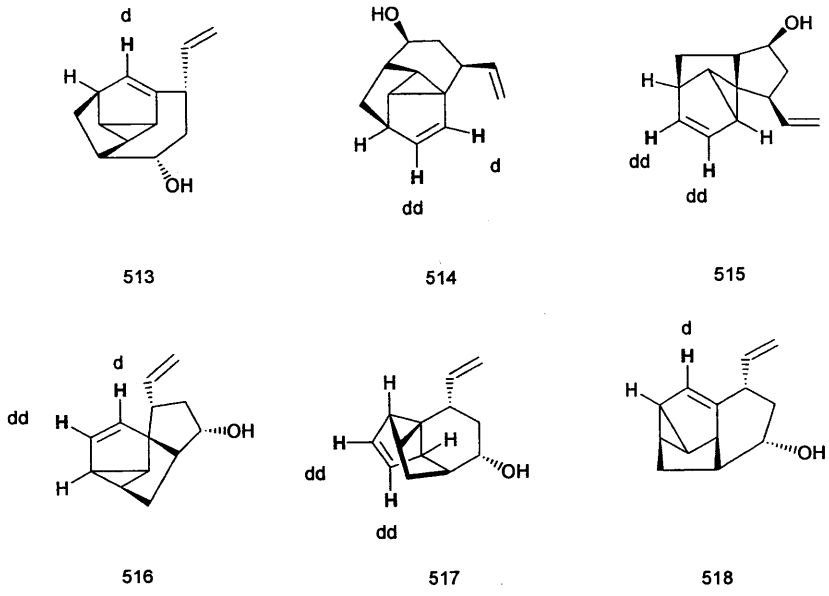


Fig. 9. ^{1}H NMR of the olefinic protons of the photochemical product of *(S,S),(R,R)* **508.**



We have now to distinguish between compounds **515** and **517** and we do this from the cyclopropane protons. One of the cyclopropane protons in the final product is a doublet-doublet-doublet (J = 3.2, 6.7 and 6.7) at 0.87 ppm (Figure 10).

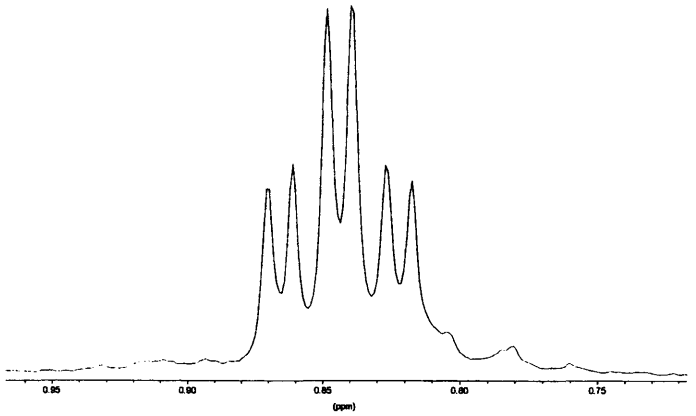
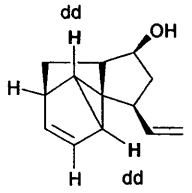
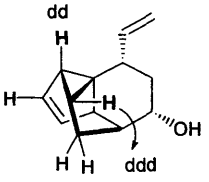


Fig. 10, ^{1}H NMR of the cyclopropane proton of the photochemical product of ***(S,S),(R,R)* 508.**



515



517

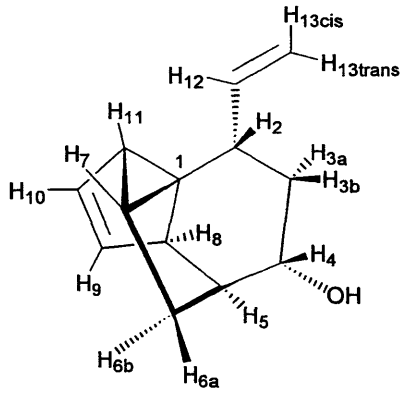
This is only possible in structure **517** where one cyclopropane proton is doublet-doublet-doublet. This is not possible in the structure **515** where each cyclopropane proton has two adjacent hydrogens and only two couplings are possible.

We therefore conclude from the ^{1}H NMR analysis supported by assignments from COSY and spectra H-H and H-C correlation that the structure of the product is **517**.

5.2.3a nOe of the Photochemical Product 517.

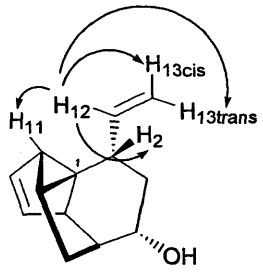
If one of the protons of compound **517** is irradiated at its resonance frequency, this leads to a through space interaction and it is detected as a more intense or weaker signal. This is known as the *nuclear Overhauser effect* (nOe).[128] The nOe data of product **517**

agrees with this assignment and demonstrate that our product does indeed have the (R,R),(S,S) relationship between OH and vinyl group.

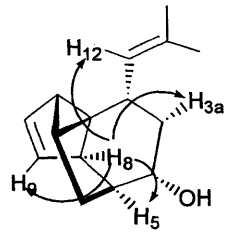


517

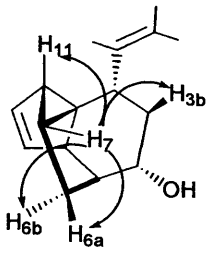
The first proton to be irradiated was H_{12} and it interacted with H_{13cis}, $H_{13trans}$, H_2 at 2.57 ppm, H_{11} at 2.64 ppm.



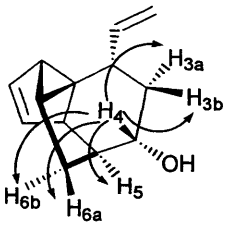
The second proton to be irradiated was H_8 at 3.03 ppm and it interacted with H_{12}, H_9 at 5.56 ppm, H_5 at 2.42 ppm and H_{3a} at 1.82 ppm.



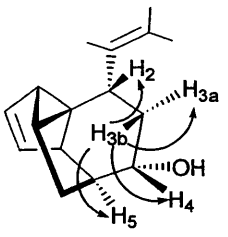
The third proton to be irradiated was H_7 at 0.83 ppm and it interacted with H_6 at 1.6 ppm, H_{3b} at 2.22 ppm and H_{11} at 2.64 ppm.



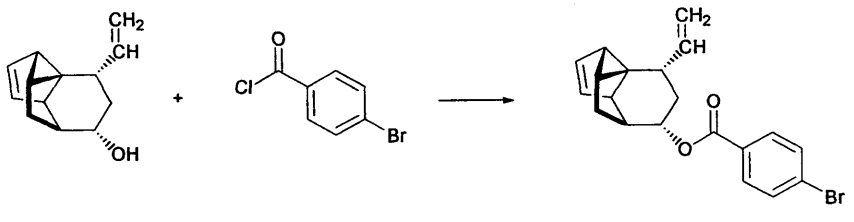
The fourth proton to be interacted was H_4 at 4.03 ppm and it interacted with H_6 at 1.6 ppm, H_{3a} at 1.82 ppm, H_{3b} at 2.22 ppm and H_5 at 2.42 ppm.



Finally, H_{3b} was irradiated and it interacted with H_{3a} at 1.82 ppm, H_5 at at 2.42 ppm, H_2 at 2.57 ppm and H_4 at 4.03 ppm.



We reacted the product **517** with 4-bromobenzoyl chloride **519** in order to obtain a crystal for X-ray analysis to confirm the structure.



517 519 520

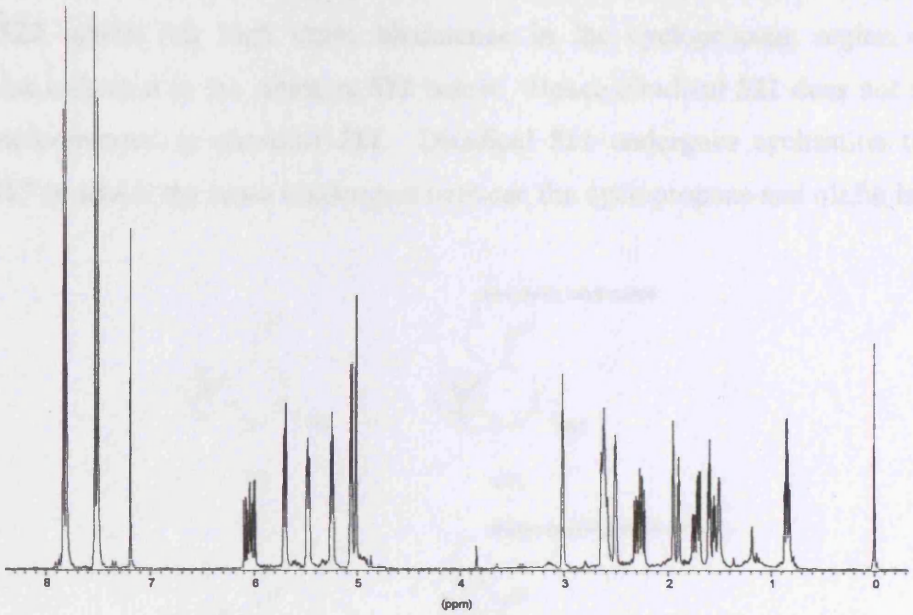
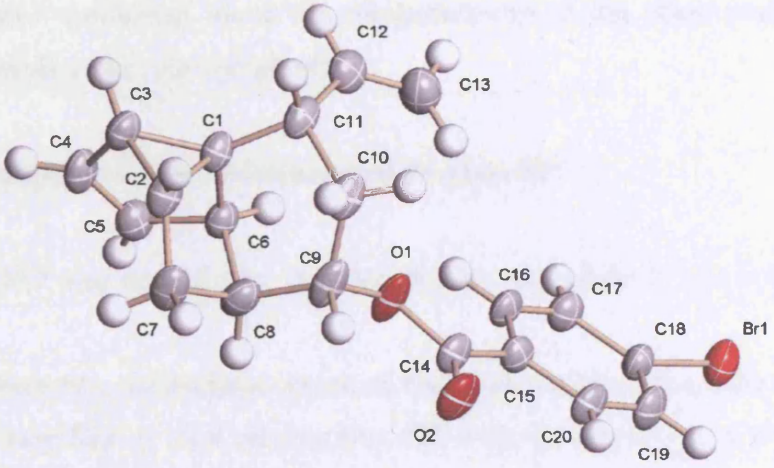
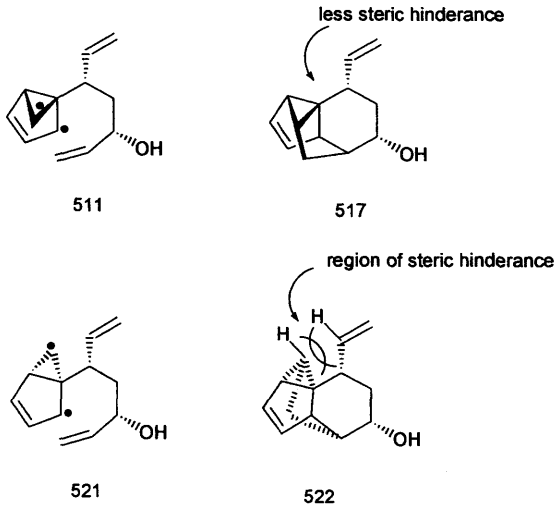


Fig. 11, ^{1}H NMR of product **520**.



We need to explain the origin of the selectivity of the reaction. All 4 di-radicals indicated in Scheme 14 may well be formed. However, only one can undergo intramolecular cyclisation with the olefin to give the polycyclic product **517**. This final product was confirmed by X-ray. *(R,R),(S,S)*-5-Phenyl-1,6-heptadien-3-ol **508** can undergo the cyclisation to two different diastereoisomeric di-radicals **511** and **521**. Diradical **511** has the cyclopropane forward and diradical **521** has the cyclopropane back. We would expect that these two radicals could interconvert by the reverse reaction

back to starting material and we propose that the cyclisation by diradical **521** produces product **522** which has high steric hinderance in the cyclopropane region of the molecule as indicated in the structure **522** below. Hence diradical **521** does not cyclise and is interconverted to diradical **511**. Diradical **511** undergoes cyclisation to give product **517** in which the steric hinderance between the cyclopropane and olefin is less.



511 517

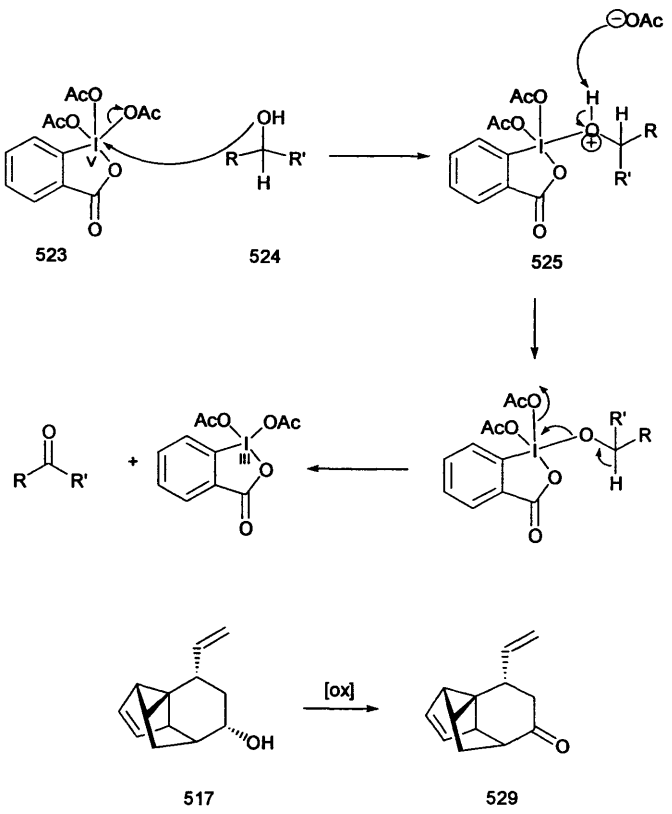
521 522

A definitive conclusion about the photochemistry of the other isomer was not possible as separation was not completed.

5.2.3b Oxidation of the Photochemical Product 517.

Alcohol **517** was oxidised by the Dess-Martin procedure to the ketone in 60% yield.

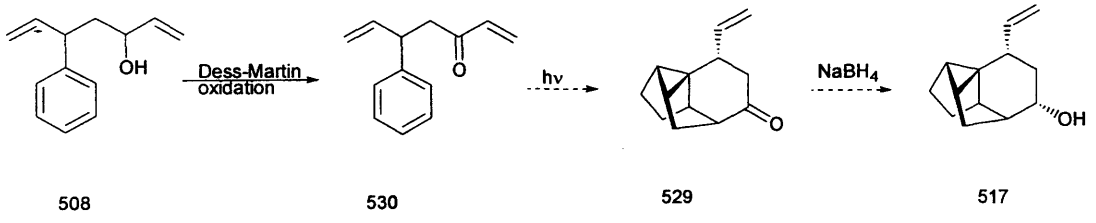
Firstly, there is a nucleophilic attack of the alcohol **524** on the iodo of the Dess-Martin periodinane **523** to form intermediate **525** with the displacement of one acetate group. Intermediate **525** then suffers a deprotonation by the acetate group to give intermediate **526**, subsequent elimination of another proton produces the ketone **528**.



Structure of the product **529** was confirmed by ^{1}H COSY and ^{1}H-^{13}C correlation.

5.2.4 The Arene-Olefin Photo-Annulation of an Enone.

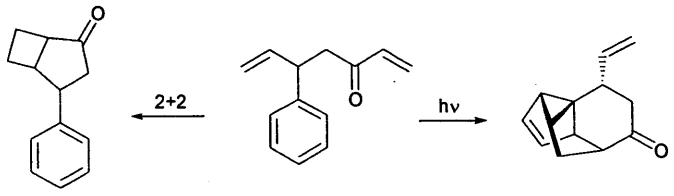
The separation of the two diastereoisomers of (SS, RR, SR, RS)-5-phenyl-1,6-heptadien-3-ol **508** is a very difficult task. The problem can be avoided by oxidising the alcohol **508** to enone **530** which has only one stereocenter. Our aim then is to test the photoannulation of enone **530** to see if we obtain ketone **529** which can then be reduced to the alcohol **517** we obtained earlier. 5-Phenyl-1,6-heptadien-3-one **530** must carry out a photochemical reaction to get ketone **529**. Then final reduction of product **529** with $NaBH_4$ would give alcohol **517**.



The photochemistry of 5-phenyl-1,6-heptadien-3-one **530** will also be interesting as it has two chromophores, the enone and the benzene ring along with another olefin. The photochemical addition of an enone to an olefin is a well studied reaction.[129]

5-Phenyl-1,6-heptadien-3-ol **508** as a mixture of diastereoisomers was converted in 5-phenyl-1,6-heptadien-3-one **530** in 89% yield by Dess-Martin oxidation, the mechanism was shown in section 5.2.3b.

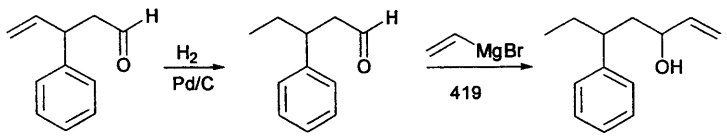
An ether solution of 5-phenyl-1,6-heptadien-3-one **530** was irradiated at 254 nm for 24 hours. This reaction was followed by TLC but it was difficult to see what was going on in the reaction. It is of interest to point out that in this photochemical reaction there is a competitive reaction between [2+2] cycloaddition reaction to produce **531** and the arene-olefin photoaddition reaction to undergo **529.** The reaction of enone **530** caused disappearance of starting material but no definitive product was isolated.



531 530 529

5.2.5 Alternative Method to Avoid the [2+2] Cycloaddition Reaction.

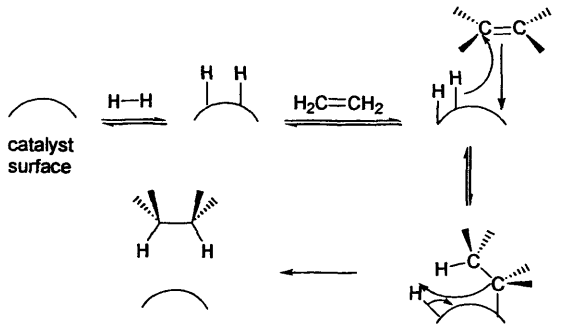
To avoid the [2+2] cycloaddition reaction, the double bond of 3-phenyl-4-pentenal **496** was reduced



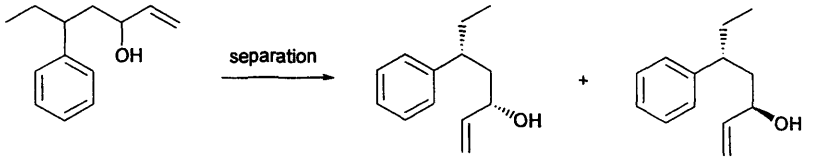
496 532 533

3-Phenyl-4-pentenal **496** was reacted with a "pinch" of Pd/C under H_2 conditions in methanol to give 3-phenyl-pentanal **532** in 96% yield. The hydrogenation takes place

on the surface of the heterogeneous catalyst Pd/C. The major function of the catalyst is the activation of hydrogen to generate metal bound hydrogen on the catalyst surface.



The reaction of 3-phenyl-pentanal **532** with vinyl magnesium bromide in THF gave 5-phenyl-1-hepten-3-ol **533.** In this case separation of 5-phenyl-1-hepten-3-ol **533** by chromatotron was not needed. After a flash chromatography separation column, two different isomers were achieved, **534** in 17% yield and **535** in 23% yield.



533 534 535

Both diastereoisomers have one signal at 0.75 ppm as a triplet which corresponds to the CH_3 next to the CH_2. The only difference between the isomers is the signal of the proton on the hydroxy carbon, in product **534** we see this signal at 3.75 ppm and in product **535** at 3.92 ppm.

5.2.6 Photochemical Reaction of 5-Phenyl-1-hepten-3-ol (534).

In this part of the project the same photochemical reaction was carried with (R,S),(S,R)-5-phenyl-1-hepten-3-ol **534** as described for the alcohol **508**. The single diastereoisomer of 5-phenyl-1-hepten-3-ol **534** was dissolved in dry ether and irradiated at 254 nm in a water cooled quartz tube for 24 hours. After work-up and purification of the crude a single product diastereoisomer was obtained in 57% yield.

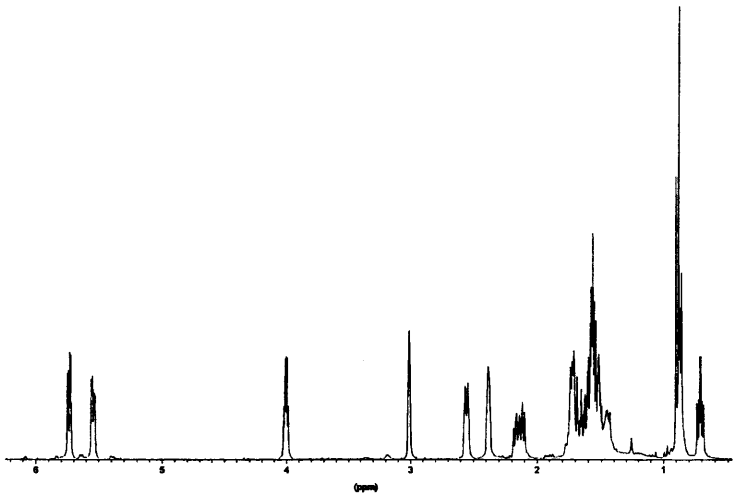
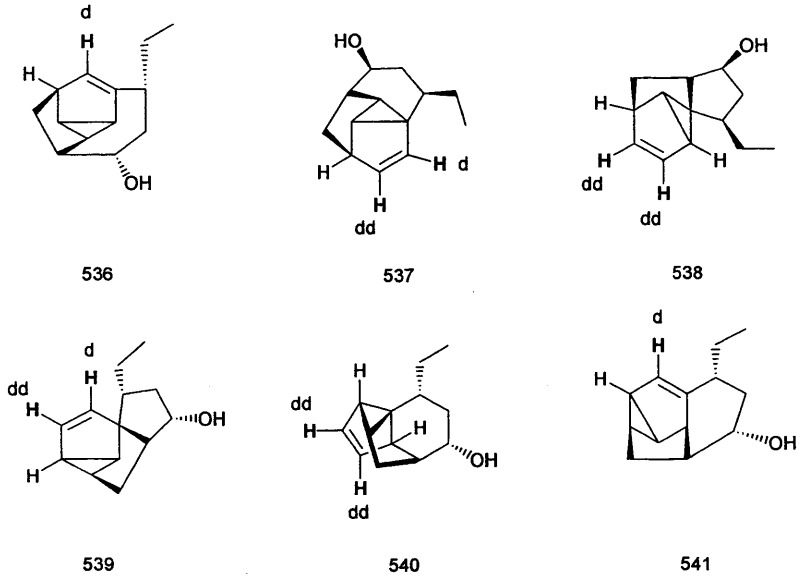


Fig. 10, ^{1}H NMR of photochemical reaction of 5-phenyl-1-hepten-3-ol **534.**

In order to determine the structure of this product, our attention once more was focused on the signals which correspond to the olefinic protons. ^{1}H NMR of the final isomer showed two signals at 5.5 ppm and 5.75 ppm with a multiplicity of doublet time doublet (Fig. 10). There are 6 different ways in which the arene-olefin reaction can take place with 5-phenyl-1-hepten-3-ol **534**, the six possible products are shown in structures **536-541**.



We can see immediately that only **538** and **540** have a proton adjacent to both olefinic hydrogens. For compounds **536, 537, 539** and **541**, one of the olefinic

hydrogens is next to a quaternary center in which is not possible to get coupling. We are following the same steps as we did with the final isomer **517** (page 124).

We have now to distinguish between compounds **538** and **540** and we do this from the cyclopropane protons. Once again one of the cyclopropane protons in the final product is a doublet-doublet-doublet (J = 2.92, 6.43, 9.35) at 0.7 ppm (Fig. 11).

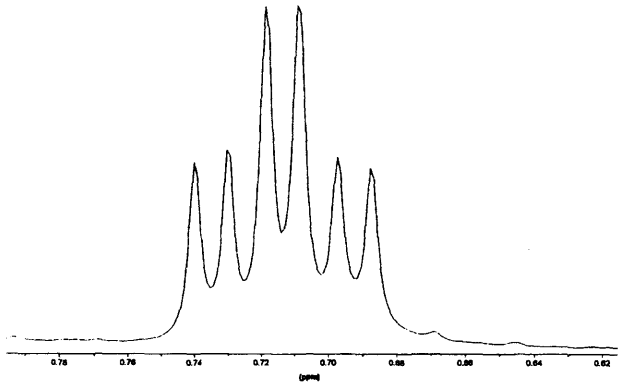
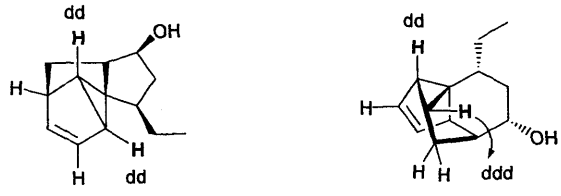


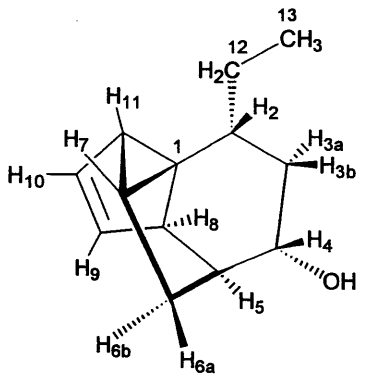
Fig. 11, ^{1}H NMR of the cyclopropane proton of the photochemical product of ***(R,S),(S,R)* 534.**



538 540

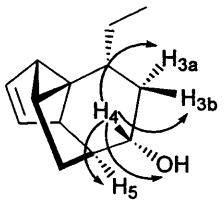
This is only possible in the structure **540** in which one cyclopropane proton is doublet-doublet-doublet. This is not possible in the structure **538** in which each cyclopropane proton has two adjacent hydrogens and only two couplings are possible.

We therefore conclude from the ^{1}H NMR analysis supported by assignments from COSY and spectra H-H and H-C correlation that the structure of the product is **540**. Once again the nOe data supported this conclusion and demonstrates that our product does indeed the *CIS* relationship between OH and ethyl group.

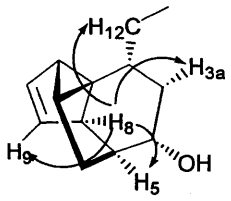


540

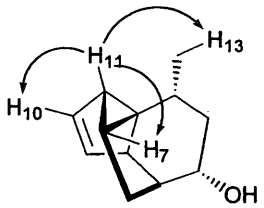
The first proton to be irradiated was H_4 at 4 ppm, it interacted with H_5 at 2.38 ppm, H_{3b} at 2.15 ppm, H_{3a} at 1.6 ppm and OH at 1.5 ppm.



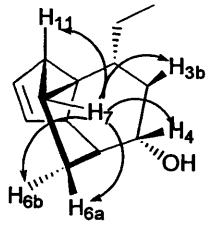
The second proton to be irradiated was H_8 at 3.03 ppm, it interacted with H_5 at 3.38 ppm, H_9 at 5.55 ppm, H_{12} and H_{3a} at 1.7 ppm.



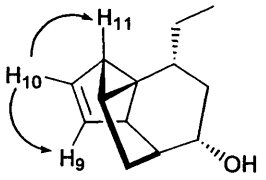
The third proton to be irradiated was H_{11} at 2.55 ppm, it interacted with H_7 at 0.7 ppm, H_{13} at 0.87 ppm and H_{10} at 5.75 ppm.



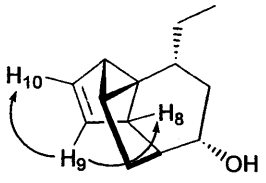
The fourth proton to be irradiated was H_7 at 0.7 ppm, it interacted with H_{11} at 2.55 ppm, H_{3b} at 2.15 ppm, H_6 at 1.6 ppm and H_4 at 4 ppm.



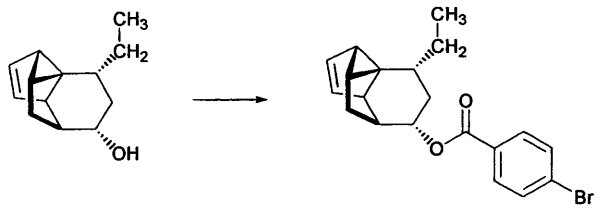
The fifth proton to be irradiated was H_{10} at 5.75 ppm, it interacted with H_5 at 5.56 ppm and H_{11} at 2.55 ppm.



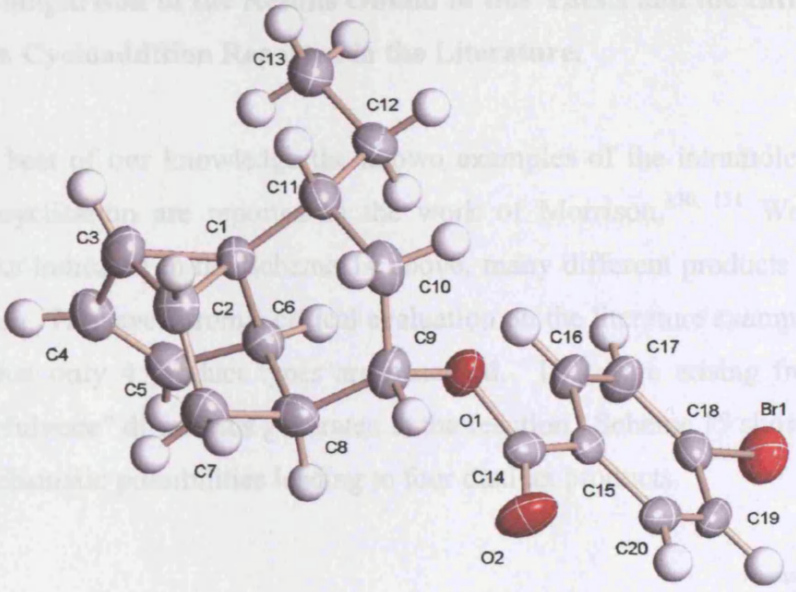
Finally H_9 at 5.56 ppm was irradiated, it interacted with H_{10} at 5.75 ppm and H_8 at 3.03 ppm.



Final confirmation of the isomer **540** was to obtain crystals by conversion of alcohol **540** with 4-bromobenzoyl chloride **519** to ester **542** in the same way as we did with the product **517.**



540 542



The same conditions were run for the *(R,R),(S,S)*-5-phenyl-1-hepten-3-ol **535.** The reaction did work but GC/MS showed two different peaks at 14.1 and 14.3 time of retention. This means that two different isomers were obtained and it was difficult to separate because TLC showed just one spot.

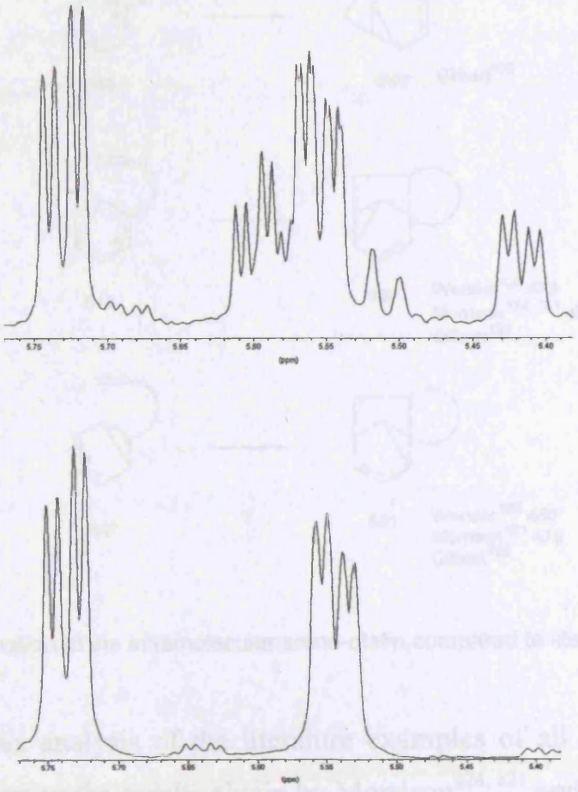
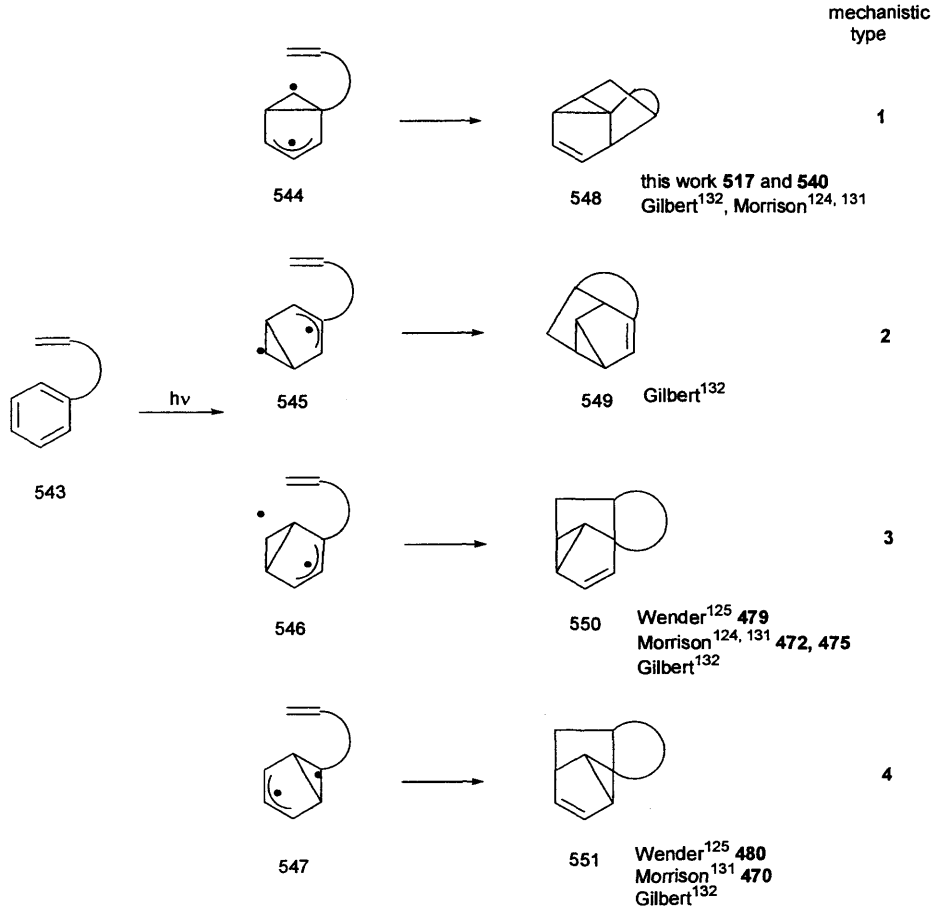


Fig. 12, ^{1}H NMR of the olefinic protons of photochemical reaction of alcohol **534** (below spectrum) and **535** (above spectrum).

5.2.7 Comparison of the Results Obtain in this Thesis and the Intramolecular Arene-Olefin Cycloaddition Reported in the Literature.

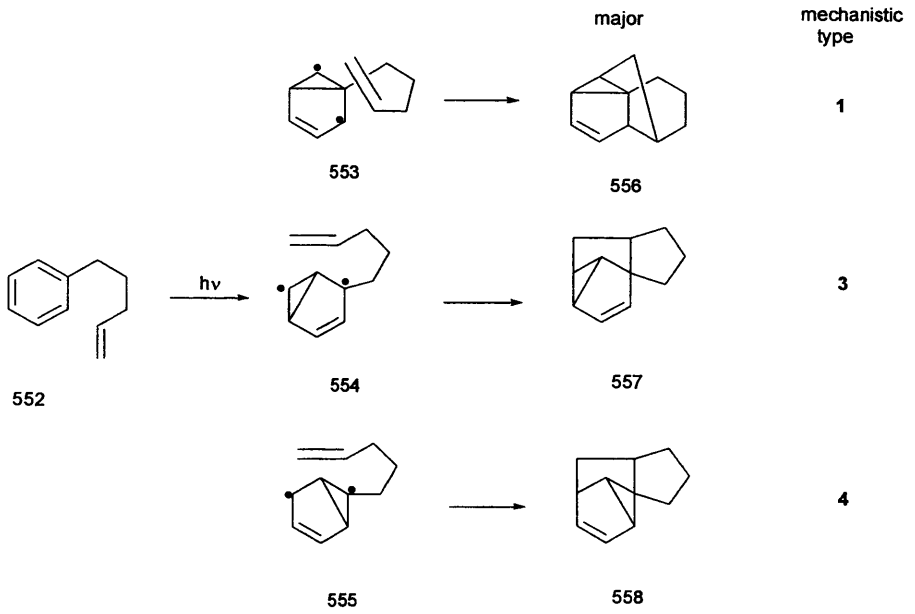
To the best of our knowledge the known examples of the intramolecular arene-olefin photocyclisation are reported in the work of Morrison,[130, 131] Wender[125] and Gilbert.[132] As indicated in the Scheme 14 above, many different products are possible in this reaction. However, from a critical evaluation on the literature examples, we have discovered that only 4 product types are observed. These are arising from the four possible "prefulvene" di-radicals generated in the reaction. Scheme 15 shows these four different mechanistic possibilities leading to four distinct products.



Scheme 15. Explanation of the intramolecular arene-olefin compared to literature examples.

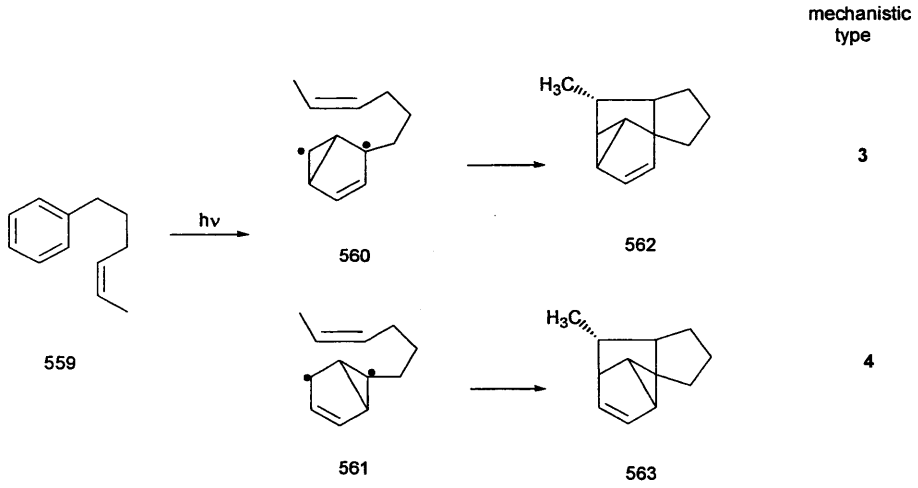
Scheme 15 shows analysis of the literature examples of all four reaction types. Our own work is closest to the results obtain by Morrison[124, 131] and Gilbert.[132] Scheme 16 shows the first results from the work of Gilbert where the highest quantum yield is

the type 1 product **556**, small amounts of type 3 **557** and 4 **558** products are also observed.



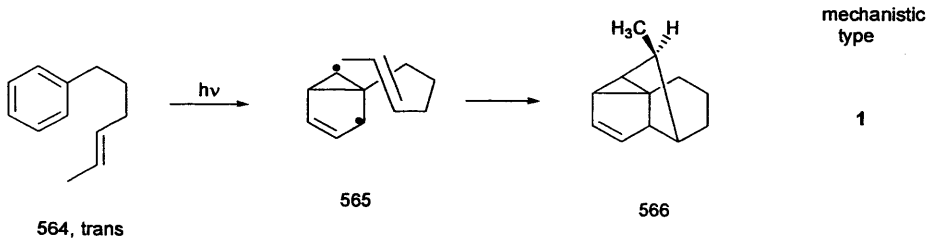
Scheme 16

When a methyl group is present on the olefin in the *CIS* configuration, type 1 product is not observed and only type 3 **562** and type 4 **563** products are obtained. This is shown in the scheme 17.



Scheme 17

However, when the double bond is in the *TRANS* configuration only Type 1 **479** product is observed (scheme 18).[125, 130, 132]

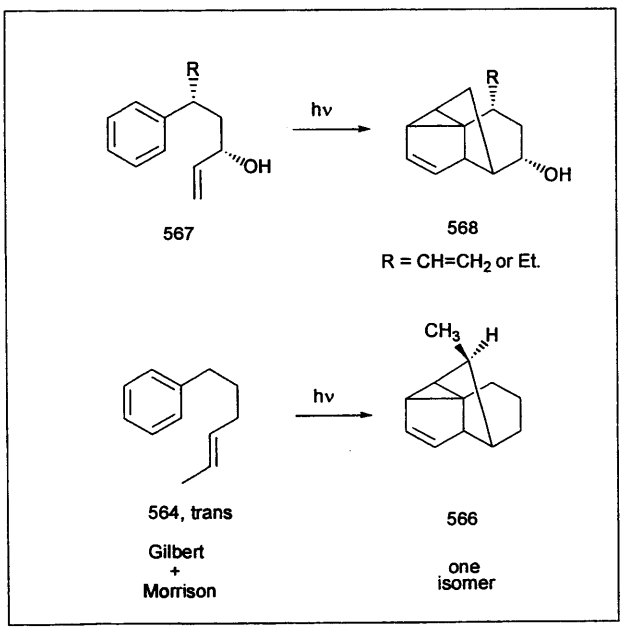


Scheme 18

The results summarised in scheme 15, 16 and 17 clearly indicate that subtle alteration in the side chain of the substrates changes the observed products and in the case of the *TRANS* compound **564** a single product is obtained. In our case, we have a compound **534** with two stereogenic centers added to the penten-side chain of the structure **552**. The separated diastereoisomer **534** leads to a single type 1 product whereas the other diastereoisomer **535** gives a mixture of photochemical products. Our results show that control of the reaction manifold is possible from the stereochemistry of the side chain. This result will enable this highly efficient synthesis of complex polycyclic structures to be controlled and used in organic synthesis.

5.2.8 Summary of Comparison of Morrison-Gilbert-Our Work.

A direct comparison of the most selective reaction of the Morrison-Gilbert work, shows that the *TRANS* compound **564** leads to a single type 1 product and our (R,S),(S,R) compound **534** also leads to a single type 1 product.



Chapter 6

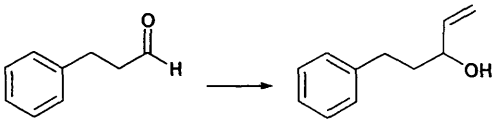
Experimental

5.1 General Experimental.

All reactions were performed under an atmosphere of nitrogen (unless otherwise stated) and solvent extractions were dried with anhydrous magnesium sulphate. Tetrahydrofuran and benzene were distilled from sodium-benzophenone. Diethyl ether was distilled from lithium aluminium hydride. Chloroform was distilled from calcium hydride. Petroleum ether refers to the 40-60°C boiling fraction. Thin layer chromatography (TLC) analysis was performed using silica GEL 60 f_{254} aluminium TLC plates, Merck 5554. Flash column chromatography was carried out using sorbsil C60 silica gel, 40-60 μm. The chromatotron used was the Harrison Research model 7924T, and the plates used were made from silica gel 60 PF_{254} with $CaSO_4$. Melting points were measured using a Kofler hotstage and are uncorrected. Elemental analysis were carried out by Butterworth Laboratories, Teddington, Middlesex. Infrared (IR) spectra were recorded using a Perkin Elmer 298 IR spectrometer; peaks are referred to as strong (s), medium (m), weak (w) and broad (br). Mass spectra wre recorded on a Kratos Concept Sector mass spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 250 (250 MHz ^1H, 62.9 MHz ^{13}C), Bruker AM 300 (300 MHz ^1H, 75 MHz ^{13}C), or Bruker DRX 400 (400 MHz ^1H, 100.6 MHz ^{13}C), spectrometer. NMR spectra recorded in $CDCl_3$ were calibrated to $CHCl_3$ (^1H, δ 7.27; ^{13}C, δ 77.4), all chemical shifts were taken directly from the spectra, and *J* values are given in hertz.

5.2 Experimental.

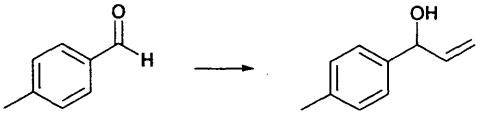
5-Phenylpent-1-en-3-ol[133] (52).



51 52

Vinylmagnesium chloride (50 mL, 1.7 M solution in THF) was added via a canula to a 3-neck, 250 mL round bottomed flask fitted with a nitrogen bubbler, condenser and a rubber septum. 3-Phenyl-propionaldehyde **50** (5.6 mL, 42.2 mmol) in 10 mL THF was added using a dropping funnel, slowly while cooling and stirring. The solution was then heated under reflux for 4 hours at 80°C. After cooling a saturated solution of ammonium chloride (25 mL) was added to remove un-reacted Grignard reagent. HCl (1M, 50 mL) was added to protonate the alcohol. The organic layer was extracted with diethyl ether (3 x 20 mL), dried, removal of the solvent under reduced pressure produced 5-phenylpent-1-en-3-ol **52** as a yellow oil (4.044 g, 59%); ν_{max}/cm^{-1} (CH_2Cl_2) 3380 (br, s), 3090 (m), 3080 (m), 3040 (m), 2930 (m), 2860 (m), 1610 (br, m), 1530 (m), 1500 (m), 1455 (m), 1320 (m), 1040 (m), 980(m), 750(m), 700 (s); δ_H (250 MHz, $CDCl_3$) 1.58 (1H, m, 3-H), 1.85 (2H, m, 2-H), 2.71 (2H, m, 1-H), 4.12 (1H, OH), 5.13 (1H, dd, *J* 1.4, 9.8, 5_{cis}-H), 5.25 (1H, dd, *J* 1.4, 16.4, 5-H) 5.91 (1H, ddd, *J* 5.8, 9.8, 16.4, 4-H) 7.23(5H, m, Ph); δc (62.9 MHz, $CDCl_3$) 33.0 (CH_2), 38.0 (CH_2), 73.0 (CH) 115.0 (CH_2), 126.0 (CH), 128.9 (2 CH, Ph), 129.1 (2 CH, Ph), 135.5 (CH, Ph), 143.0 (C, Ph); *m/z* (EI) 162 (M^+, 83), 144 (60), 129 (100), 117 (12), 105 (50), 91 (99),77 (20), 57 (30).

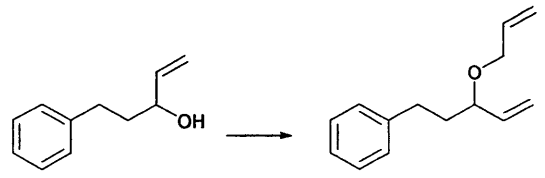
1-(4-methylbenzene)prop-2-en-1-ol[134] (59).



58 59

In the same way at 70°C for 2 hours, *p*-toluenaldehyde **58** (5 g, 41.66 mmol) and vinyl magnesium chloride (37 mL, 1.7 M solution in THF) gave 1-(4-methylbenzene)prop-2-en-1-ol **59** (3.6 g, 58%) as a yellow oil; δ_H (250 MHz, $CDCl_3$) 2.30 (3H, s, CH_3), 5.10 (1H, dd, *J* 1.4, 10.3, 3-H_{cis}), 5.30 (1H, dd, *J* 17.2, 1.4, 3-H_{trans}), 5.90 (1H, d, *J* 6.4, 1-H), 6.0 (1H, ddd, *J* 6.3, 10.3, 17.2, 2-H).

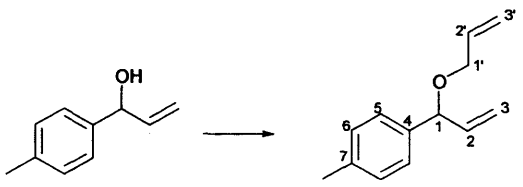
(3-Allyloxypent-4-enyl)benzene[135] **(53).**



52 53

Sodium hydride (0.648 g; 0.026 mol) in THF (100 mL) was cooled in an ice bath with stirring, 5-phenylpent-1-en-3-ol **52** (3.521 g; 0.022mol) was added in portions. The mixture was heated under reflux (80°C) for 2 hours and then allowed to cool at room temperature. DMPU (4 mL) was added followed by allyl bromide (3.81 mL; 0.044mol) and the solution again heated to reflux for 4 hours. On cooling the reaction was quenched with a saturated solution of ammonia chloride (50 mL) and diluted with diethyl ether (50 mL). The ether layer was separated and the ether was removed under reduced pressure. Purification by flash chromatography gave (3-allyloxypent-4-enyl)benzene **53** as a pale yellow oil (2.2065 g; 60%); ν_{max}/cm^{-1} (CH_2Cl_2) 2980 (m), 2920 (m), 2880 (m), 2760 (m), 1600 (m), 1555 (m), 1450 (m), 1404 (m), 1375 (m), 1270 (m), 1030 (br, m), 945 (m), 875 (s), 700 (m), 650 (s); δ_H (250 MHz, $CDCl_3$) 1.87 (2H, m, 2-H), 2.72-2.83 (2H, m, 1-H), 3.70 (1 H, ddd, *J* 7.6, 13.7, 16.5, 3-H), 3.82 (1H, ddt, *J* 1.4, 5.7, 12.8, 1'$_b$-H), 4.03 (1H, ddt , *J* 1.4, 5.3, 12.8, 1'$_a$-H), 5.22 (4H, m, 5-H and 3'-H), 5.72 (1H, ddd, *J* 7.6, 11, 16.5, 4-H), 5.93 (1H, m, 2'-H), 7.23 (5H, m, Ph); δ_C (62.9 MHz, $CDCl_3$) 32.3 (CH_2, 2C), 38.0 (CH_2, 1C), 69.6 (CH_2,1'C), 80.2(CH, 3C), 116.9 (CH_2, 5C or 3'C), 117.5 (CH_2, 5C or 3'C), 126.0 (CH, 2'C), 128.9 (CH, Ph), 129.1 (CH, Ph), 135.5 (CH, Ph), 139.0 (CH, 4C), 143.0 (C, Ph); *m/z* (EI) 202 (M^+, 14), 104 (100), 97 (86), 91(76), 79 (48), 67 (32).

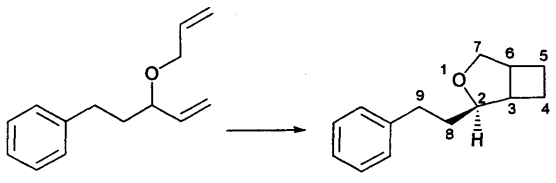
1(1-Allyloxyallyl)-4-methylbenzene (60).



59 60

Sodium hydride (60% dispersion in mineral oil, 0.4 g, 10.17 mmol) was added portion wise to an ice-cooled solution of 1-*p*-tolyl-prop-2-en-1-ol **59** (1.5 g, 10.17 mmol) in dry THF (5 mL). The resulting mixture was refluxed for two hours and allowed to cool to RT. Allylic bromide (1.76 mL, 20.34 mmol) and 400 µl DMPU were added and the mixture refluxed for a further 18 hours. TLC (Pet/Et_2O 3:1) after this time showed complete disappearance of SM and one product spot Rf = 0.38. Reaction mixture was worked up by addition of 10 mL H_2O. The product was extracted into ether, ether layer washed with brine, dried and the ether removed under reduced pressure. Purification by flash chromatography (petroleum ether : diethyl ether 4:1) gave *1(1-allyloxyallyl)-4-methylbenzene* **60** as a yellow oil (1.4 g, 70%); δ_H (300 MHz, $CDCl_3$) 2.30 (3H, s, CH_3), 3.96 (1H, dd, *J* 4.1, 5.5, 1'-H_a), 3.97 (1H, dd, *J* 5.5, 1.5, 1'-H_b), 4.77 (1H, d, *J* 6.42, 1-H), 5.20 (4H, m, 3-H and 3'-H), 5.94 (2H, m, 2-H and 2'-H), 7.15 (2H, d, *J* 7.9, 6-H), 7.25 (2H, d, *J* 7.9, 5-H); δ_C (75 MHz, $CDCl_3$) 21.5 (CH_3, CH_3-Ar), 69.5 (CH_2, 1'C), 82.3 (CH, 1C), 116.4 (CH_2, 3C), 117.2 (CH_2, 3'C), 127.3 (2 CH, Ph), 129.5 (2 CH, Ph), 135.2 (CH, 2C), 137.7 (C, Ph), 138.4 (C, Ph), 139.4 (CH, 2'C); *m/z* (EI) 188 (M^+, 10), 84 (32), 91 (28), 119 (100), 131 (40), 147 (45), (found M^+, 188.12015. $C_{13}OH_{16}$ requires 188.12012).

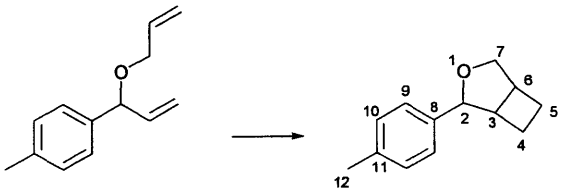
***Exo*-2-phenethyl-3-oxa-bicyclo[3.2.0]heptane (54).**



53 54

(3-Allyloxypent-4-enyl)benzene **53** (179 mg, 0.89 mmol), diethyl ether (10 mL) and a catalytic amount of $Cu(SO_3CF_3)_2.C_6D_6$ (10 mg) were added to a quartz photochemistry tube. The mixture was subjected to UV light for 17 hours. The reaction was diluted with ether (20 mL) and washed with ice/aqueous ammonium hydroxide (2 x 20 mL). The organic layer was washed with brine (30 mL), dried and evaporated to give a thick yellow oil. Chromatography on silica gel with petroleum ether / diethyl ether (3:1) as the eluent gave *exo-2-phenethyl-3-oxa-bicyclo[3.2.0]heptane* **54** as a pale yellow oil (120 mg, 60%); ν_{max}/ cm^{-1} (CH_2Cl_2) 3040 (m), 2940 (br, s), 2860 (s), 1610 (m), 1500 (m), 1410 (m), 1380 (m), 1350(m), 1105 (s), 1060 (m), 960 (m), 865 (m); δ_H (300 MHz, $CDCl_3$) 1.61-1.72 (4H, m, 8-H, 4_{endo}-H, 5_{endo}-H), 2.15 (2H, m, 4_{exo}-H, 5_{exo}-H), 2.65 (3H, m, overlapping 9-H and 3-H), 2.85 (1H, m, 6-H), 3.80 (2H, m, 7-H), 3.95 (1H, dd, *J* 5.3, 8.7, 2-H), 7.23 (5H, m, Ph); δ_C (75 MHz, $CDCl_3$) 24.0 ($2CH_2$, 4C and 5C), 33.0 (CH_2, 9C), 36.0 (CH_2, 8C), 39.4 (CH, 6C), 44.0 (CH, 3C), 73.4 (CH_2, 7C), 85.9 (CH, 2C), 126.4 (CH, Ph), 138.2 (CH, Ph), 142.1 (C, Ph); *m/z* (EI) 202 (M^+, 55), 104 (100), 9 (70), 91 (90), 79 (30); (found M^+, 202.13573. $C_{14}OH_{18}$ requires 202.13577).

***Exo*-2-(4-methylbenzene)-3-oxa-bicyclo[3.2.0]heptane (61).**

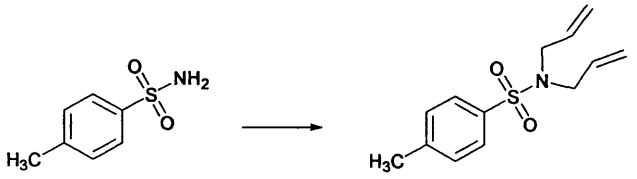


60 61

1(1-Allyloxyallyl)-4-methylbenzene **60** (0.100 mg; 0.53 mmol), diethyl ether (10 mL) and a catalytic amount of $Cu(SO_3CF_3)_2.C_6D_6$ (10 mg) were added to a quartz photochemistry tube. The mixture was subjected to UV light for 48 hours. The reaction was diluted with ether (20 mL) and washed with ice/aqueous ammonium hydroxide (2 x 20 mL). The organic layer was washed with brine (30mL), dried and evaporated to give a thick yellow oil. Chromatography on silica gel with petroleum ether / diethyl ether (3:1) as the eluent gave *exo-2-(4-methylbenzene)-3-oxa-bicyclo[3.2.0]heptane* **61** as a pale yellow oil (55 mg; 55%); ν_{max}/ cm^{-1} (CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 1.81-1.92

(1H, m, 5_{endo}-H), 2.02-2.13 (1H, m, 4_{endo}-H), 2.44-2.65 (5H, m, overlapping 12-H, 5_{exo}-H and 4_{exo}-H), 3.06-3.16 (1H, m, 6-H), 3.37-3.48 (1H, m, 3-H), 3.85 (2H, d, *J* 3.8, 7-H), 5.02 (1 H, s, 2-H), 7.32-7.43 (4-H, m, 9-H and 10-H); δ_C (75 MHz, $CDCl_3$) 21.4 (CH_3, 12C), 24.3 (CH_2, 5C), 24.5 (CH_2, 4C), 39.8 (CH, 6C), 45.3 (CH, 3C), 73.9 (CH_2, 7C), 87.0 (CH, 2C), 126.2 (CH, 9C), 129.3 (CH, 10C), 137.0 (C, 8C), 139.6 (C, 11C); *m/z* (EI) 188 (M^+, 40), 173 (35), 119 (100), 91 (40), (found M^+, 188.12016. $C_{13}OH_{16}$ requires 188.12012).

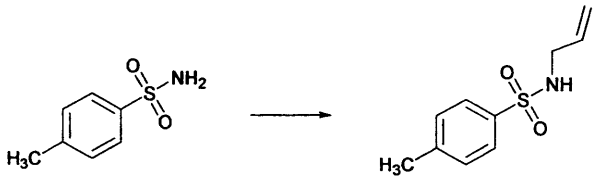
_N,N_-Diallyl-4-methylbenzenesulphonamide[136] (76).



75 76

Sodium hydride (1.34 g, 56 mmol) was added portion wise to an ice-cooled solution of toluene-4-sulphonamide **75** (4 g, 23.36 mmol) in dry THF (12 mL). The resulting mixture was heated to reflux for 1 hour and allowed to cool to room temperature. Allyl bromide (6.77 g, 56 mmol) and DMPU (200 μL) were then added, and the mixture was heated to reflux for 2 hours, allowed to cool to room temperature and quenched by addition of water (30 mL). The resulting mixture was then extracted into diethyl-ether (2 x 100 mL) then combined organic layers, washed with saturated sodium chloride solution, dried and the solvent was removed under reduced pressure to give the crude product. Purification by flash chromatography (petroleum ether / diethyl ether 2:1) gave *N,N*-diallyl-4-methylbenzenesulphonamide **76** as a colourless oil (1.972 g, 38%); δ_H ^{1}H NMR (250 MHz, $CDCl_3$) 2.45 (3H, s, CH_3), 3.59 (4H, d, *J* 5.7, 1-H), 5.33 (2H, d, *J* 10.3, 3-H), 5.39 (2H, d, *J* 17.2, 3-H), 5.84 (2H, ddt, *J* 5.7, 10.3, 17.2, 2-H), 7.33 (2H, d, *J* 8.5, Ph), 7.15 (2H, d, *J* 8.5, Ph); δ_C ^{13}C NMR (62.9 MHz, $CDCl_3$) 21.8 (CH_3, Me), 49.7 (2 CH_2, 1C), 119.3 (2 CH_2, 3C), 127.5 (2 CH, Ph), 130 (2 CH, Ph), 133 (2 CH, 2C), 137.8 (C, Ph), 143.6 (C, Ph); *m/z* (EI) 251 (M^+, 40), 56 (67), 86 (78), 91 (100).

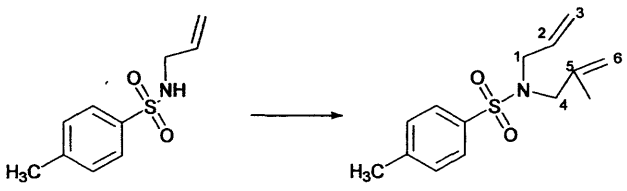
_N_-Allyl-4-methylbenzenesulphonamide[137] (78).



75 78

Sodium hydride (0.67 g, 28 mmol) was added portion wise to an ice-cooled solution of toluene-4-sulphonamide **75** (4 g, 23.36 mmol) in dry THF (12 mL). The resulting mixture was heated under reflux for 1 hour and allowed to cool to room temperature. Allyl bromide (23.36 mmol, 2.021 mL) and DMPU (200 μL) were then added, and the mixture was heated under reflux for 2 hours, allowed to cool to room temperature and quenched by addition of water (30 mL). The resulting mixture was then extracted with diethyl-ether (2 x 100 mL) the combined organic layers were washed with saturated sodium chloride solution, dried and the solvent was removed under reduced pressure to give the crude product. Purification by chromatography column (petroleum ether / diethyl ether 3:1) gave *N*-allyl-4-methylbenzenesulphonamide **78** as a colourless oil (0.857 g, 17%); δ_H ^{1}H NMR (250 MHz, $CDCl_3$) 2.45 (3H, s, CH_3), 3.59 (2H, dd, *J* 5.72, 1.37, 1-H), 4.40 (1H, s, br, NH), 5.10 (1H, dd, *J* 10.3, 1.37, 3_{cis}-H), 5.25 (1H, dd, *J* 17.2, 1.37, 3-H), 5.73 (1H, ddt, *J* 5.72, 10.3, 17.2, 2-H), 7.15 (2H, d, *J* 8.47, Ph), 7.30 (2H, *J* 8.47, Ph); δ_C ^{13}C NMR (62.9 MHz, $CDCl_3$) 21.8 (CH_3, Me), 46.1 (CH_2, 1C), 118.2 (CH_2, 3C), 127.5 (2 CH, Ph), 130 (2 CH, Ph), 133.4 (CH, 2C), 137.0 (C, Ph), 143.8 (C, Ph); *m/z* (EI) 211 (M^+, 34), 78 (56), 123 (100), 156 (70).

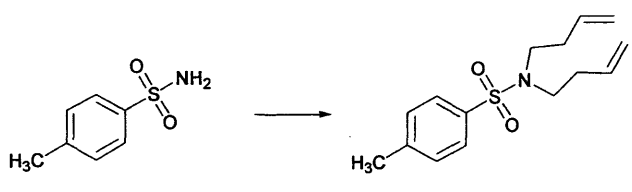
_N_-Allyl-4-methyl-_N_-(2-methylallyl)benzenesulphonamide (84).



78 84

Sodium hydride (0.12 g, 4.9 mmol) was added portion-wise to an ice-cooled solution of *N*-allyl-4-methyl-benzenesulphonamide **78** (0.860 g, 4.07 mmol) in dry THF (5 mL). The resulting mixture was heated to reflux for 1 hour and allowed to cool to room temperature. 3-Chloro-2-methyl-1-propene (0.37 g, 4.07 mmol) and DMPU (200 μL) were then added, and the mixture was heated to reflux for 3 hours, allowed to cool to room temperature and quenched by addition of water (30 mL). The resulting mixture was then extracted into diethyl-ether (2 x 50 mL) the combined organic layers were washed with saturated sodium chloride solution, dried and the solvent was removed under reduced pressure to give the crude product. Purification by flash chromatography (petroleum ether / diethyl ether, 1:1) gave *N-allyl-4-methyl-N-(2-methylallyl)benzenesulphonamide* **84** as a colourless oil (0.88 g, 82%); δ_H ^{1}H NMR (300 MHz, $CDCl_3$) 1.90 (3H, s, CH_3), 2.60 (3H, s, CH_3-Ar), 3.90 (2H, s, 4-H), 3.97 (2H, d, *J* 6.6, 1-H), 5.05 (1H, s, 6_{cis}-H), 5.11 (1H, s, 6_{trans}-H), 5.26 (1H, d, *J* 10.3, 3_{cis}-H), 5.31 (1H, d, *J* 17.2, H-3_{trans}), 5.73 (1H, ddt, *J* 6.6, 10.3, 17.2, 2-H), 7.50 (2H, d, *J* 7.1, 9-H), 7.90 (2H, d, *J* 7.1 , 10 H); δ_C ^{13}C NMR (75 MHz, $CDCl_3$) 20.2 (CH_3, CH_3-allyl), 21.8 (CH_3, Me-Ph), 49.7 (CH_2, 1C), 53.1 (CH_2,1'C), 114.8 (CH_2, 3'C), 119.3 (CH_2, 3C), 127.5 (2 CH, Ph), 130.0 (2CH, Ph), 133.0 (CH, 2C), 137.8 (C, Ph), 140.4 (C, 2'C), 143.6 (C, Ph); *m/z* (EI) 265 (M^+, 20.0), 110 (35), 155 (73), 91 (100), (found M^+, 265.1135. $C_{12}H_{19}NO_2S$ requires 265.1136).

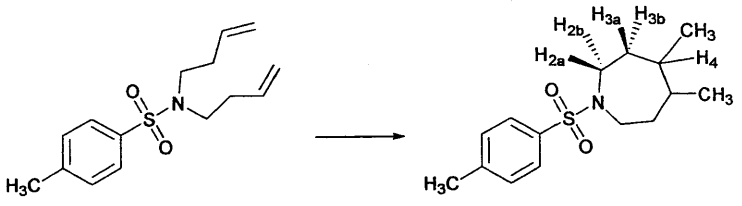
_N,N_-Di-but-3-enyl-4-methtylbenzenesulphonamide[138] (86).



75 86

Sodium hydride (2.4 equiv, 1.34 g) was added portion wise to an ice-cooled solution of *p*-toluene-sulphonamide **75** (4 g, 23.36 mmol) in dry THF (12 mL). The resulting mixture was heated to reflux for 1 hour and allowed to cool to room temperature. 4-Bromo-1-butene (2.36 mL) and DMPU (200 μL) were then added, and the mixture was heated to reflux for 3 hours, allowed to cool to room temperature and quenched by addition of water (30 mL). The resulting mixture was then extracted into diethyl-ether (2 x 50 mL) the combined organic layers were washed with saturated sodium chloride solution, dried and the solvent was removed under reduced pressure to give the crude product. Purification by flash chromatography (petroleum ether : diethyl ether, 2:1) gave *N,N*-di-but-3-enyl-4-methtylbenzenesulphonamide **86** (0.109 mg, 4%); δ_H ^{1}H NMR (250 MHz, $CDCl_3$) 2.17 (3H, s, CH_3), 2.35-2.50 (4H, m, 2-H), 3.30-3.35 (4H, m, 1-H), 5.15-5.25 (4H, m, 4-H), 5.75 (2H, ddt, *J* 18, 9.7, 6.60, 3-H), 7.28 (2H, d, *J* 8.40, Ph), 7.64 (2H, d, *J* 8.40, Ph); δ_C ^{13}C NMR (62.9 MHz, $CDCl_3$) 21.9 (CH_3, Me), 34.1 (2 CH_2, 2C), 48.6 (2 CH_2, 1C), 117.0 (2 CH_2, 4C), 127.5 (2 CH, Ph), 130.0 (2 CH, Ph), 135.7 (2 CH, 3C), 137 (C, Ph), 143.8 (C, Ph); *m/z* (EI) 279 (M^+, 57), 78 (56), 146 (100).

4,5-Dimethyl-1-(toluene-4-sulphonyl)azepane (88).

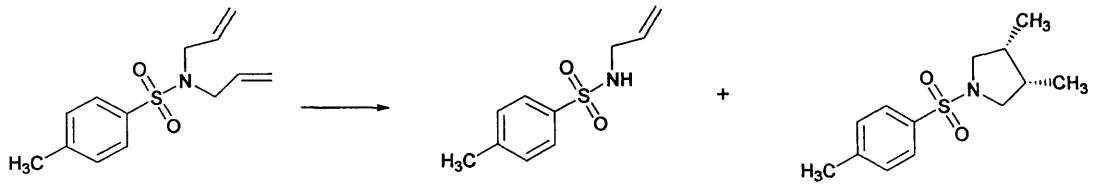


86 88

$ZrCp_2Cl_2$ (0.145 g, 0.39 mmol) was dissolved in dry THF (3 mL). The mixture was stirred for 5 min at – 78 °C. BuLi (2 equiv, 0.487 mL) was added to the solution and then it was stirred for 15 min at – 78°C. *N,N*-Di-but-3-enyl-4-methtyl-benzenesulphonamide **86** (0.39 mmol, 0.109 g) was added to the mixture and stirring was continued for 1 hour at –78°C. The cold bath was removed and the solution was stirred overnight at room temperature. MeOH (10 mL) was added to the solution and the resulting mixture was then extracted into diethyl ether (2 x 10 mL). The combined organic layers were washed with saturated sodium chloride solution, dried and the

solvent removed under reduced pressure. The resulting oil was purified by column chromatography (petroleum ether : diethyl ether 2:1) to yield *4,5-dimethyl-1-(toluene-4-sulphonyl)azepane* **88** as a colourless oil (5 mg, 5%); δ_H ^{1}H NMR (250 MHz, $CDCl_3$) 0.92 (6H, d, *J* 6, alk-CH_3), 1.10-1.15 (2H, m, 4-H), 1.40-1.50 (2H, m, 3-H_a or 3-H_b), 1.60-1.65 (2H, m, 3-H_a or 3-H_b), 2.20 (3H, s, CH_3-Ar), 3.18 (2H, ddd, *J* 2.9, 10.1, 10.8, 2-H_a or 2-H_b), 3.58 (2H, ddd, *J* 3.2, 5.9, 13.1, 2-H_a or 2-H_b), 7.1 (2H, d, *J* 8.4, Ph), 7.9 (2H, d, *J* 8.4, Ph); δ_C ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C 21.6 (2 CH_3), 21.8 (CH_3-Ar), 36.2 (2 CH_2, 3C), 39.9 (2 CH, 4C), 46.35 (2 CH_2, 2C), 127.5 (2 CH, Ph), 129.9 (2 CH, Ph), 136.5 (C, Ph), 143.3 (C, Ph); *m/z* 282 (M^+, 67), 89 (65), 146 (100), 112 (34).

_N_-Allyl-4-methylbenzenesulphonamide[137] (78) and *cis*-3,4-dimethyl-1-(toluene-4-sulphonyl)pyrrolidine[139] (79).



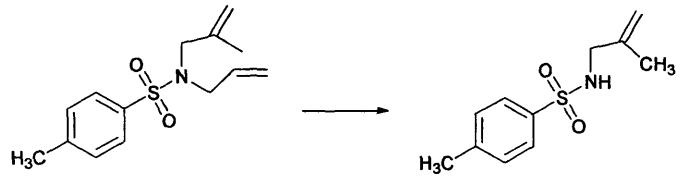
76 78 79

$ZrCp_2Cl_2$ (0.293 g, 0.977 mmol) was dissolved in dry THF (3 mL). The mixture was stirred for 5 min at – 78 °C. BuLi (1.992 mmol, 1.245 mL) was added to the solution and stirring was continued for 15 min at – 78°C. *N-N*-Diallyl-4-methyl-benzenesulphonamide **76** (0.25 g, 0.976 mmol) was added to the mixture which was then stirred for 1 hour at –78°C. The cold bath was removed and the solution was stirred overnight at room temperature. MeOH (10 mL) was added to the solution and the resulting mixture was then extracted into diethyl ether (2x 10 mL). The combined organic layers were washed with saturated sodium chloride solution, dried and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography (petroleum ether : diethyl ether 2:1). Two different compounds were obtained. One of the compounds was the *cis*-3,4-dimethyl-1-(toluene-4-sulphonyl)pyrrolidine **79** (10 mg, 4%) the expected product6 and the other compound was *N*-allyl-4-methylbenzenesulphonamide **78** (14 mg, 7%);

(78) δ_H ^{1}H NMR (250 MHz, $CDCl_3$) 2.45 (3H, s, CH_3), 3.59 (2H, dd, *J* 5.7, 1.4, 1-H), 4.40 (1H, s, NH), 5.10 (1H, dd, *J* 10.3, 1.4, 3_{cis}-H), 5.25 (1 H, dd, *J* 17.2, 1.4, 3-H), 5.73 (1H, ddt, *J* 5.7, 10.3, 17.2, 2-H), 7.15 (2H, d, *J* 8.5, Ph), 7.30 (2 H, *J* 8.5, Ph); δ_C ^{13}C NMR (62.9 MHz, $CDCl_3$) 21.8 (CH_3, Me), 46.1 (CH_2, 1C), 118.0 (CH_2, 3C), 127.5 (2 CH, Ph), 130.0 (2 CH, Ph), 133.4 (CH, 2C), 137.0 (C, Ph), 143.8 (C, Ph); *m/z* (EI) 211 (M^+, 34), 78 (56), 123 (100), 156 (70).

(79) δ_H ^{1}H NMR (250 MHz, $CDCl_3$) 1.04 (6H, d, *J* 6, CH_3), 1.75 (2H, ddq, *J* 7.1, 7.5, 6.0, 3-H), 2.27 (2H, dd, *J* 7.1, 9.0, 2-H_a or 2-H_b), 2.45 (3H, s, CH_3), 2.8 (2H, dd, *J* 7.5, 9.0, 2-H_a or 2-H_b), 7.15 (2H, *J* 8.47, Ph), 7.3 (2H, *J* 8.47, Ph).

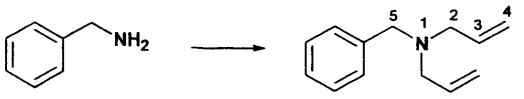
4-Methyl-*N*-(2-methylallyl)benzenesulphonamide[140] (85).



84 85

$ZrCp_2Cl_2$ (0.222 g, 0.754 mmol) was dissolved in dry THF (3 mL). The mixture was stirred for 5 min at – 78 °C. BuLi (2 x 0.754 mmol, 0.9425 mL) was added to the solution and then it was stirred for 15 min at – 78°C. *N*-Allyl-*N*-(2-methylallyl)-4-toluenesulphonamide **84** (0.2 g, 0.754 mmol) was added to the mixture which was stirred for 1 hour at –78°C. The cold bath was removed and the solution was stirred overnight at room temperature. MeOH (10 mL) was added to the solution and the resulting mixture was then extracted into diethyl ether (2 x 10 mL). The combined organic layers were washed with saturated sodium chloride solution, dried and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography (petroleum ether : diethyl ether 1:1) to yield 4-methyl-*N*-(2-methylallyl)benzenesulphonamide **85** as a yellow oil in 5% yield; δ_H ^{1}H NMR (250 MHz, $CDCl_3$) 1.90 (3H, s, CH_3), 2.60 (3H, s, CH_3-Ar), 3.90 (2H, s, 2-H), 5.05 (1H, s, 4-H_{trans}), 5.11 (1H, s, 4-H_{cis}), 7.5 (2H, d, *J* 7.1, Ph), 7.90 (2H, d, *J* 7.1, Ph); *m/z* (EI) 225 (M^+, 45), 148 (56), 91 (100).

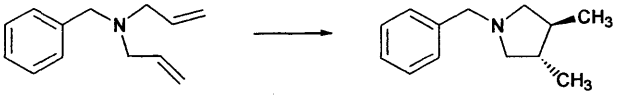
Diallylbenzylamine[141] (91).



90 91

Benzyl amine **90** (2.14 g, 20 mmol) was dissolved in 10 mL of (4:1) THF/DMSO mixture. Sodium hydrogencarbonate (3.36 g,40 mmol) was poured into the solution followed by drop wise addition of allyl-bromide (40 mmol, 3.46 mL). Finally, a catalytic amount of sodium iodide (0.5 equiv) was introduced and the mixture was heated to reflux for 5 hours. After consumption of the amine as indicated by TLC the solution was concentrated in vacuum. The residue is treated with water and extracted with AcOEt (2 x 20 mL). The organic layer was washed with water, dried and concentrated in vacuum to give diallylbenzylamine **91** as a yellow oil (2.272 g, 61%) which did not need further purification; δ_H ^{1}H NMR (250 MHz, C_6D_6) 3.30 (4H, d, *J* 6.2, 2-H), 3.75 (2H, s, 5-H), 5.32 (2H, dd, *J* 10.1, 1.9, 4-H_{cis}), 5.40 (2H, dd, *J* 17.2, 1.9, 4-H $_{trans}$), 6.12 (2H, ddt, *J* 6.4, 10.1, 17.2, 3-H), 7.30 (5H, m, Ph); δ_C ^{13}C NMR (62.9 MHz, C_6D_6) 57.2 ($2CH_2$, 2C), 58.5 (CH_2, 5C), 117.6 ($2CH_2$, 4C), 127.6 (CH, Ph), 129.0 (2 CH, Ph), 129.5 (2 CH, Ph), 137 (2 CH, 2C), 140.5 (C, Ph); *m/z* (EI) 187 (M^+, 30), 110 (20), 160 (38), 91 (100), (found M^+, 187.1361. $C_{13}H_{17}N$ requires 187.1361).

1-Benzyl-3,4-dimethylpyrrolidine[144] (95).

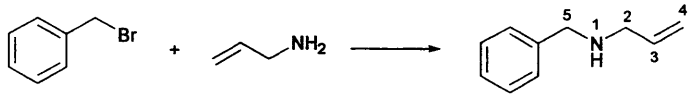


91 95

To a solution of Cp_2ZrCl_2 (0.012 g, 0.04 mmol) and diallylbenzyl **91** (300 mg, 1.6 mmol) was added BuMgCl (2 M, 3.2 mmol) – 78 °C in THF. The solution was stirred at the same temperature for 1 hour and then was refluxed for 14 hours. MeOH (1 mL) was added to the reaction and the solvent was removed under reduced pressure. To the crude was added water and extracted with Et_2O. The combined ether extract was dried and evaporated under reduced pressure. The crude was purified with flash chromatography (10:1 petroleum ether : diethyl ether) to yield 1-benzyl-3,4-

dimethylpyrrolidine **95** as a yellow oil (0.60 g, 20%); δ_H ^{1}H NMR (250 MHz, $CDCl_3$) 1.04 (6H, d, *J* 6), 1.75 (2H, ddq, *J* 7.1, 7.5, 6.0), 2.27 (2H, dd, *J* 7.1, 9.0), 2.80 (2H, dd, *J* 7.5, 9.0), 3.57 (1H, d, *J* 13), 3.67 (1H, d, *J* 13), 7.20-7.40 (5H, m, Ph); δ_C ^{13}C NMR (62.9 MHz, $CDCl_3$) 18.4 (2 CH_3, Me), 40.7 (2 CH, 3C and 4C), 61.4 (CH_2, 1C), 62.2 (2 CH_2, 2C and 5C), 126.75 (CH, Ph), 128.1 (2 CH, Ph), 128.8 (2 CH, Ph), 139.4 (C, Ph); *m/z* (EI) 185 (M^+, 100), 91 (53); (found 185.2357. $C_{13}H_{19}N$ requires 185.2357).

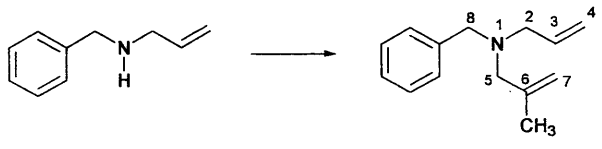
N-Allyl-N-benzylamine[142] (93).



96 97 93

Benzyl bromide **96** (2 g, 11.7 mmol) was added drop wise to neat allyl amine **97** (5.26 mL, 70.2 mmol) at 0°C. After 16 hours at room temperature, the reaction was quenched with aqueous $NaHCO_3$ solution (10 mL), extracted with Et_2O (3 x 10 mL), the combined ether extract was dried and evaporated under reduced pressure to give the crude product. Purification by silica gel chromatography gave *N*-allyl-*N*-benzylamine **93** as a yellow oil (1.373 g, 80%); δ_H ^{1}H NMR (250 MHz, C_6D_6) 1.54 (1H, s, NH), 3.23 (2H, d, *J* 5.9, 2-H), 3.73 (2H, s, 5-H), 5.06 (1H, dd, *J* 10.3, 1.2, 4-H_{cis}), 5.14 (1H, dd, *J* 17.4, 1.2, 4-H_{trans}), 5.88 (1H, ddt, *J* 17.4, 10.3, 5.9, 3-H), 7.17-7.27 (5H, m, Ph); δ_C ^{13}C NMR (62.9 MHz, C_6D_6) 51.7 (CH_2, 2C), 53.2 (CH_2, 5C), 115.9 (CH_2, 4C), 126.9 (CH, Ph), 128.1 (2 CH, Ph), 128.3 (2 CH, Ph), 136.8 (CH, 3C), 140.2 (C, Ph); *m/z* (EI) 148 (M^+, 40), 131 (23), 91 (100).

N-Allyl-N-benzyl-N-(2-methylallyl)amine[143] (98).



93 98

N-Allyl-*N*-benzylamine **93** (1.334 g, 9.07 mmol) was dissolved in 10 mL of (4:1) THF/DMSO mixture. Sodium hydrogencarbonate (0.76 g, 9.07 mmol) was poured into the solution followed by drop wise addition of methyl-allyl-chloride (12 mmol, 0.82

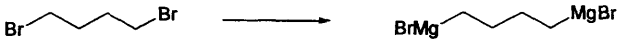
mL). Finally, a catalytic amount of sodium iodine (0.26 g, 4.5 mmol) was introduced and the mixture was heated to reflux for 5 hours. After consumption of the amine the solution was concentrated in vacuum. The residue is treated with water and extracted with AcOEt. The organic layer was washed with water, dried and concentrated in vacuum to give *N*-allyl-*N*-benzyl-*N*-(2-methylallyl)amine **98** was as a yellow oil (1.185 g, 65%) which did not need further purification; δ_H ^{1}H NMR (300 MHz, $CDCl_3$) 1.95 (3H, s, CH_3), 3.10 (2H, s, 5-H), 3.20 (2H, d, *J* 6.8, 2-H), 3.68 (2H, s, 8-H), 5.25 (4H, m, 4-H, 7-H), 6.05 (1H, ddt, *J* 6.8, 10.3, 17.4, 3-H), 7.17-7.27 (5H, m, Ph); δ_C ^{13}C NMR (75 MHz, C_6D_6) 21.2 (CH_3), 56.9 (CH_2), 58.5 (CH_2), 61.1 (CH_2), 113.0 (CH), 117.0 (CH_2), 127.5 (C) 128.0 (CH_2), 129.3 (2 CH), 136.0 (CH), 140.6 (2CH), 144.5 (C); *m/z* (EI) 202 (M^+, 58), 146 (24), 160 (28), 91 (100).

1-Benzyl-3,3,4-trimethylpyrrolidine[24] (103).

98 103

To a solution of Cp_2ZrCl_2 (0.058 g, 0.2 mmol) and *N*-allyl-*N*-benzyl-*N*-(2-methylallyl)amine **98** (400 mg, 2 mmol) was added BuMgCl (2M, 4 mmol) –78 °C in THF. The solution was stirred at the same temperature for 1 hour and then was refluxed for 14 hours. MeOH (2 mL) was added to the reaction and the solvent was removed under reduced pressure. To the crude product was added water and extracted with Et_2O. The combined ether extract was dried and evaporated under reduced pressure The crude was purified by flash chromatography (10:1 petroleum ether : diethyl ether) to yield 1-benzyl-3,3,4-trimethylpyrrolidine **103** as a yellow oil (0.134 g, 33%); δ_H ^{1}H NMR (250 MHz, $CDCl_3$) 0.85 (3H, d, *J* 7, CH_3), 0.89 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.87 (1H, dq, *J* 7, 7.6, 4-H), 2.21 (1H, d, *J* 9.2, 2-H), 2.28 (1H, d, *J* 9.2, 1-H), 2.55 (1H, d, *J* 8.9, 5-H), 2.87 (1H, dd, *J* 7.6, 8.9, 5-H), 3.55 (1H, d, *J* 13, 1-H), 3.65 (1H, d, *J* 13, 1-H), 7.17-7.27 (5H, m, Ph); δ_C ^{13}C NMR (62.9 MHz, $CDCl_3$) 13.5 (CH_3), 23.3 (CH_3), 28.7 (CH_3), 39.9 (C, 3C), 42.8 (CH, 4C), 61.3 (CH_2, 5C), 62.0 (CH_2, 6C), 69.8 (CH_2, 1C), 127.1 (CH, Ph), 128.5 (2CH, Ph), 128.9 (2CH, Ph), 140.2 (C, Ph); *m/z* (EI) 204 (M^+, 82), 91 (100), (found M^+, 204.1752. $C_{14}H_{22}N$ requires 204.1752).

Preparation of Butane-1, 4-di(magnesium bromide)[23] (65) and general remarks of formation of diGrignard reagents.

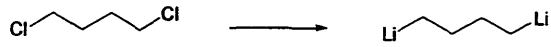


65

Magnesium turnings (670 mg, 27.6 mmol) were just covered with anhydrous diethyl ether (4 mL) under a nitrogen atmosphere and a small iodine crystal was added to clean the metal surface. Approximately 0.2 mL 1,4-dibromobutane was added and effervescence and exotherm were observed to indicate the onset of reaction with magnesium. The remainder of the dibromide was added gradually over a 30 minute period at a sufficient rate to maintain an exotherm (total volume of dibromide added: 1.65 mL, 13.8 mmol). The cloudy mixture was then heated to reflux and diethyl ether was added as necessary to aid stirring as a gel was formed. After 1 hour, virtually all magnesium had dissolved. Titration of a quenched portion of the bisGrignard reagent with standardised aqueous HCl solution showed the concentration to be 1.34 mM.

NOTE: This same method was applied to the formation of other bisGrignard reagents, namely those of corresponding **105**, **106** and **107** precursors. Disappointingly, even with repeated attempts produce a shiny surface on the metal, e.g. by grinding with a glass rod, and by keeping all reagents under dry and inert conditions, the reactions could not be satisfactorily initiated. However, the corresponding bisGrigard reagent of α, α'-dibromo-*o*-xylene **127** was formed by reaction with magnesium using the same method as described above for 1, 4-dibromobutane. **110** and **114** were not reacted with magnesium in an analogous fashion in attempts to form magnesiumbromide Grignard reagents instead of magnesiumchloride Grignard reagents. At this stage therefore, it is unclear whether it is steric factors of the greatly hindered bicyclic system or the greater ability of –Br as a leaving group compared with –Cl that accounts for the relative ease of formation of 1,4-butane-di(magnesiumbromide) **65** and the general difficulties observed with formation of diGrignard reagents of this bicyclic system from their dichloride precursor.

General procedures for formation of dilithioalkanes from dichloroalkanes based on formation of 1, 4-dilithiobutane[23] (66) from 1, 4-dichlorobutane.

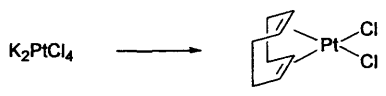


66

Lithium wire (3.9 g, 562 mmol) containing 1% Na was chopped into small pieces to increase its shiny surface area and suspended in anhydrous diethyl ether (100 mL). 1, 4-dichlorobutane (14 mL, 128 mmol) was made up to 50 mL solution with anhydrous diethyl ether and approximately 1/10 of the solution was added to the lithium metal at 0 °C. Repeated attempts to sonicate and stir the mixture vigorously failed to initiate a reaction. Finally, with vigorous stirring and large amounts of added anti-bumping granules to help grind the metal surface, the reaction was initiated and a precipitate of lithium chloride was observed. With the remainder of the dichloride added, the solution was stirred vigorously at room temperature for 16 hours. The milky-white precipitate was then filtered through celite by cannulation under nitrogen. Quenching of a portion of the solution with water followed by titration against standard aqueous HCl eluded a concentration of 0.179 mol dm^{-3} of the 1, 4-dilithiobutane compound **66** in ether.

NOTE: Repeated attempts to make similar lithioalkanes were optimised where carried out under an argon atmosphere to prevent nitrate layer forming around lithium metal. Reaction of lithium metal with nitrogen forms the black nitride layer and hinders reaction of the metal with the chloroalkanes. In addition, flattening of the lithium metal with a hammer in paraffin followed by washings with anhydrous ether or THF under argon atmosphere produces a much more satisfactory, larger, very clean and shiny surface area of the metal to which solvents and substrates can then be added. All of the lithium compounds **111** and **115** were made via this modified method.

Preparation of Dichloro(1, 5-cyclooctadiene)platinum(II)[23] (63).

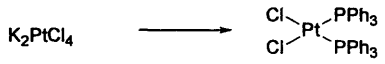


63

Potassium tetrachloroplatinate (1.0 g, 2.4 mmol) was dissolved in water (16 mL) to give a deep red solution. To this filtered solution were added glacial acetic acid (2.5 mL) and 1, 5-cyclooctadiene (0.97 mL, 7.9 mmol). After heating to 90 °C for 30 minutes, the red mixture had turned pale yellow and a precipitate had formed. Removal

of solvents *in vacuo* gave a concentrated product which was washed successively with water (10 mL), ethanol (10 mL) and diethyl ether (10 mL) then dried to yield 639 mg (72%) of the title compound as off-white needles; Mp: 265 °C (lit[23] Mp 220-278 °C); δ_H ^{1}H NMR ($CDCl_3$, 250 MHz) 2.5 ($2CH_2$, m), 3.0 ($2CH_2$, m), 5.8 (4CH, m).

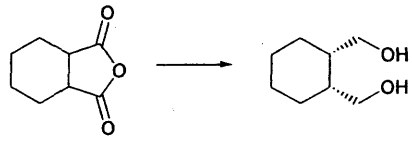
Cis-bistriphenylphosphine platinum(II)dichloride[23](64).



64

Potassium tetrachloroplatinate (500 mg, 1.2 mmol) was dissolved in water (6.5 mL) and added to a boiling solution of triphenylphosphine (625 mg, 2.4 mmol) in ethanol (7.5 mL). A white precipitate was formed immediately and this was heated at 60 °C for a further two hours. The precipitate was then filtered and washed successively with hot water (2 mL), hot ethanol (2 mL) and diethyl ether (2 mL). The white solid was then recrystallised from chloroform/hexane to afford 543 mg (57%) white crystalline product; Mp: 267-287 °C (lit[23] Mp 275 °C); δ_H ^{1}H NMR (CD_2Cl_2, 250MHz) 7.4-7.8 (30H, m, Ph); δ_P ^{31}P NMR (CD_2Cl_2, 250MHz) 13.9 ($2P_{PPh}$, s with Pt satellites, *J* 3634 - *cis*); MS: Poor ionisation, no parent ion observed.

Cis-1, 2-bis(hydroxymethyl)cyclohexane[145] (109).

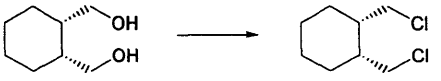


108 109

Lithium aluminium hydride (300 mg, 7.9 mmol) was cautiously added to anhydrous THF (15 ml) under nitrogen. The suspension was chilled to 0 °C and cyclohexane-1, 2-dicarboxylic anhydride **108** (1.0 g, 6.5 mmol) was steadily added as a solution of THF (5.0 ml). The resulting mixture was heated to reflux for 3 hours then cooled to 0 °C and quenched with saturated aqueous sodium sulphate solution (2.5 mL). Resulting salts were filtered and washed with diethyl ether and the filtrate concentrated

to a wet residue by evaporation under reduced pressure. The residue was then partitioned between dichloromethane (20 mL) and water (10 mL) and separated aqueous phase extracted with dichloromethane (10 mL). The combined organic layers were washed with brine (15 mL), dried and evaporated under reduced pressure to yield *cis*-1, 2-bis(hydroxymethyl)cyclohexane **109** as a colourless oil (739 mg, 79%); FTIR (cm^{-1}): ~3600-3100 broad, ~3000-2800 broad, 1455, 1030. (Disappearance of carbonyl from starting material.) δ_H ^1H NMR ($CDCl_3$, 250 MHz) 1.50-1.90 (4H, m, 3-H, 4-H, 5-H, 6-H), 2.10 (2H, m, 1-H, 2-H), 3.70-4.10 (8H, m, 7-H, 8-H); δ_C ^{13}C NMR ($CDCl_3$, 62.9 MHz) 24.5 (2 CH_2, 4C, 5C), 27.6 (2 CH_2, 3C, 6C), 40.3 (2 CH, 1C, 2C), 64.6 (2 CH_2O); *m/z* 145 (M^+, 90), 122 (95), 64 (100).

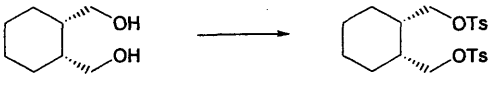
Cis-1, 2-bis(chloromethyl)cyclohexane[146] (110).



109 110

Thionyl chloride (5.0 mL, 69 mmol) was added cautiously to *cis*-1, 2-di(hydroxymethyl)cyclohexane **109** (720 mg, 5 mmol) and the mixture refluxed for 30 minutes. Excess thionyl chloride was subsequently removed under reduced pressure to yield orange oil. The crude product was diluted with diethyl ether (20 mL) and washed successively with saturated aqueous sodium bicarbonate solution (2 x 10 mL) and brine (10 mL), dried and evaporated under reduced pressure to yield *cis*-1, 2-bis(chloromethyl)cyclohexane **110** as a yellow oil (656 mg, 72%); δ_H ^1H NMR ($CDCl_3$, 400 MHz) 1.3-1.9 (8H, m, 3-H, 4-H, 5-H, 6-H), 2.0 (2H, m, 1-H, 2-H), 3.80–5.50 (8H, m, 7-H, 8-H); δ_C ^{13}C NMR ($CDCl_3$, 100.6 MHz), 24.2 (2 CH_2, 4-C, 5-C), 26.8 (2 CH_2, 3-C, 6-C), 39.1 (2 CH, 1-C, 2-C), 66.4 (2 CH_2Cl).

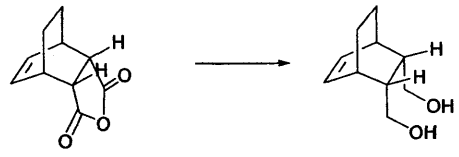
Cis-1,2-bis-(toluene-4-sulphonyloxymethyl)cyclohexane[147] (117).



109 117

Cis-1, 2-bis(hydroxymethyl)cyclohexane **109** (200 mg, 1.38 mmol) was dissolved in anhydrous dichloromethane and triethylamine (383 µl, 2.77 mmol) was added. The mixture was chilled to 0 °C and *p*-toluenesulphonyl chloride (514 mg, 2.77 mmol) was added steadily drop-wise as a solution of anhydrous dichloromethane (5 mL). After stirring at room temperature for 16 hours, the crude reaction mixture was washed successively with water (10 mL), 1M HCl (10 mL) and brine (10 mL). The organic phase was then dried and evaporated under reduced pressure to yield *cis*-1,2-bis-(toluene-4-sulphonyloxymethyl)cyclohexane **117** (428 mg, 71%) as a white solid; δ_H ^{1}H NMR ($CDCl_3$, 250 MHz) 1.20-1.30 (4H, m, 2-H, 3-H) 1.96 (1H, m, 1-H) 2.36 (3H, s, CH_3) 3.85 (2H, d, *J* 2.1, 4-H) 7.20 (2H, d, *J* 8.3, Ph) 7.60 (2H, d, *J* 8.3, Ph); δ_C ^{13}C NMR ($CDCl_3$, 100.6 MHz) 22.1 (CH_3, Me), 23.2 (CH_2), 26.2 (CH_2), 37.0 (CH_2), 70.7 (CH_2), 128.3 (2 CH, Ph), 130.3 (2 CH, Ph), 133.2 (C, Ph), 145.3 (C, Ph); *m/z* (EI) 453 (M^+, 50%), 281 (100), 137 (73), (found M^+, 453.14041. $C_{22}H_{29}O_6S_2$ requires 265.1136).

***Endo*-5, 6-bis(hydroxymethyl)bicyclo[2.2.2]oct-2-ene[149] (113).**



112 113

$LiAlH_4$ (1.25 g, 32.9 mmol) was suspended in dry THF (20 mL) and cooled to 0 °C. *Endo*-bicyclo[2.2.2]oct-2-ene-5, 6-dicarboxylic anhydride **112** (3.15 g, 17.7 mmol) was added steadily, drop-wise as a solution of anhydrous THF (30 mL) and the mixture refluxed for 16 hours. After cooling to 0 °C, the reaction was quenched with saturated aqueous sodium sulphate solution. The filtered salts were washed with THF and diethyl ether then the filtrate evaporated under reduced pressure to give *endo*-5, 6-bis(hydroxymethyl)bicyclo[2.2.2]oct-2-ene **113** as a yellow oil (2.9 g, 98%); δ_H ^{1}H NMR ($CDCl_3$, 300 MHz) 1.30 (2H, dm, *J* 8.9, 7-H_b), 1.70 (2H, dm, *J* 8.9, 7-H_a), 2.15 (2H, m, 5-H), 2.35 (2H, m, 1-H), 3.40 (2H, dm, *J* 10.7, C*H*H-OH), 3.50 (2H, dm, *J* 10.7, C*H*H-OH), 4.50 (2H, s, OH), 6.05 (2H, m, 2-H); δ_C ^{13}C NMR ($CDCl_3$, 75 MHz) 25.8 (2 CH_2, 7C), 34.8 (2 CH, 1C), 45.8 (2 CH, 5C), 65.4 (2 CH_2O), 133.0 (2 CH, 2C);

MS: +EI, M+ = 168 daltons, FAB, MH+ = 169 daltons, ionisation insufficient for accurate mass analysis.

***Endo*-5, 6-bis(chloromethyl)bicyclo[2.2.2]oct-2-ene (114).**

113 114

Thionyl chloride (4.6 mL, 63 mmol) was added cautiously to *endo*-5, 6-bis(hydroxymethyl)bicyclo[2.2.2]oct-2-ene **113** (1.0 g, 6.0 mmol) at 0 °C and the mixture subsequently refluxed for 30 minutes. Removal of excess thionyl chloride under reduced pressure gave a crude product which was purified by flash chromatography (60-80 °C petrol, neat to start then increasing concentration of diethyl ether added) to yield *endo-5, 6-bis(chloromethyl)bicyclo[2.2.2]oct-2-ene* **114** as a yellow oil (1.0 g, 83%);. FTIR (cm^{-1}): 3020.0, 2938.4, 1215.3, 960.0, 854.2, 757.8, 668.1; δ_H ^1H NMR ($CDCl_3$, 300 MHz) 1.30 (2H, dm, *J* 8.6, 7-H_b), 1.62 (2H, dm, *J* 8.6, 7-H_a), 2.43 (2H, dm, *J* 3.8, 5-H), 2.52 (2H, m, 1-H), 3.66 (2H, dm, *J* 12.4, CH*H*Cl), 4.79 (2H, tm, *J* 12.4, CH*H*Cl), 6.20 (2H, m, 2-H); δ_C ^{13}C NMR ($CDCl_3$, 75 MHz) 25.1 (2 CH_2, 7-C), 33.5 (2 CH, 1-C), 44.8 (2 CH, 5-C), 63.7 (2 CH_2Cl), 133.0 (2 CH, 2-C); MS and accurate mass analysis: insufficient ionisation for analysis.

***Endo*-5, 6-Bis[methylene(*p*-toluenesulphonate)]bicyclo[2.2.2]oct-2-ene[150] (118).**

113 118

Endo-5, 6-bis(hydroxymethyl)bicyclo[2.2.2]oct-2-ene **113** (500 mg, 3.0 mmol) was dissolved in anhydrous dichloromethane (2.5 mL). Triethylamine (830 µl, 6.0

mmol) was added and the mixture cooled to 0 °C. *p*-Toluenesulphonyl chloride (1.13 g, 6.0 mmol) was added steadily, drop-wise as a solution of dry dichloromethane (2.5 mL) and the reaction warmed to room temperature. After stirring for 16 hours, the crude reaction mixture was diluted with dichloromethane (10 mL) and washed with water (5 mL). The aqueous phase was extracted with dichloromethane (10 mL) and the combined organic phases were washed successively with 1M aqueous HCl solution (10 mL), 5% aqueous sodium bicarbonate solution (10 mL) and brine (10 mL). The organic phase was then dried with magnesium sulphate and evaporated *in vacuo*. Crude yield 1.0g. After column chromatography (petroleum ether : diethyl ether 7:1) only 15 mg of the desired bis-tosylate product **118** were retrieved, the majority of the reaction appeared to have given a mono-tosylate product. δ_H ^{1}H NMR ($CDCl_3$, 250 MHz) 1.20-1.50 (4H, m, 7-H), 2.10-2.50 (4H, m, 1-H, 4-H, 5-H, 6-H), 2.40 (6H, m, CH_3), 3.50 (2H, tm, *J* 9.1, C*H*HOH), 3.74 (2H, dd, *J* 9.1, 5.6, C*H*HOH), 5.94 (2H, m, 2-H and 3-H), 7.34 (4H, d, *J* 8.3, Ph) 7.83 (4H, d, *J* 8.3, Ph).

General procedure for formation of ditriflates.[151]

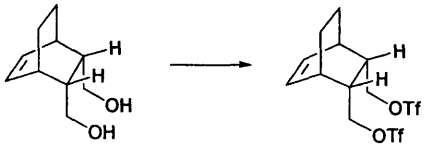
Cis-1, 2-bis(hydroxymethyl)cyclohexane **123** and *endo*-5, 6-bis(hydroxymethyl)-bicyclo[2.2.2]oct-2-ene **124** were both converted to the corresponding ditriflates as follows. In each case the corresponding diol precursor (1.9 mmol) was dissolved in anhydrous dichloromethane (15 mL) and pyridine (1.0 mL, 1.2 mmol) was added at –15 °C. Trifluoromethanesulphonic anhydride (0.6 mL, 3.8 mmol) was then added steadily, drop-wise to each diol solution and stirred at –15 °C for 5 minutes before gradually being allowed to warm to room temperature. After stirring at room temperature for 30 minutes, the solutions had turned pale pink in colour and TLC analysis (diethyl ether/petrol, 1:9) showed incomplete conversion of the alcohols to new products. The reactions were stirred at room temperature for a further 16 hours by which time TLC analysis still showed presence of starting materials. The reactions were worked up as follows: The crude reaction mixtures were washed with water (10 mL) and the aqueous layers were extracted with dichloromethane (10 mL). The combined organic phases were washed with brine (10 mL), dried and evaporated under reduced pressure. Flash chromatography of the crude products in petroleum ether : diethyl ether 6:1 yielded the triflates.

Cis-1, 2-bis(trifluoromethanesulphonate)cyclohexane[151] (123)

109 123

Yield: 193 mg (24%); δ_H ^{1}H NMR ($CDCl_3$, 250 MHz) 0.81 (4H, m, 4-H, 5-H), 1.21-1.72 (4H, m, 3-H, 6-H), 2.21 (2H, m, 1-H, 2-H), 3.63 (2H, m, C*H*HOH), 3.84 (2H, m, C*H*HOH).

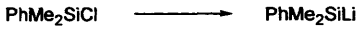
***Endo*-5, 6-bis[methylene-(trifluoromethanesulphonate)]bicyclo[2.2.2]oct-2-ene (124).**



113 124

Yield: 220 mg (27%); R_f = 0.12 (petroleum ether : diethyl ether 9:1); FTIR (cm^{-1}): 3041.6, 2935.1, 2863.6, 1725.2, 1376.0, 1166.6, 1111.1, 1041.6, 926.7, 849.8, 775.5, 719.7; δ_H ^{1}H NMR ($CDCl_3$, 250 MHz) 1.23 (2H, dm, *J* 8.6, 7-H_b), 1.41 (2H, dm, *J* 8.6, 7-H_a), 2.41 (2H, ddm, *J* 2.6, 5.9, 5-H), 2.61 (2H, dm, *J* 2.6, 1-H), 3.31 (2H, ddm, *J* 7.9, 5.9, C*H*HO), 3.83 (2 H, tm, *J* 7.9, C*H*HO), 6.22 (2H, m, 2-H); δ_C ^{13}C NMR ($CDCl_3$, 62.9 MHz) 25.0 (2 CH_2, 7C), 32.9 (2 CH, 1C), 45.7 (2 CH, 5C), 73.5 (2 CH_2O), 134.1 (2 CH, 2C); MS accurate mass analysis: poor ionisation meant analysis not possible.

Preparation of Dimethylphenylsilyl lithium[152] (120).

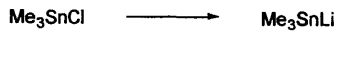


119 120

Lithium wire (3 mm, 15 mmol) was flattened in paraffin and transferred to a reaction vessel under argon. The metal was washed with anhydrous THF (3 x 5 mL)

and suspended in anhydrous THF (6 mL) at –8 °C. Dimethylphenylsilyl chloride **119** (850 mg, 5.0 mmol) was added steadily, drop-wise as a solution of THF (6.5 mL). The mixture was stirred for 16 hours at 8 °C by which time a deep red solution of dimethylphenylsilyl lithium **120** had formed. Quenching of an aliquot of the blood-red solution with water followed by titration against standardised HCl solution showed the solution to have concentration of 0.21 mol dm^{-3}.

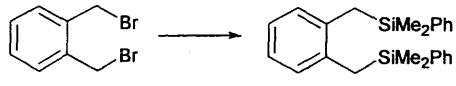
Preparation of Trimethyltin lithium[149] (126).



125 126

Lithium metal (15 cm, 675 mmol) was flattened in paraffin with a hammer and suspended in anhydrous THF under argon. After washing the metal with anhydrous THF three times, the lithium was suspended in 10 mL of the dry solvent. Trimethyltin chloride **125** (2.0 g, 5.1 mmol) was added drop-wise at 0 °C as a solution of THF (10 mL) and after 10 minutes the mixture became green in colour. The reaction was stirred at room temperature for a further two hours then filtered through celite by cannulation under nitrogen. Titration of a quenched portion of the resulting solution against standardised aqueous HCl solution eluded the molarity of the olive-green solution as 0.55 mol dm^{-3}.

Preparation of α,α'-bis(dimethylphenylsilyl)-*o*-xylene (134).



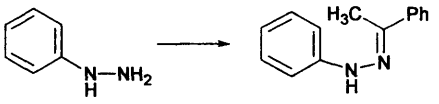
127 134

Dimethylphenylsilyl lithium solution **120** (13 mL, 0.178 M in THF, 2.3 mmol) was added to α,α'-dibromo-*o*-xylene **127** (200 mg, 0.75 mmol) steadily, drop-wise at 0 °C and then stirred at room temperature for 24 hours. The reaction mixture was then concentrated by removal of solvents *in vacuo* and the crude product partitioned between diethyl ether (20 mL) and dilute aqueous HCl solution (10 mL). The aqueous layer was separated and extracted with diethyl ether (20 mL) and the combined ethereal layers

were dried and evaporated under reduced pressure. Flash chromatography in neat 40-60 °C petrol gave *α,α'-bis(dimethylphenylsilyl)-o-xylene* **134** as a (50 mg, 17%); δ_H ^{1}H NMR ($CDCl_3$, 250 MHz) 0.22 (12H, s, 4 CH_3), 2.03 (2CH_2, s, 1 H), 6.70-7.01 (4H, m, Ph), 7.31-7.52 (10H, m, Ph); δ_C ^{13}C NMR ($CDCl_3$, 62.9 MHz) 2.6 (4 CH_3, Me) 23.7 (2 CH_2, 1C) 124.6, 128.2, 129.4, 129.7 and 134.0 (14 aromatic CH) 137.0 and 139.5 (4 quaternary aromatic C) *m/z* 374 (M^+, 60), 224 (55), 209 (40), 162 (75), 135 (100), 107 (50), (found M^+, 374.18860. $C_{24}H_{30}Si_2$ requires 374.18861).

SYNTHESIS OF HYDRAZONES.

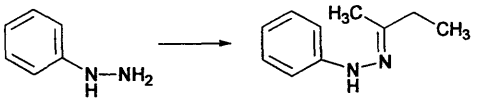
Acetophenone phenylhydrazone[153] (146).



149 146

A solution of phenylhydrazine **149** (5.495 g, 50.8 mmol) in glacial acetic acid (10 mL) and water (10 mL) was added to a solution of acetophenone (4.12 g, 34.3 mmol) in glacial acetic acid (20 mL) contained in a boiling tube. The mixture was cooled in ice and shaken for 5 minutes, colourless crystals of hydrazone precipitated. The product was filtered, washed with dilute acetic acid and water to yield the acetophenone phenylhydrazone **146** as a colourless crystals (3.45 g, 48%); δ_H (250 MHz; $CDCl_3$) 2.41 (3H, s, CH_3), 7.10 (1H, m), 7.42-7.73 (8H, m), 8.0 (1H, m).

Butanone phenylhydrazone[154] (298).

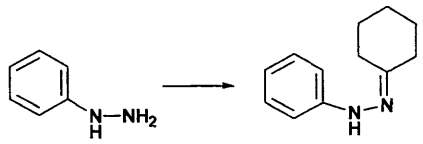


149 298

Phenylhydrazine **149** (1.08 g, 0.01 mol) was added to a solution of methyl-ethyl-ketone (0.78 g, 0.01 mol) in toluene (10 mL) and glacial acetic acid (5 mL) in a 50 mL rounded bottom flask. The mixture was refluxed for 3 hours at 95°C. Then toluene and

acetic acid were removed under pressure to yield butanone phenylhydrazone **298** (1.68 g, 80%) as a brown solid, the product unstable in air and so is used immediately.

Cyclohexanone-phenylhydrazone[155] (300).



149 300

In the same way phenylhydrazine **149** (1.08 g, 0.01 mol) and cyclohexanone (0.98 g, 0.01 mol) gave cyclohexanone-phenylhydrazone **300** as a brown solid (1.12 g, 60%); δ_H (250 MHz; $CDCl_3$) 1.90-2.02 (6H, m, 3-H and 4-H), 2.52-2.72 (4H, m, 2-H), 7.01 (1H, m, Ph), 7.30 (2H, m, Ph), 7.50 (2H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 25.7 (CH_2, 4-C), 27.4 (CH_2, 3C), 35.7 (CH_2, 2C), 113.3 (2CH, 6C), 119.9 (CH, 5C), 129.5 (2CH, 7C), 146.4 (C, 8C), 151.5 (C, 1C); *m/z* (EI) 189 (M^+, 50), 102 (100).

SYNTHESIS OF INDOLES FROM PHENYLHYDRAZONES.

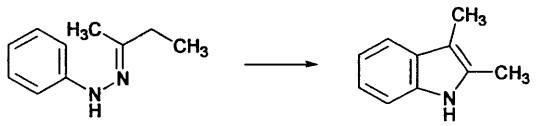
2-Phenylindole (147).

146 147

To choline chloride.$2ZnCl_2$ ionic liquid (1.85 g, 4.53 mmol) was added acetophenone phenylhydrazone **146** (318 mg, 1.51 mmol) at room temperature. The mixture was heated at 95°C for 4 hours. Then direct sublimation from the ionic liquid of the product gave 2-phenylindole **147** as a yellow crystals (267 mg, 91%); δ_H (250 MHz; $CDCl_3$) 6.82 (1H, s), 7.09-7.22 (2H, m), 7.25-7.48 (4H, m), 7.55-7.67 (3H, m) 8.28 (1H, s, br, NH); δ_C (62.9 MHz; $CDCl_3$) 100.4 (CH, 3C), 111.3 (CH, 7C) 120.7 (CH, 4C), 121.1 (CH, 6C), 122.8 (CH, 5C), 125.6 (2 CH, Ph), 128.1 (CH, Ph), 129.5 (2

CH, Ph), 129.7 (C, 3_a-C), 132.8 (C, Ph), 137.3 (C, 7_a-C), 138.3 (C, 2-C); *m/z* (EI) 193 (M^+, 100), 165 (20), 89 (20), Mp 186° (lit.[156] Mp 186.5-187.5°).

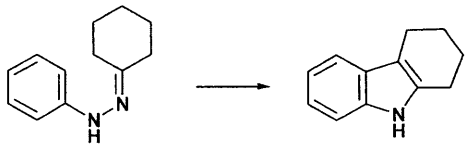
2,3-Dimethylindole (273).



272 307

In the same way as for the preparation of 2-phenylindole **147** above at 95°C for 1 hour in choline chloride.$2ZnCl_2$ ionic liquid (2.77 mmol), butanone phenylhydrazone **272** (300 mg, 1.84 mmol) gave 2,3-dimethylindole **307** as a yellow crystals (150 mg, 56%).

1,2,3,4-Tetrahydrocarbazole[156] (308).

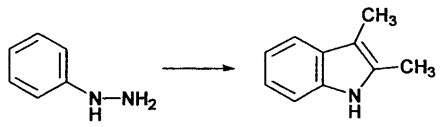


300 308

In the same way as for the preparation of 2-phenylindole **147** above for 4 hours at 150°C in choline chloride.$2ZnCl_2$ ionic liquid (5.52 mmol) cyclohexanone phenylhydrazone **300** (200 mg, 1.84 mmol) gave 1,2,3,4-tetrahydrocarbazole **308** as a white crystals (120 mg, 38%).

ONE POT REACTION WITH 3 EQ. OF ChCl.2ZnCl$_2$.

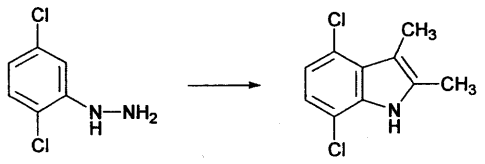
2,3-Dimethylindole (273).



149 273

To choline chloride.2ZnCl$_2$ ionic liquid (3.406 g, 8.31 mmol) were added ethyl-methyl-ketone **298** (194 mg, 2.77 mmol) and phenylhydrazine **149** (300 mg, 2.77 mmol) at room temperature. The mixture was heated at 95°C for 1 hour. Then direct sublimation from the ionic liquid of the product gave 2,3-dimethylindole **273** as a yellow crystals (320 mg, 80%); δ_H (250 MHz; $CDCl_3$) 2.18 (3 H, s, CH_3) 2.26 (3 H, s, CH_3) 7.05 (2 H, m, $2H_{aromatics}$) 7.15 (1 H, m, $H_{aromatic}$) 7.38 (1 H, m, $H_{aromatic}$) 7.50 (1 H, s, br, N*H*); δ_C (62.9 MHz; $CDCl_3$) 8.8 (CH_3) 11.9 (CH_3) 107.5 (C, 3-C) 110.4 (CH, 7-C) 118.3 (CH, 4-C) 119.4 (CH, 6-C) 121.3 (CH, 5-C) 129.8 (C, 3_a-C) 131.0 (C, 2-C) 135.6 (C, 7_a-C); *m/z* (EI) 145 (M^+, 60), 144 (100), 130 (50); Mp 105-107° (lit.[156] Mp 107°). Anal. Found: C, 82.45; H. 9.52; N, 9.74. $C_{10}H_{11}N$ requires C, 83; H, 7.5; N, 9.65.

4,7-Dichloro-2,3-dimethylindole (313).

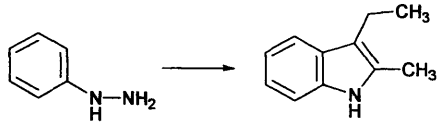


312 313

In the same way as for the preparation for 2,3-dimethylindole **273** above at 95°C for 4 hours in choline chloride.2ZnCl$_2$ ionic liquid (1.38 g, 3.39 mmol), ethyl-methyl-ketone **314** (82 mg, 1.13 mmol) and 2,5-dichloro-phenylhydrazine **312** (200mg, 1.13mmol) gave 4,7-dichloro-2,3-dimethylindole **313** as a white crystals (200 mg, 72%); δ_H (250 MHz; $CDCl_3$) 2.30 (3H, s CH_3), 2.40 (3H, s, CH_3), 6.90 (1H, d, *J* 8.2, 5-H or 6-H), 6.96 (1H, d, *J* 8.2, 5-H or 6-H), 7.95 (1H, s, br, NH); δ_C (62.9 MHz; $CDCl_3$)

10.8 (CH_3), 11.8 (CH_3), 109.4 (C, 3C), 114.6 (C, 7C), 120.8 (CH, 6C or 5C), 120.9 (CH, 6C or 5C), 124.7 (C, 4C), 127.6 (C, 3_aC), 133.1 (C, 2C), 133.6 (C, 7_aC); *m/z* (EI) 213 (M^+, 70), 212 (100), 198 (60); Mp 89-90° (lit.[157] Mp 90-91°).

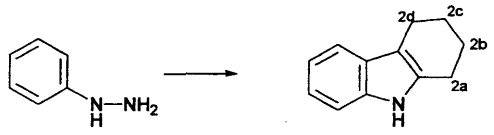
3-Ethyl-2-methylindole (315).



149 315

In the same way as for the preparation for 2,3-dimethylindole **273** above at 95°C for 4 hours in choline chloride.$2ZnCl_2$ ionic liquid (2.77 mmol), 2-pentanone **314** (232 mg, 2.77 mmol) and phenylhydrazine **149** (300 mg, 2.77 mmol) gave 3-ethyl-2-methylindole **315** as a white crystals (205 mg, 48%); δ_H (250 MHz; $CDCl_3$) 1.20 (3H, t, *J* 6.2, CH_3), 2.29 (3H, s, CH_3), 2.69 (2H, q, *J* 6.2, CH_2), 7.0-7.60 (5H, m, 4 $H_{aromatics}$ and NH); δ_C (62.9 MHz; $CDCl_3$) 11.4 (CH_3), 15.4 (CH_3), 17.3 (CH_2), 110.2 (CH, 7C), 113.9 (C, 3C), 118.1 (CH, 4C), 118.9 (CH, 6C), 120.7 (CH, 5C), 128.5 (C, 3_aC), 130.1 (C, 2C), 135.3 (C 7_aC); *m/z* (EI) 159 (M^+, 30), 144 (100); Mp 43-44° (lit.[160] Mp 44-45°).

1,2,3,4-Tetrahydrocarbazole (308).

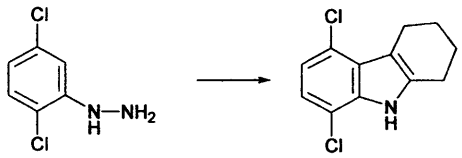


149 308

To choline chloride.$2ZnCl_2$.ionic liquid (3.406 g, 8.31 mmol) were added cyclohexanone **299** (271 mg, 2.77 mmol) and phenylhydrazine **149** (300 mg, 2.77 mmol) at room temperature. The mixture was heated at 95°C for 4 hour. Then direct sublimation from the ionic liquid of the product gave 1,2,3,4-tetrahydrocarbazole **308** (245 mg, 55%) as a white crystals. Then work up of the ionic liquid with water gave white solid which were filtered off in a buchner funnel. Sublimation of the white solid gave 1,2,3,4-tetrahydrocarbazole **308** as a white crystals (120 mg, 27%). Total yield

82%. δ_H (250 MHz; $CDCl_3$) 2.10 (4H, m, 2_a-H and 2_d-H), 2.90 (4H, m, 2_b-H and 2_c-H), 7.15 (2H, 2 dt, *J* 7.03, 13.5, 5-H and 6-H), 7.30 (1H, d, *J* 7.6, 7-H), 7.52 (1H, d, *J* 7.89, 4-H); δ_C (62.9 MHz; $CDCl_3$) 21.4 (CH_2), 23.7 (CH_2), 23.7 (CH_2), 110.6 (C, 3C), 110.8 (CH, 7C), 118.2 (CH, 4C), 119.5 (CH, 6C), 121.4 (CH, 5C), 128.3 (C, 3_aC), 134.5 (C, 2C), 136.1 (C, 7_aC); *m/z* (EI) 171 (M^+, 40), 143 (100); Mp 117-119° (lit.[156] Mp 118-119°).

5,8-Dichloro-1,2,3,4-tetrahydrocarbazole (316).

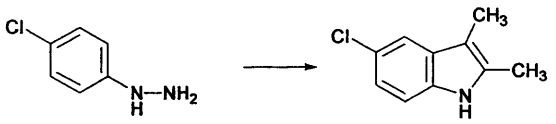


312 316

In the same way as for the preparation for 1,2,3,4-tetrahydrocarbazole **308** above at 95°C for 4 hours choline chloride.$2ZnCl_2$ ionic liquid (1.38 g, 3.39 mmol), cyclohexanone **299** (110 mg, 1.13 mmol) and 2,5-dichloro-phenylhydrazine **312** (200 mg, 1.13 mmol) gave 5,8-dichloro-1,2,3,4-tetrahydrocarbazole **316** as a yellow crystals (155 mg, 59%); δ_H (250 MHz; $CDCl_3$) 1.87 (4H, m, 2 CH_2), 2.75 (2H, m, 2 CH), 3.05 (2H, m, 2 CH), 6.90 (1H, d, *J* 8.2, 5-H or 6-H), 6.96 (1H, d, *J* 8.2, 5-H or 6-H), 7.95 (1H, s, br, NH); δ_C (62.9 MHz; $CDCl_3$) 23.0 (CH_2), 23.3 (CH_2), 23.6 (CH_2), 23.7 (CH_2), 112.1 (C, 3C), 114.8 (C, 7C), 120.7 (CH, 5C or 6C), 120.9 (CH, 5C or 6C), 124.7 (C, 4C), 126.6 (C, 3_aC), 133.9 (C, 2C), 136.2 (C, 7_aC); *m/z* (EI) 239 (M^+, 100), 205 (20), 154 (15); (found 239.0269. $C_{12}H_{11}NCl_2$ requires 239.02685); Mp 90-91° (lit.[162] Mp 91-93°).

ONE POT REACTION with 1 EQ. of ChCl.2ZnCl$_2$.

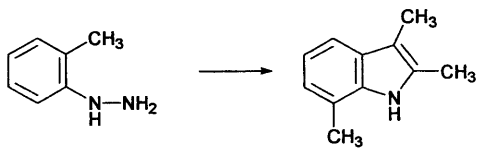
5-Chloro-2,3-dimethylindole (328).



327 328

In the same way as for the preparation for 1,2,3,4-tetrahydrocarbazole **308** above at 120°C for 2 hours in choline chloride.2$ZnCl_2$ ionic liquid (455 mg, 1.11 mmol), ethylmethylketone **298** (81 mg, 1.11 mmol) and 4-chloro-phenylhydrazine hydrochloride **327** (200 mg, 1.11 mmol) gave 5-chloro-2,3-dimethylindole **328** as a white crystals (221 mg, 88%); δ_H (250 MHz; $CDCl_3$) 2.18 (3H, s, CH_3), 2.3 (3H, s, CH_3), 7.01 (1H, dd, *J* 8.5, 1.8, 6-H), 7.08 (1H, d, *J* 8.5, 7-H), 7.4 (1H, d, *J* 1.8, 4-H); δ_C (62.9 MHz; $CDCl_3$) 8.75 (CH_3), 11.96 (CH_3), 107.46 (C, 3C), 111.36 (CH, 7C), 117.92 (CH, 4C), 121.37 (CH, 6C), 125.1 (C, 5C), 131.04 (C, 3_aC), 132.77 (C, 2C), 139.92 (C, 7_aC); *m/z* (EI) 179 (M^+, 70), 178 (100), 164 (55); Mp 142-143° (lit.[158] Mp 141-142°).

2,3,7-Trimethylindole (332).

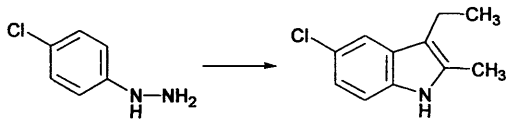


331 332

In the same way as for the preparation for 1,2,3,4-tetrahydrocarbazole **308** above at 120°C for 3 hours in choline chloride.2 $ZnCl_2$ ionic liquid (521 mg, 1.26 mmol), ethylmethylketone **298** (91 mg, 1.26 mmol) and o-tolylhydrazine hydrochloride **331** (200 mg, 1.26 mmol) gave 2,3,7-trimethylindole **332** as a yellow crystals (140 mg, 71%); 53% after sublimation and 18% after work-up and sublimation; δ_H (250 MHz; $CDCl_3$) 2.15 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.32 (3H, s, CH_3), 6.82 (1H, d, *J* 7.12, 6-H), 6.92 (1H, t, *J* 7.57, 5-H), 7.24 (1H, d, *J* 7.80, 4-H); δ_C (62.9 MHz; $CDCl_3$) 7.5 (CH_3), 10.5 (CH_3), 15.5 (CH_3), 106.6 (C, 3C), 114.7 (C, 7C), 118.1 (CH, 4C), 118.2

(CH, 6C), 120.6 (CH, 5C), 127.9 (C, 3_aC), 129.2 (C, 2C), 133.6 (C, 7_aC); *m/z* (EI) 159 (M^+, 70), 158 (100), 144 (40); Mp 75-76° (lit.[159] Mp 76-77°).

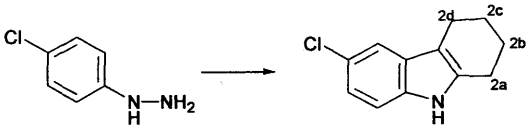
5-Chloro-3-ethyl-2-methylindole (329).



327 329

In the same way as for the preparation for 1,2,3,4-tetrahydrocarbazole **308** above at 120°C for 2 hours choline chloride.2$ZnCl_2$ ionic liquid (455 mg, 1.11 mmol), 2-pentanone **314** (96 mg, 1.11 mmol) and 4-chlorophenylhydrazine hydrochloride **327** (200 mg, 1.11 mmol) gave 5-chloro-3-ethyl-2-methylindole **329** as a white crystals (145 mg, 64%); δ_H (250 MHz; $CDCl_3$) 1.19 (3H, t, *J* 7.5, CH_3), 3.34 (3H, s, CH_3), 2.65 (2H, q, *J* 7.5, CH_2), 7.02 (1 H, dd, *J* 8.5, 1.8, 6-H), 7.12 (1H, d, *J* 8.5, 7-H), 7.45 (1H, s, 4-H), 7.64 (1H, s, br, NH); δ_C (62.9 MHz; $CDCl_3$) 11.9 (CH_3), 15.6 (CH_3), 17.6 (CH_2), 111.43 (CH, 7C), 114.3 (C, 3C), 118.0 (C, 4C), 121.3 (CH, 6C), 125.1 (C, 5C), 130.1 (C, 3_aC), 132.2 (C, 2C), 134.0 (C, 7_aC); *m/z* (EI) 193 (M^+, 30), 180 (30), 178 (100); Mp 74-75° (lit.[161] Mp 76°).

6-Chloro-1,2,3,4-tetrahydrocarbazole (330).

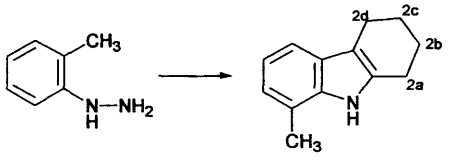


327 330

In the same way as for the preparation for 1,2,3,4-tetrahydrocarbazole **308** above at 120°C for 2 hours in choline chloride.2$ZnCl_2$ ionic liquid (455 mg, 1.11 mmol), cyclohexanone **299** (98 mg, 1.11 mmol) and 4-chloro-phenylhydrazine hydrochloride **327** (200 mg, 1.11mmol) gave 6-chloro-1,2,3,4-tetrahydrocarbazole **330** as a white crystals (190 mg, 84%); δ_H (250 MHz; $CDCl_3$) 1.90 (4H, m, 2_b-H and 2_c-H), 2.67 (4H, m, 2_a-H and 2_d-H), 7.03 (1H, dd, *J* 2.1, 8.5, 6-H), 7.15 (1H, d, *J* 8.5, 7-H), 7.46 (1H, d, *J*

2.1, 4-H), 7.65 (1H, s, br, NH); δ_C (62.9 MHz; $CDCl_3$) 21.1 (CH_2), 23.4 (CH_2), 23.5 (CH_2), 23.6 (CH_2), 110.5 (C, 3C), 111.6 (CH, 7C), 117.7 (CH, 4C), 121.4 (CH, 6C), 125.1 (C, 5C), 129.4 (C, 3_aC), 134.4 (C, 2C), 136.1 (C, 7_aC); *m/z* (EI) 205 (M^+, 30), 179 (30), 177 (100); Mp 147-148° (lit.[156] Mp 146-147°).

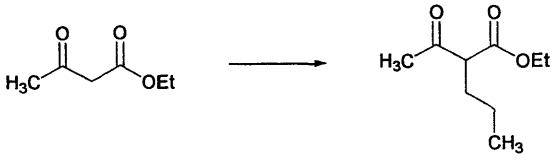
8-Methyl-1,2,3,4-tetrahydrocarbazole (333).



331 333

In the same way as for the preparation for 1,2,3,4-tetrahydrocarbazole **308** above at 120°C for 3 hours in choline chloride.$2ZnCl_2$ ionic liquid (521 mg, 1.26 mmol), cyclohexanone **299** (109 mg, 1.26 mmol) and o-tolylhydrazine hydrochloride **331** (200 mg, 1.26 mmol) gave 8-methyl-1,2,3,4-tetrahydrocarbazole **333** as a yellow crystals (180 mg, 76%); 51% after sublimation and 25% after work-up and sublimation; δ_H (250 MHz; $CDCl_3$) 1.90 (4H, m, 2_a-H and 2_d-H), 2.45 (3H, s, CH_3), 2.75 (4H, m, 2_b-H and 2_c-H), 6.80 (1H, d, *J* 7.3, 6-H), 6.90 (1H, t, *J* 7.3, 5-H), 7.20 (1H, d, *J* 7.6, 4-H), 7.50 (1 H, s, br, NH); δ_C (62.9 MHz; $CDCl_3$) 17.0 (CH_3), 21.49 (CH_2), 23.7 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 111.1 (C, 3C), 115.9 (CH, 4C), 119.7 (CH, 5C), 119.8 (C, 7C), 122.1 (CH, 6C), 127.8 (C, 3_aC), 134.1 (C, 2C), 135.5 (C, 7_aC); *m/z* (EI) 185 (M^+, 40), 157 (100); Mp 93-94° (lit.[156] Mp 93-95°).

Ethyl-2-propylacetoacetate[163] (393).



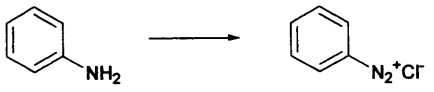
391 393

Sodium ethoxide (3.45 g, 0.5 mol) was added portion wise to an ice-cooled solution of ethylacetoacetate **391** (3 g, 0.23 mol) in dry THF (15 mL). The resulting

mixture was heated to reflux for 1 hour and allowed to cool to room temperature. Propyl bromide (5.6 g, 0.5 mol) was then added, and the mixture was heated to reflux for 3 hours, allowed to cool to room temperature and quenched by addition of water (30 mL). The resulting mixture was then extracted into diethyl-ether (2 x 100 mL) then combined organic layers, washed with saturated sodium chloride solution, dried and the solvent was removed under reduced pressure to give the crude product. Purification by flash chromatography (petroleum ether : diethyl ether 3:1) gave ethyl-2-pro

(3H, t, *J* 7.3, CH_3CH_2), 1.50 (5H, t, *J* 7.1, CH_3CH_2O and $CH_2CH_2CH_3$), 2.00 (2H, m, $CHCH_2CH_2$), 2.40 (3H, s, CH_3CO), 3.64 (1H, t, *J* 7.3, *CH*CO), 4.34 (2H, q, *J* 7.1, OCH_2CH_3); δ_C (62.9 MHz, $CDCl_3$) 14.1 (CH_3), 14.4 (CH_3), 20.9 (CH_2), 28.9 (CH), 30.5 (CH_2), 60.0 (CH_3), 61.5 (CH_2), 170.2 (CO), 203.5 (CO).

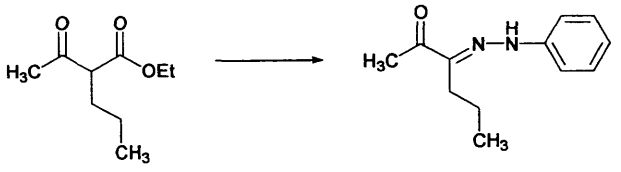
Benzenediazonium chloride[164] (355).



355

Aniline (539 mg, 5.8 mmol) 3 mL of concentrated hydrochloric acid in 6 mL of water and sodium nitrate was stirred at 0°C for 1 hour, then was ready for the next reaction.

3-(Phenylhydrazone)hexan-2-one (395).

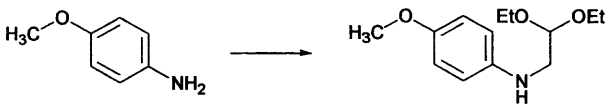


394 395

8 mL of 50% aqueous potassium hydroxide was added to an ice-cold solution of ethyl-2-propylacetoacetate **394** (1 g, 5.81 mmol) in 5 mL of ethanol. The mixture was then diluted with 10 mL of ice-water and the cold diazonium salt solution was added.

Stirring was continued for 5 minutes and 3-(phenylhydrazone)hexan-2-one **395** was collected by filtration as a red solid (20 mg, 2%); δ_H (250 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7.3, CH_3CH_2), 1.80 (2H, quintet, *J* 7.4, CH_3CH_2), 2.70 (3H, s, CO), 2.82 (2H, t, *J* 7.4, CH_2CH_2C=), 7.61 (5H, m, Ph).

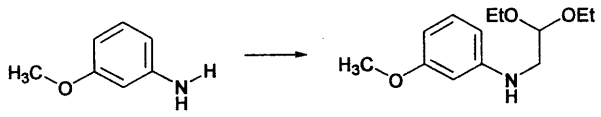
(2,2-Diethoxyethyl)-(4-methoxyphenyl)amine (409).



409 410

4-Methoxyaniline **409** (1 g, 7.29 mmol), bromoacetaldehyde diethylacetal **363** (1.43 g, 7.29 mmol), sodium carbonate (0.77 g, 7.29 mmol) and n-butanol (5 mL) were heated under reflux in a nitrogen atmosphere with the exclusion of moisture for 3 days. The reaction mixture was filtered and the butanol was removed under reduced pressure to give a brown liquid. This product was dissolved in ether (100 mL), washed with water (2 x 75 mL), the ether layer was dried and the ether was removed under reduced pressure to give a brown liquid. The crude product was chromatographed on a column of silica gel prepare in petroleum ether : diethyl ether (5:1) to yield *(2,2-diethoxyethyl)-(4-methoxyphenyl)amine* **410** as a yellow oil (1.1 g, 63%); δ_H (300 MHz, $CDCl_3$) 1.21 (6H, t, *J* 7.11, 4-H), 3.20 (2H, d, *J* 5.5, CH_2-N), 3.55 (2H, dq, *J* 7, 9.3, C*H*H-CH_3), 3.70 (2H, dq, *J* 7, 9.3, C*H*-CH_3), 3.75 (3H, s, OCH_3), 4.68 (1H, t, *J* 5.5, 2-H), 6.53 (2H, d, J_{ortho} 9.2, 2'-H), 6.70 (2H, d, J_{ortho} 9.2, 3'-H); δ_C (75 MHz, $CDCl_3$) 15.7 (2 CH_3, 4-C), 47.8 (CH_2, 1C), 56.1 (CH_3, OCH_3), 62.7 (2 CH_2, 3C), 101.4 (CH, 2C), 114.9 (2CH, 2'C) 115.3 (2 CH, 3'C), 124.6 (C, 1'C), 152.7 (C, 4'C); (found 239.15213. $C_{13}H_{21}NO_3$ requires 239.15214).

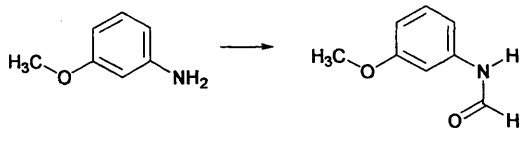
(2,2-Diethoxyethyl)-(3-methoxyphenyl)amine[106] (412).



402 412

3-Methoxyaniline **402** (1.202 g, 8.77 mmol), bromo-acetaldehyde diethylacetal **363** (1.73 g, 8.77 mmol), sodium carbonate (0.93 g, 8.77 mmol) and n-butanol (5 mL) were heated under reflux in a nitrogen atmosphere with the exclusion of moisture for 3 days. The reaction mixture was filtered and the butanol was removed under reduced pressure to give a brown liquid. This product was dissolved in ether (100 mL), washed with water (2 x 75 mL), the ether layer was dried and the ether was removed under reduced pressure to give a brown liquid. The crude product was chromatographed on a column of silica gel prepare in petroleum ether : diethyl ether (4:1) to yield (2,2-diethoxyethyl)-(3-methoxyphenyl)amine **412** as a yellow oil (1.77 g, 79%); δ_H (300 MHz, $CDCl_3$) 1.20 (6H, t, *J* 7, CH_3-CH_2), 3.45 (2H, d, *J* 4.9, CH_2-N), 3.50 (2H, dq, *J* 7, 9.3, *CH*H-CH_3), 3.70 (2H, dq, *J* 7, 9.3, *CH*H-CH_3), 3.80 (3H, s, OCH_3), 4.10 (1H, s, *H*-N), 4.60 (1H, t, *J* 4.9, *CH*-OEt), 6.30 (3H, m, Ph), 7.11 (1H, t, *J* 8.5, Ph); δ_C (75 MHz, $CDCl_3$) 15.7 (2 CH_3, CH_3CH_2), 54.9 (CH_2, CH_2N), 55.4 (CH_3, CH_3O), 63.5 (2 CH_2, CH_2O), 98.3 (CH, Ph), 100.8 (CH, Ph), 101.3 (CH, *CH*N), 104.9 (CH, Ph), 130.4 (CH, Ph), 149.7 (C, Ph), 161.2 (C, Ph); *m/z* (EI) 239 (M^+, 20), 136 (90), 103(100), 75 (77).

_N_-(3-Methoxyphenyl)formamide[106] (404).

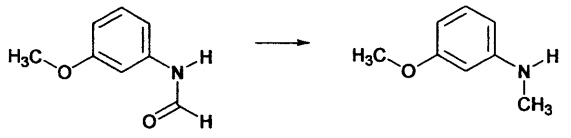


402 404

A mixture of 3-methoxyaniline **402** (2.55 g, 20 mmol) and formic acid (98%, 8 mL) was refluxed for 1 hour. The excess of formic acid was removed under reduced pressure to leave a faint yellow thick pasty mass. It was triturated with 10% ice-cold dil HCl (10 mL), and then washed with water. The solid residue was taken up in ether, the solution dried and the solvent removed under reduced pressure to give an almost colourless paste which solidified on standing to give *N*-(3-methoxyphenyl)formamide **404** in quantitative yield. The paste was recrystallised from CCl_4 to give *N*-(3-methoxyphenyl)formamide **404** as a colourless thin plates (2.56 g, 85%), M.p. 52-53°, (lit 51-52°); δ_H (250 MHz, $CDCl_3$) 3.80 (3H, s, OCH_3), 7.02 (1H, dd, *J* 0.95, 8.03, Ph), 7.22 (3H, m, Ph), 7.81 (1H, s, H-N), 8.35 (1H, d, *J* 1.38, HCO); δ_C (62.9 MHz, $CDCl_3$) 55.0 (CH_3, OCH_3), 106.3 (CH, Ph), 110.9 (CH, Ph), 112.5 (CH, Ph), 130.9 (CH, Ph),

138.3 (C, Ph), 160.4 (C, Ph), 163.6 (CH, HCO); *m/z* (EI) 151 (M^+, 100), 123 (80), 94 (65), 93 (50).

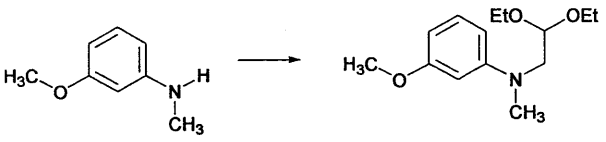
N-Methyl-3-methoxyaniline[106] (405).



404 405

N-(3-Methoxyphenyl)formamide **404** (2.56 g, 17.1mmol) was taken up in dry ether (100mL). $LiAlH_4$ (0.625 g, 16.4mmol) in excess was quickly added and the whole was heated under reflux on a water-bath with the exclusion of moisture for 8 hr. The excess of $LiAlH_4$ was decomposed with wet-ether (100 mL), and the mixture was treated with ice-cold 10% H_2SO_4 (100 mL). The aqueous layer was basified and extracted with ether (3 x 100 mL). The ether extract was separated, washed with water, dried and the ether removed under reduce pressure to leave *N*-methyl-3-methoxyaniline **405** almost colourless liquid (1.202 g, 51%); δ_H (250 MHz, $CDCl_3$) .3.83 (3H, s, N-CH_3), 3.63 (1H, s, N-H), 3.75 (3H, s, O-CH_3), 6.14 (1H, t, *J* 2.3, 2'-H), 6.25 (2H, m, Ph), 7.07 (1H, t, *J* 8.03, 5'-H); δ_C (62.9 MHz, $CDCl_3$) 31.1 (CH_3N), 55.5 (CH_3O), 98.7 (CH, 6'C), 102.7 (CH, 5'C), 106.1 (CH, 4'C), 130.3 (CH, 2'C), 151.2 (C, 1'C), 161.3 (C, 3'C), *m/z* (EI) 137 (M^+, 100), 136 (65).

(2,2-Diethoxyethyl)-(3-methoxyphenyl)methylamine[106] (406).

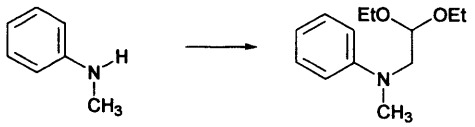


405 406

N-Methyl-3-methoxyaniline **405** (1.202 g, 8.77 mmol), bromoacetaldehyde diethylacetal (1.73 g, 8.77 mmol), sodium carbonate (0.93 g, 8.77 mmol) and n-butanol (5 mL) were heated under reflux in a nitrogen atmosphere with the exclusion of moisture for 3 days. The reaction mixture was filtered and the butanol was removed

under reduced pressure to give a brown liquid. This product was dissolved in ether (100 mL), washed with water (2 x 75 mL), dried and the ether was removed under reduced pressure to give **406** as a brown liquid (1.77 g, 79%); δ_H (300 MHz, $CDCl_3$) 1.20 (6H, t, *J* 7, CH_3CH_2), 3.0 (3H, s, CH_3N), 3.45 (2H, d, *J* 4.9, CH_2N), 3.50 (2H, dq, *J* 7, 9.3, $CHHCH_3$), 3.70 (2H, dq, *J* 7, 9.3, $CHHCH_3$), 3.80 (3H, s, OCH_3), 4.60 (1H, t, *J* 4.9, *CH*OEt), 6.30 (2H, m, Ph), 6.40 (1H, dd, *J* 1.1, 7.6, Ph), 7.10 (1H, t, *J* 8.5, Ph); δ_C (75 MHz, $CDCl_3$) 15.4 (2 CH_3, CH_3CH_2), 39.5 (CH_3, CH_3N), 55.0 (CH_3, CH_3O), 56.1 (CH_2, CH_2N), 63.3 (2 CH_2, CH_2O), 98.3 (CH, Ph), 100.8 (CH, Ph), 101.3 (CH, *CH*N), 104.9 (CH, Ph), 129.7 (CH, Ph), 150.0 (C, Ph), 160 (C, Ph); *m/z* (EI) 253 (M^+, 10), 150 (100), 103 (70), 75 (55).

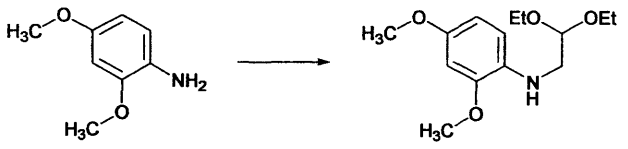
(2,2-Diethoxyethyl)methylphenylamine[106] (409).



408 409

N-Methylaniline **408** (3 g, 28 mmol), bromo acetaldehyde diethylacetal (5.51 g, 28 mmol), sodium carbonate (2.97 g, 28 mmol) and n-butanol (8 mL) were heated under reflux in a nitrogen atmosphere with the exclusion of moisture for 3 days. The reaction mixture was filtered and the butanol was removed under reduced pressure to give a brown liquid. This product was dissolved in ether (100 mL), washed with water (2 x 75 mL), dried and the ether was removed under reduced pressure to give (2,2-diethoxyethyl)methylphenylamine **409** as a brown liquid (4.45 g, 71%); δ_H (300 MHz, $CDCl_3$) 1.20 (6H, t, *J* 7, CH_3CH_2), 3.0 (3H, s, CH_3N), 3.45 (2H, d, *J* 4.9, CH_2N), 3.50 (2H, dq, *J* 7, 9.3, $CHHCH_3$), 3.70 (2H, dq, *J* 7, 9.3, $CHHCH_3$), 4.60 (1H, t, *J* 4.9, *CH*OEt), 6.70 (3H, m, Ph), 7.20 (2H, m, Ph); δ_C (75 MHz, $CDCl_3$) 15.4 ($2CH_3$, CH_3CH_2), 39.3 (CH_3, CH_3N), 56.1 (CH_2, CH_2N), 63.3 ($2CH_2$, CH_2O), 101.0 (CH, *CH*N), 111.7 (2 CH, Ph), 116 (CH, Ph), 129.1 (CH, Ph), 149.1 (C, Ph); *m/z* (EI) 223 (M^+, 20), 120 (100), 103 (80), 75 (65).

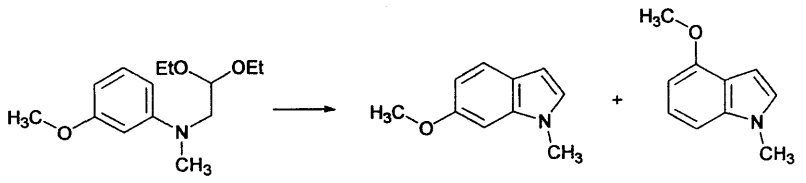
(2,2-Diethoxyethyl)-(2,4-dimethoxyphenyl)amine (414).



413 414

2,4-Dimethoxyaniline **413** (2 g, 13.1 mmol), bromo acetaldehyde diethylacetal (2.57 g, 13.1 mmol), sodium carbonate (1.38 g, 13.1 mmol) and n-butanol (5 mL) were heated under reflux in a nitrogen atmosphere with the exclusion of moisture for 3 days. The reaction mixture was filtered and the butanol was removed under reduced pressure to give a brown liquid. This product was dissolved in ether (100 mL), washed with water (2 x 75 mL), dried and the ether was removed under reduced pressure to give a brown liquid. The product was purified by flash chromatography (3:1 petroleum ether : diethyl ether) to yield *(2,2-diethoxyethyl)-(2,4-dimethoxyphenyl)amine* **414** as a yellow oil (2.7 g, 79%); δ_H (300 MHz, $CDCl_3$) 1.20 (6H, t, *J* 7, CH_3CH_2), 3.20 (2H, d, *J* 5.5, CH_2N), 3.50 (2H, dq, *J* 7, 9.3, *CH*HCH$_3$), 3.70 (2H, dq, *J* 7, 9.3, *CH*HCH$_3$), 3.74 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.10 (1H, s, *H*N), 4.70 (1H, t, *J* 5.5, *CH*OEt), 6.35 (1H, d, *J* 2.64, 3-H_{Ph}), 6.42 (1H, dd, *J* 2.64, 8.5, 5H_{Ph}), 6.55 (1H, d, *J* 8.5, 6-H_{Ph}); δ_C (75 MHz, $CDCl_3$) 15.7 (2 CH_3, CH_3CH_2), 47.3 (CH_2, CH_2N), 56.1 (CH_3, CH_3O), 57.0 (CH_3, CH_3O), 62.7 (2 CH_2, CH_2O), 99.5 (CH, Ph), 101.6 (CH, *CH*N), 103.9 (CH, Ph), 110.9 (CH, Ph), 132.5 (C, Ph), 148.6 (C, Ph), 152.5 (C, Ph); *m/z* (EI) 269 (M^+, 25), 166 (100), 151 (55), 103 (70), 75 (85), (found 269.1626 $C_{14}H_{23}NO_4$ requires 269.1627).

6-methoxy-1-methylindole[106] (416) and 6-methoxy-1-methylindole[106] (417).



414 416 417

To choline chloride.2$ZnCl_2$ ionic liquid (326 mg, 0.79 mmol) was (2,2-diethoxyethyl)-(3-methoxyphenyl)methylamime **414** (200 mg, 0.79 mmol) at room temperature. The reaction was heated at 100°C for 6 hours, then water (5 mL) was added and the mixture was extracted continuously with CH_2Cl_2. The crude product was purified by flask-chromatography petroleum ether : diethylether (4:1) to yield 6-methoxy-1-methylindole **416** as a yellow oil (15 mg, 11%) and 6-methoxy-1-methylindole **417** as a white solid (17 mg, 13%); δ_H (300 MHz, $CDCl_3$) **416** 3.70 (3H, s, NCH_3), 3.90 (3H, s, OCH_3), 6.40 (1H, dd, *J* 0.9, 3.3, 3-H), 6.78 (1H, d, *J* 0.6, 2.3, 7-H), 6.79 (1H, dd, *J* 2.3, 9.3, 5-H), 6.95 (1H, dd, *J* 3.2, 0.6, 2-H), 7.50 (1H, d, *J* 9.4, 4-H); δ_C (300 MHz, $CDCl_3$) 33.0 (CH_3, NCH_3), 56.0 (CH_3, OCH_3), 93.3 (CH, 5C), 102.2 (CH, 3C), 111.1 (CH, 7C), 124.3 (CH, 4C), 130.5 (CH, 2C); *m/z* (EI) 161 (M^+, 100), 146 (90), 118 (80); **417** δ_H (300 MHz, $CDCl_3$) 3.8 (3 H, s, NCH_3), 4.0 (3H, s, OCH_3), 6.52 (1H, d, *J* 7.6, 7-H), 6.6 (1H, dd, *J* 3.2, 3-H), 6.96 (2H, m, 2-H and 5-H), 7.15 (1H, t, *J* 8.2, 6-H); δ_C (75 MHz, $CDCl_3$) 34 (CH_3, NCH_3), 57 (CH_3, OCH_3), 97 (CH, 3C), 99 (CH, 7C), 104 (CH, 2C or 5C), 123 (CH, 6C), 127 (CH, 2C or 5C); *m/z* (EI) 161 (M^+, 90), 146 (100), 118 (60).

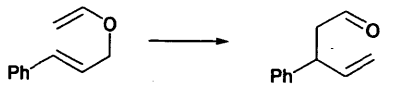
(3-Vinyloxypropenyl)benzene[165] (495).

493 495

3-Phenylprop-2-en-1-ol **493** (51.23 g, 381.8 mmol) and mercuric acetate (6.37 g, 20 mmol) were added to ethyl vinyl ether **494** (195 mL, 1910 mmol). The reaction mixture was then refluxed at 33°C for 24 h. Excess vinyl ether and ethanol formed in the reaction were removed by distillation (under reduced pressure) to give the crude product. Flash-chromatography with petroleum ether : diethyl ether (98:2) as an eluent gave (3-vinyloxypropenyl)benzene **495** as a colourless oil (21.5 g, 35%); δ_H (300 MHz, $CDCl_3$) 3.98 (1H, dd, *J* 6.7, 2, 2′-H_b), 4.18 (1H, dd, *J* 14.3, 2, 2′-H_a), 4.29 (2H, dd, *J* 5.8, 1.2, 3-H_a and 3-H_b), 6.22 (1H, dt, *J* 16.1, 5.8, 2-H), 6.42 (1H, dd, *J* 14.3 6.7, 1′-H), 6.55 (1 H, d, *J* 16.1, 1-H), 7.22 (5H, m, Ph); δ_C (75 MHz, $CDCl_3$) 69.2 (CH_2, 3C), 87.7 (CH_2, 2′C), 125.8 (CH, 2C), 126.9 (2CH, Ph), 128.3 (CH, 1C), 129.0 (2CH, Ph), 133.3

(CH, Ph), 136.9 (C, Ph), 151.8 (CH, 1'C); *m/z* (EI) 160 (M^+, 4), 142 (4), 132 (4), 131 (4), 129 (2),118 (10), 117 (100).

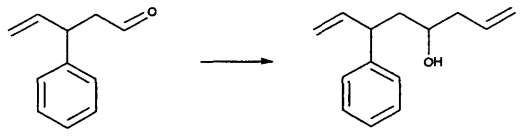
3-phenyl-4-pentenal[166] (496).



495 496

(3-vinyloxypropenyl)benzene **495** (5.20 g, 32.5 mmol) was heated in a Youngs tube under vacuum at 125°C for 22 h. Then the crude product was purified by Kugel Rohr distillation under reduced pressure (200°C; 2 mbar) to give 3-phenyl-4-pentenal **496** as a colourless oil (1.74 g, 33%); δ_H (300 MHz, $CDCl_3$) 2.83 (1H, ddd, *J* 1.7, 7.3 16.6, 2_a-H), 2.91 (1H, ddd, *J* 2, 7.9, 16.6, 2_b-H), 4.00 (1H, dt, *J* 7.3, 7, 3-H), 5.12 (1H, dd, *J* 16.9, 5-H_{trans}), 5.16 (1H, dd, *J* 10.5, 5-H_{cis}), 7.32 (5 H, m, Ph); δ_C (75 MHz, $CDCl_3$) 43.8 (CH, 3C), 48.9 (CH_2, 2C), 115.5 (CH_2, 5C), 127.2 (CH, Ph), 128 (2 CH, Ph), 129.2 (2 CH, Ph), 140 (CH, 4C), 142 (C, Ph), 201 (CHO); *m/z* (EI) 160 (M^+, 32), 142 (9), 131 (12), 117 (100), 91 (34); (found 160.08885. $C_{11}H_{12}O$ requires 160.08882).

***(SS, RR, RS, SR)*-6-Phenyl-1,7-octadien-4-ol (499).**

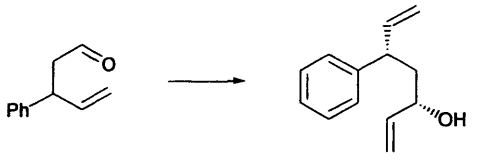


496 499

3-phenyl-4-pentenal **496** (0.260 g, 1.62 mmol) in THF (5 mL) was added drop wise to allyl magnesium bromine 1.3 M in THF (4 mL); while cooling in ice. The reaction progress was followed by TLC (petroleum ether : diethyl ether 2:1). After 4 h the reaction was judged to be complete. The reaction mixture was left to cool to room temperature. Once cooled, a saturated solution of ammonium chloride was added (10 mL). The mixture was extracted with ether (3 x 20 mL), the combined extract was dried and the solvent removed under reduced pressure to give the crude product. Flash

chromatography in eluent (petroleum ether : diethyl ether, 10:1) gave *(SS, RR, RS, SR)-6-Phenyl-1,7-octadien-4-ol* **499** as a yellow oil (0.285 g, 87%); δ_H (300 MHz, $CDCl_3$) 1.63 and 1.74 (1H, br, OH 2 diastereoisomers), 1.85 (2H, m, 5-H_a, 5-H_b), 2.22 (2H, m, 3-H_a, 3-H_b), 3.45 (1H, ddd, *J* 12.3, 8.2, 4.4, 6-H one diastereoisomer), 3.58 (1H, ddd, apparent quintet $J_{average}$ 7.6, 4-H), 3.72 (1H, ddd, *J* 12.3, 7.9, 4.3, 6-H), 5.10 (4H , m, 1-H_{cis}, 1-H_{trans}, 8-H_{cis}, 8-H_{trans}), 5.80 (1H, m, 2-H), 5.90 (1H, ddd, *J* 16.9, 9.9, 8.2, 7-H one diastereoisomer), 6.03 (1H, ddd, *J* 17.2, 10.2, 7.3, 7-H other diastereoisomer), 7.25 (5H, m, Ph); δ_C (75 MHz, $CDCl_3$) 42.5, 42.6, 42.7 and 42.8 (CH_2, 3C and 5C from 2 diastereoisomers), 46.7 and 46.7 (CH, 4C 2 diastereoisomers), 68.6 and 68.8 (CH, 4C, 2 diastereoisomers), 114.2 and 115.3 (CH_2, 8C, 2 diastereoisomers), 118.7 (CH_2, 1C), 126.7 and 126.8 (CH, 2C, 2 diastereoisomers), 127.8 and 128.2 (2CH, Ph, 2 diastereoisomers), 128.9 and 129.0 (2CH, Ph, 2 diastereoisomers), 134.9 (CH, Ph), 141.7 and 142.9 (CH, 7C, 2 diastereoisomers), 143.7 and 144.7 (C, Ph, 2 diastereoisomers); *m/z* (EI) 202 (M^+, 11), 184 (28), 160 (11), 143 (18), 117 (100), 91 (28), 84 (37), 51 (27); (found 202.13580. $C_{14}H_{18}O$ requires 202.13577).

***(3S, 5S), (3R, 5R)* 5-Phenyl-1,6-heptadien-3-ol (508).**

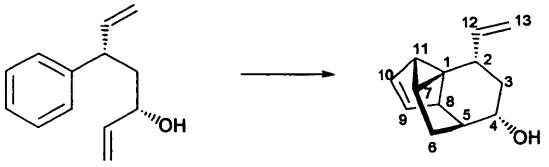


496 508

3-Phenyl-4-pentenal **496** (0.683 g, 4.26 mmol) in THF (10 mL) was added drop wise to vinyl magnesium bromine 1.0 M in THF (15 mL); while cooling in ice. The reaction progress was followed by TLC (petroleum ether : diethyl ether 10:1). After 4 h the reaction was judged to be complete. The reaction mixture was left to cool to room temperature. Once cooled, saturated solution of ammonium chloride was added (25 mL). The mixture was extracted with ethet (3 x 20 mL), the combined extract was dried and the solvent removed under reduced pressure to give the crude product. Flash chromatography in eluent (petroleum ether : diethyl ether 10:1) gave *(RR, SS, RS, SR) 5-phenyl-1,6-heptadien-3-ol* **508** as a pale yellow oil (0.576 g, 72%). Chromatotron separation in petroleum ether : diethyl ether (10:1) gave 0.1 g of *(3S, 5S), (3R, 5R) 5-*

phenyl-1,6-heptadien-3-ol **508**; ν_{max}/cm^{-1} (CH_2Cl_2) 1580 (m), 1520 (m), 1400 (s), 1280 (s), 900 (m), 700 (broad, s); δ_H (300 MHz, $CDCl_3$) 1.86 (3H, m, 4-H_a, 4-H_b and OH), 3.53 (1H, dt, *J* 15.2, 7.6, 5-H), 3.93 (1H, broad doublet, *J* 5.3, 3-H), 5.12 (4H, m, 1-H_{cis}, 1-H_{trans}, 7-H_{cis}, 7-H_{trans}), 5.83 (1H, ddd, *J* 16.8, 10.4, 6.3, 2-H), 5.99 (1H, ddd, *J* 17.4, 10.4, 7.2, 6-H), 7.25 (5H, m, Ph); δ_C (75 MHz, $CDCl_3$) 42.7 (CH_2, 4C), 46.4 (CH, 5C), 71.2 (CH, 3C), 114.6 (CH_2, 7C), 115.1 (CH_2, 1C), 126.8 (CH, Ph), 128.2 (2 CH, Ph), 129.0 (2 CH, Ph), 141.5 (CH, 2C), 142.5 (CH, 6C), 143.8 (C, Ph); *m/z* (EI) 188 (M^+, 10), 170 (40), 155 (35), 142 (40), 117 (100), (found 188.12011. $C_{13}H_{16}O$ requires 188.12012).

***(1R, 2R, 4R, 5R, 7S, 8S, 11S), (1S, 2S, 4S, 5S, 7R, 8R, 11R)*-4-Hydroxy-2-vinyltetracyclo[3.2.1.3^{1,8}.0^{7,11}]uncec-9-ene (517).**

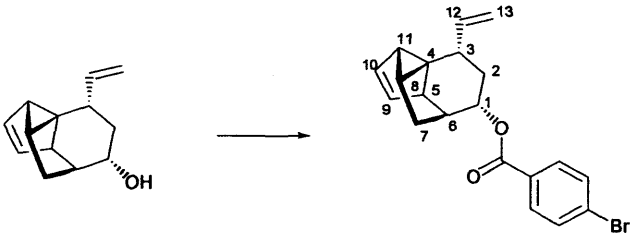


508 517

(3S, 5S), (3R, 5R)-5-Phenyl-1,6-heptadien-3-ol **508** (100 mg, 0.53 mmol) was dissolved in dry ether 10mL) in a quartz photolysis tube, water-cooled by a cold finger extending into the solution. Irradiation was carried out at 254 nm, using a Rayonet™ photochemical reactor for 48hr, when TLC showed there was no starting material, the solvent removed under reduced pressure and the crude was purified by column in eluent petroleum ether : diethyl ether 3:1 to give *(1R, 2R, 4R, 5R, 7S, 8S, 11S), (1S, 2S, 4S, 5S, 7R, 8R, 11R)-4-Hydroxy-2-vinyltetracyclo[3.2.1.3^{1,8}.0^{7,11}]uncec-9-ene* **517** as a colourless oil (30 mg, 30%); δ_H (300 MHz, $CDCl_3$) 0.83 (1H, dd, *J* 3.2, 6.7, 6.7, 7-H), 1.45 (1H, br, OH), 1.60 (2H, m, 6-H_a, 6-H_b), 1.82 (1H, dt, *J* 14.6, 2.05, 3-H_a), 2.22 (1H, ddd, *J* 5.3, 7.9, 14.6, 3-H_b), 2.40 (1H, m, 5-H), 2.56 (1H, m, 2-H), 2.64 (1H, m, 11-H), 3.03 (1H, broad singlet, 8-H), 4.03 (1H, broad quintet, *J* 2.4, 4-H), 5.06 (1H, dt, *J* 2, 10.3, 13-H_{cis}), 5.12 (1H, dt, *J* 2, 17.2, 13-H_{trans}), 5.55 (1 H, dd, *J* 2.6, 5.9, 9-H), 5.75 (1 H, dd, *J* 2.7, 5.5, 10-H), 6.14 (1 H, ddd, *J* 5.5, 10.5, 17.2, 12-H); δ_C (75 MHz, $CDCl_3$) 25.2 (CH_2, 6C), 26.5 (CH, 7C), 39.0 (CH_2, 3C), 43.5 (CH, 11C), 45.5 (CH, 2C), 47.8 (CH, 8C), 49.7 (C, 1C), 60.4 (CH, 5C), 74.9 (CH, 4C), 114.7 (CH_2, 13C), 129.8 (CH,

10C), 130.8 (CH, 9C), 141.8 (CH, 12C); (found 188.12012. $C_{13}H_{16}O$ requires 188.12012).

***(1S, 3S, 4S, 5R, 6S, 8R, 11R), (1R, 3R, 4R, 5S, 6R, 8S, 11S)*-4-Bromo-benzoic acid-3-vinyltetracyclo[3.2.1.3^{1,8}.0^{7,11}]uncec-9-enyl ester (520).**

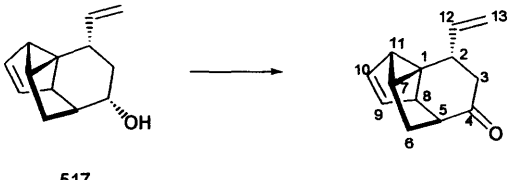


517 520

(1R, 2R, 4R, 5R, 7S, 8S, 11S), (1S, 2S, 4S, 5S, 7R, 8R, 11R)-4-Hydroxy-2-vinyltetracyclo[3.2.1.3^{1,8}.0^{7,11}]uncec-9-ene **517** (0.106 mmol, 20 mg) was dissolved in CH_2Cl_2 (2 mL) and then DMAP (3 mg, 0.016 mmol), 4-bromo-benzoyl-chloride (20 mg, 0.052 mmol) and Et_3N (11 mg, 0.106 mmol) were added to the mixture. After 3 hours a TLC (eluent 4:1 petroleum ether: diethyl ether) showed that the reaction was completed. The solution was poured into a separatory funnel containing 5 mL water and 5 mL of ether. The layers were separated and the ether layer was extracted with 2 x 5 mL of water. The ether layer was dried and the ether removed under vacuum to give the crude product. Flash chromatography (petroleum ether : diethyl ether 3:1) gave *(1S, 3S, 4S, 5R, 6S, 8R, 11R), (1R, 3R, 4R, 5S, 6R, 8S, 11S)-4-Bromo-benzoic acid-3-vinyltetracyclo[3.2.1.3^{1,8}.0^{7,11}]uncec-9-enyl ester* **520** as a yellow oil which was converted to a white solid on recrystallisation from petrol (15 mg, 38%); Mp 84-85°C; δ_H (300 MHz, $CDCl_3$) 0.83 (1H, ddd, *J* 3.2, 6.7, 6.7, 8-H), 1.57 (1H, ddd, *J* 2.9, 3.8, 14, 7-H_a or 7-H_b), 1.72 (1H, ddd, *J* 2.6, 6.2, 14, 7-H_a or 7-H_b), 1.82 (1H, dt, *J* 14.6, 2, 2-H_a), 2.22 (1H, ddd, *J* 5.3, 7.9, 14.6, 2-H_b), 2.50 (1H, m, 6-H), 2.60 (2H, m, 3-H and 11-H), 3.03 (1H, broad singlet, 5-H), 5.06 (1H, dt, *J* 2, 10.3, 13-H_{cis}), 5.12 (1H, dt, *J* 2, 17.2, 13-H_{trans}), 5.24 (1H, broad quintet, *J* 2.3, 1-H), 5.49 (1H, dd, *J* 2.6, 5.9, 9-H), 5.70 (1H, dd, *J* 2.3, 5.5, 10-H), 6.14 (1H, ddd, *J* 5.5, 10.5, 17.2, 12-H), 7.51 (1H, d, *J* 8.5, Ph), 7.82 (1H, d, *J* 8.5, Ph); δ_C (75 MHz, $CDCl_3$) 24.7 (CH_2, 7C), 26.3 (CH, 8C), 35.7 (CH_2, 2C), 43.3 (CH, 11C), 44.9 (CH, 3C), 48.3 (CH, 5C), 49.2 (C, 4C), 57.2 (CH, 6C), 76.6

(CH, 1C), 114.5 (CH_2, 13C), 127.9 (C, Ph), 129.8 (CH, 10C), 129.9 (CH, 9C), 131.1 (2 CH, Ph), 131.7 (2 CH, Ph), 140.63 (CH, 12C), 165.06 (C, Ph).

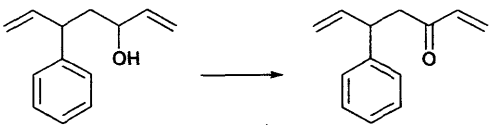
***(1R, 2R, 5R, 7S, 8S, 11S), (1S, 2S, 5S, 7R, 8R, 11R)*-2-vinyltetracyclo[3.2.1.3^{1,8}.0^{7,11}]uncec-9-en-4-one (529).**



517 529

A solution of alcohol **517** (15 mg, 0.080 mmol) in CH_2Cl_2 (1 mL) was added to a stirred solution of Dees-Martin reagent (67 mg, 0.16 mmol) in CH_2Cl_2 (2 mL). After 3 hours the solution was poured into a separating funnel containing 5 mL of NaOH 1N and 5 mL of ether. The layers were separated and the ether layer was extracted with water (2 x 10 mL). The ether layer was dried and the solvent removed under vacuum to give the crude product. Flash chromatography (petroleum ether : diethyl ether 15%) gave the product **529** as a yellow oil (9 mg, 60%); ν_{max}/cm^{-1} (CH_2Cl_2) 2950 (m) 1700 (m); δ_H (300 MHz, $CDCl_3$) 1.05 (1H, m, 7-H), 1.60 (1H, dt, *J* 3, 3.15, 6-H_a), 1.90 (1H, ddd, *J* 2.1, 6.3, 13.2, 6-H_b), 2.47 (1H, dd, *J* 3, 16.8, 3-H_a), 2.57 (1H, m, 2-H), 2.74 (2H, m, 11-H and 5-H), 2.81 (1H, dd, *J* 7.2, 15.6, 3-H_b), 3.03 (1H, s, br, 8-H), 5.05-5.15 (2H, m, 13-H), 5.52 (1H, dd, *J* 2.1, 5.4, 10-H), 5.84 (1H, dd, *J* 2.1, 6, 9-H), 5.98 (1H, ddd, *J* 5.1, 10.5, 11.5, 12-H); δ_C (75 MHz, $CDCl_3$) 26.4 (CH_2, 6C), 26.7 (CH, 7C), 41.1 (CH, 2C), 41.8 (CH, 11C), 45.7 (CH_2, 3C), 50.1 (CH, 8C), 51.0 (C, 1C), 67.0 (CH, 5C) 114.6 (CH_2, 13C), 127.7 (CH, 10C), 130.9 (CH, 9C), 139.6 (CH, 12C), 217.4 (C=O).

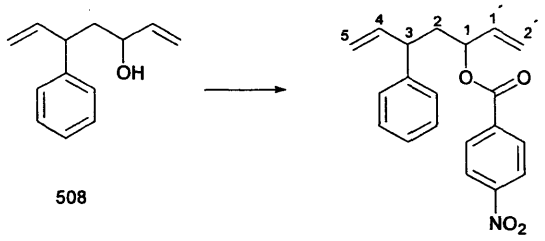
5-Phenyl-1,6-heptadien-3-one (530).



508 530

A solution of *(RR, SS, RS, SR) 5-Phenyl-1,6-heptadien-3-ol* **508** (300 mg, 1.59 mmol) in CH_2Cl_2 (3 mL) was added to a stirred solution of Dees-Martin reagent (1011 mg, 2.39 mmol) in CH_2Cl_2 (8 mL). After 2 hours the solution was poured into a separating funnel containing 15 mL of NaOH 1N and 30 mL of ether. The layers were separated and the ether layer was extracted with 2 x 30 mL of water. The ether layer was dried and the ether removed under vacuum to give the crude product. Flash chromatography (petroleum ether : diethyl ether 5:1) gave *5-Phenyl-1,6-heptadien-3-one* **530** as a yellow oil (309 mg, 89%); ν_{max}/cm^{-1} (CH_2Cl_2) 3100 (m), 2900 (m), 1700 (s), 1620 (m), 1500 (m); δ_H (300 MHz, $CDCl_3$) 2.96 (1H, dd, *J* 7, 16.4, 4_a-H or 4_b-H), 3.05 (1H, dd, *J* 7, 16.4, 4_a-H or 4_b-H), 4.0 (1 H, q, *J* 7, 5-H), 4.96-5.08 (2 H, m, 7-H), 5.80 (1 H, dd, *J* 1.2, 10.2, 1-H_{cis}), 5.95 (1H, ddd, *J* 6.7, 10.2, 16.9, 6-H), 6.17 (1H, dd, *J* 1.2, 17.5, 1-H_{trans}), 6.31 (1H, dd, *J* 10.23, 17.52, 2-H), 7.1-7.3 (5H, m, Ph); δ_C (75 MHz, $CDCl_3$) 44.5 (CH_2, 4C), 45.0 (CH, 5C), 114.7 (CH_2, 7C), 126.6 (CH, Ph), 127.7 (2CH, Ph), 128.3 (CH_2, 1C), 128.6 (2CH, Ph), 136.7 (CH, 2C), 140.5 (CH, 6C), 142.9 (C, 8C), 198.7 (CO); (found 186.10441; $C_{13}H_{14}O$ requires 186.10447).

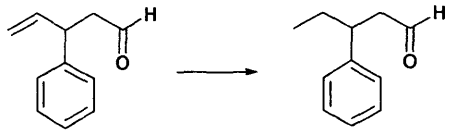
4-Nitrobenzoic acid-3-phenyl-1-vinylpent-4-enyl ester.



(RR, SS, RS, SR)-5-Phenyl-1,6-heptadien-3-ol **508** (0.059 mmol, 11 mg) was dissolved in CH_2Cl_2 (1 mL) and then DMAP (3 mg, 0.016 mmol), 4-nitro-benzoyl chloride (11 mg, 0.059 mmol) and Et_3N (6 mg, 0.059 mmol) were added to the mixture. After 2 hours a TLC (eluent 3:1 petrol:ether) showed that the reaction was completed. The solution was poured into a separatory funnel containing 5 mL water and 5 mL of ether. The layers were separated and the ether layer was extracted with 2 x 5 mL of water. The ether layer was dried and the ether removed under vacuum to give the crude product. Flash chromatography (petroleum ether : diethyl ether 3:1) gave 4-nitro-benzoic acid-3-phenyl-1-vinylpent-4-enyl ester as a yellow oil (10 mg, 52%); δ_H (300 MHz, $CDCl_3$) 2.15 (1H, m, 2_a-H), 2.32 (1H, m, 2_b-H), 3.45 (1H, q, *J* 7.6, 3-H), 5.10

(2H, m, 2′-H or 5-H), 5.30 (2H, m, 2′-H or 5-H), 5.55 (1H, q, *J* 5.2, 1-H), 5.95 (2 H, m, 1′-H and 4-H), 7.23 (5 H, m, Ph), 8.13 (2 H, d, *J* 9, $PhNO_2$), 8.27 (2H, d, *J* 9, Ph-NO_2); δ_C (75 MHz, $CDCl_3$) 39.5 (CH_2, 2C), 45.9 (CH, 3C), 74.9 (CH, 1C), 114.7 (CH_2, 5C), 117.9 (CH_2, 2′C), 123.5 (2 CH, NO_2Ph), 126.6 (CH, Ph), 127.5 (2 CH, NO_2Ph), 128.7 (2 CH, Ph), 130.7 (2 CH, Ph), 135.5 (C, NO_2Ph), 135.7 (CH, 1′C), 141.1 (CH, 4C), 143.0 (C, Ph), 150.3 (C, NO_2Ph), 163.7 (CO); *m/z* (EI) 337 (M^+, 10), 179 (100), 142 (60), 117 (60).

3-Phenylpentanal[165] (532).



496 532

3-Phenyl-4-pentenal **496** (360 mg, 2.25 mmol) was dissolved in dry methanol (4 mL) and a pinch of Pd/C was added to the mixture. Then, a balloon of H_2 was set up on the round bottomed flask and de-gas was done 3 times under water pump. Reaction was completed after 5 hours, the solution was filtered through a sintel funnel with celite. Methanol was removed under vacuum to yield *3-phenylpentanal* **532** as a yellow oil (350 mg, 96%); δ_H (300 MHz, $CDCl_3$) 0.82 (3H, t, *J* 7.3, 5-H), 1.65 (2H, m, 4-H), 2.72 (2H, dd, *J* 2, 7.3, 2-H), 3.13 (1H, q, *J* 6, 3-H), 7.20 (5H, m, Ph), 9.60 (1H, t, *J* 2, *H*CO); δ_C (75 MHz, $CDCl_3$) 11.8 (CH_3, 5C), 29.5 (CH_2, 4C), 41.7 (1 H, 3C), 50.2 (CH_2, 2C), 126.5 (CH, Ph), 127.5 (2 CH, Ph), 128.6 (2 CH, Ph), 143.6 (C, Ph), 202.0 (CO); *m/z* (EI) 162 (M^+, 30), 133 (75), 105 (80), 91 (100).

5-Phenyl-1-hepten-3-ol (533).

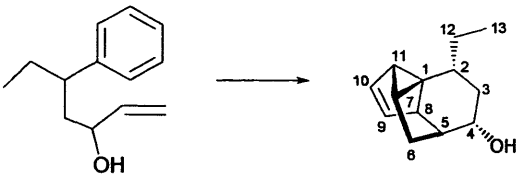
532 533

3-Phenyl-pentanal **532** (0.700 g, 4.26 mmol) in THF (5 mL) was added drop wise to vinyl magnesium bromine 1.0 M in THF (13 mL); while cooling in ice. The reaction progress was followed by TLC (petroleum ether : diethyl ether 10:1). After 3 hours the reaction was judged to be complete. The reaction mixture was left to cool to room temperature. A saturated solution of ammonium chloride was added (25 mL). The mixture was extracted with ether (3 x 50 mL), the combined extract was dried and the solvent removed under reduce pressure to give the crude product. Flash chromatography (petroleum ether : diethyl ether 5:1) gave *5-phenyl-1-hepten-3-ol* **533** as a pale yellow oil to yield two different isomers. *(R,S),(S,R)* isomer **534** (135 mg, 17%) and *(S,S),(R,R)* isomer **535** (184 mg, 23%).

***(3R, 5S), (3S, 5R)*-5-Phenyl-1-hepten-3-ol (534).** ν_{max}/cm^{-1} (CH_2Cl_2) 3650 (m), 3590 (m), 3050 (m), 2980 (m), 1600 (m), 1500 (m), 1440 (s), 1280 (s), 900(m), 700 (broad, s); δ_H (300 MHz, $CDCl_3$) 0.75 (3H, t, *J* 7.3, 7-H), 1.40-1.90 (5H, m, *H*O, 6-H and 4-H), 2.51 (1H, septete, *J* 5.2, 5-H), 3.75 (1H, broad, 3-H), 5.01 (1H, d, *J* 10.2, 1-H_{cis}), 5.11 (1H, d, *J* 17.2, 1-H_{trans}), 5.82 (1H, ddd, *J* 4.7, 10.2 and 17.2, 2-H), 7.22 (3H, m, Ph), 7.32 (2H, m, Ph); δ_C (75 MHz, $CDCl_3$) 12.1 (CH_3, 7C), 30.1 (CH_2, 6C), 43.7 (CH_2, 4C), 43.8 (CH, 5C), 70.6 (CH, 3C), 113.8 (CH_2, 1C), 126.1 (CH, Ph), 127.9 (2 CH, Ph), 128.4 (2 CH, Ph), 141.7 (CH, 2C), 144.8 (C, Ph); *m/z* (EI) 190 (M^+, 20), 143 (70), 120 (80), 105 (42), 91 (100); (found 190.13572. $C_{13}H_{18}O$ requires 190.13577).

***(3R, 5R), (3S, 5S)*-5-Phenyl-1-hepten-3-ol (535).** δ_H (300 MHz, $CDCl_3$) 0.75 (3H, t, *J* 7.3, 7-H), 1.42-2.02 (5H, m, *H*O, 6-H and 4-H), 2.52 (1H, septete, *J* 5.5, 5-H), 3.92 (1H, q, *J* 6.7, 3-H), 5.12 (2H, m, 1-H), 5.82 (1H, ddd, *J* 6.7, 10.5, 17.2, 2-H), 7.15 (3H, m, Ph), 7.32 (2H, m, Ph); δ_C (75 MHz, $CDCl_3$) 11.9 (CH_3, 7C), 29.9 (CH_2, 6C), 43.6 (CH_2, 4C), 44.2 (CH, 5C), 71.8 (CH, 3C), 115.5 (CH_2, 1C), 126.1 (CH, Ph), 127.7 (2 CH, Ph), 128.42 (2 CH, Ph), 140.9 (CH, 2C), 145 (C, Ph); *m/z* (EI) 190 (M^+, 2), 143 (70), 120 (60), 105 (40), 91 (100); (found 190.13583. $C_{13}H_{18}O$ requires 190.13577).

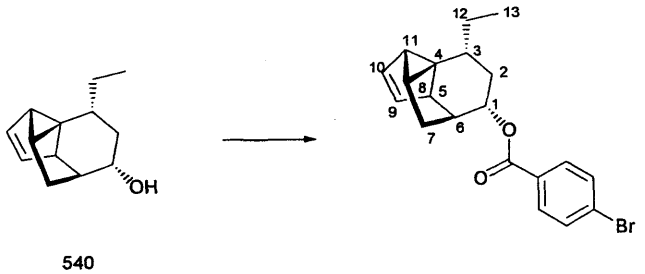
***(1S, 2S, 4R, 5R, 7S, 8S, 11S), (1R, 2R, 4S, 5S, 7R, 8R, 11R)*-4-Hydroxy-2-ethyltetracyclo[3.2.1.3^{1,8}.0^{7,11}]uncec-9-ene (540).**



534 540

(3S, 5R), (3R, 5S)-5-Phenyl-1-hepten-3-ol **534** (70 mg, 0.37 mmol) was dissolved in dry ether 10 mL) in a quartz photolysis tube, water-cooled by a cold finger extending into the solution. Irradiation was carried out at 254 nm, using a Rayonet™ photochemical reactor for 24 h, when TLC showed there was no starting material. The solvent was removed under reduced pressure and the crude was purified by column in eluent petroleum ether : diethyl ether (5:1) to give *(1S, 2S, 4R, 5R, 7S, 8S, 11S), (1R, 2R, 4S, 5S, 7R, 8R, 11R)-4-Hydroxy-2-ethyltetracyclo[3.2.1.3^{1,8}.0^{7,11}]uncec-9-ene* **540** as a yellow oil (40 mg, 57 %); δ_H (300 MHz, $CDCl_3$) 0.73 (1H, ddd, *J* 2.9, 6.4, 9.3, 7-H), 0.87 (3H, t, *J* 7.3, 13-H), 1.45 (1H, broad, OH), 1.50-1.75 (6H, m, 6-H, 3-H_b, 2-H and 12-H), 2.15 (1H, ddd, *J* 5.3, 7.3, 14.6, 3-H_a), 2.38 (1 H, broad, 5-H), 2.55 (1H, m, 11-H), 3.03 (1H, broad singlet, 8-H), 4.03 (1H, broad quintet, *J* 2.34, 4-H), 5.55 (1H, dd, *J* 2.3, 5.6, 9-H), 5.75 (1H, dd, *J* 2.6, 5.8, 10-H); δ_C (75 MHz, $CDCl_3$) 12.8 (CH_3, 13C), 24.7 (CH_2, 6C), 26.0 (CH, 7C), 26.6 (CH_2, 12C), 39.2 (CH_2, 3C), 43.1 (CH, 11C), 43.7 (CH, 2C), 46.2 (CH, 8C), 49.2 (C, 1C), 60.2 (CH, 5C), 74.9 (CH, 4C), 129.5 (CH, 10C), 130.3 (CH, 9C).

***(1R, 3S, 4S, 5S, 6R, 8S, 11S), (1S, 3R, 4R, 5R, 6S, 8R, 11R)*-4-Bromo-benzoic acid-3-ethyl-tetracyclo[3.2.1.3^{1,8}.0^{7,11}]uncec-9-enyl ester (542).**



540 542

(1S, 2S, 4R, 5R, 7S, 8S, 11S), (1R, 2R, 4S, 5S, 7R, 8R, 11R)-4-Hydroxy-2-ethyltetracyclo[3.2.1.$3^{1,8}$.$0^{7,11}$]juncec-9-ene **540** (0.079 mmol, 15 mg) was dissolved in CH_2Cl_2 (2 mL) and then DMAP (3 mg, 0.016 mmol), 4-bromo-benzoyl-chloride (30 mg, 0.079 mmol) and Et_3N (8 mg, 0.079 mmol) were added to the mixture. After 3 hours a TLC (eluent 4:1 petroleum ether : diethyl ether) showed that the reaction was completed. The solution was poured into a separatory funnel containing 5 mL water and 5 mL of ether. The layers were separated and the ether layer was extracted with 2 x 5 mL of water. The ether layer was dried and the ether removed under vacuum to give the crude product. Flash chromatography (petroleum ether : diethyl ether 3:1) gave *(1R, 3S, 4S, 5S, 6R, 8S, 11S), (1S, 3R, 4R, 5R, 6S, 8R, 11R)-4-Bromo-benzoic acid-3-ethyltetracyclo[3.2.1.$3^{1,8}$.$0^{7,11}$]juncec-9-enyl ester* **542** as a yellow oil (15 mg, 50%) which was converted to a white solid on recrystallisation from ethanol / water; Mp 64-65°C; δ_H (300 MHz, $CDCl_3$) 0.70 (1H, ddd, *J* 2.9, 6.4, 9.3, 8-H), 0.87 (3H, t, *J* 7.31, 13-H), 1.50-1.75 (6H, m, 6-H, 2-H_b, 3-H and 12-H), 2.15 (1H, ddd, *J* 5.3, 7.3, 14.6, 2-H_a), 2.55 (2H, m, 11-H and 6-H), 3.03 (1H, broad singlet, 5-H), 5.20 (1H, broad quintet, *J* 2.3, 1-H), 5.55 (1 H, dd, *J* 2.3, 5.6, 9-H), 5.75 (1H, dd, *J* 2.6, 5.8, 10-H), 7.51 (1H, d, *J* 8.5, Ph), 7.82 (1H, d, *J* 8.5, Ph); δ_C (75 MHz, $CDCl_3$) 12.7 (CH_3, 13C), 24.5 (CH_2, 7C), 26.2 (CH, 8C), 26.6 (CH_2, 12C), 36.4 (CH_2, 2C), 43.1 (CH, 11C), 43.8 (CH, 3C), 46.2 (CH, 5C), 49.2 (C, 4C), 60.2 (CH, 6C), 74.9 (CH, 1C), 129.5 (CH, 10C), 130.3 (CH, 9C).

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Appendices

Appendix 1A: Postgraduate Module CH501: Research Tecniques.

This is a compulsory first year module that covers the following topics:

Semester	Activity	Convenor/Lecture(s)
1	Safety/Security	Mrs Sutherland
1	Introduction to Key Techniques	Mr Lee
		Dr Eaton
		Dr Fawcett
		Dr Griffith
1	Use of the Library	Dr Lloyd
		Ms Wilson
1	NMR Techniques I: 1D NMR	Dr Griffith
1	NMR Techniques II: 2D NMR	Dr Griffith
2	NMR Techniques III: The nOe Effect	Dr Griffith
2	Advanced Interpretation of Spectra	Dr Griffith
2	Lecture Presentations	Prof Holloway
2	Chemdraw and Molecular Modelling	Prof Cullis
2	Applications of 'Endnote'	Dr Davies
2	Advanced Scientific Writing	Dr Malpass

Appendix 1B: Additional Modules taken during Postgraduate Training.

Year	Semester	Module	Module Title	Convenor	Attendance/ Assessment
1	2	CH401	Design in Organic Chemistry	Dr. P. R. Jenkins	Pass
1	2	CH309	Strategis in Organic Synthesis	Dr. P. R. Jenkins & Dr. S. Handa	Pass
2	1	CH413	Retrosynthetic analysis	Dr. P. R. Jenkins	Pass

Appendix 1B: Lecture and Seminar Attendance – University of Leicester.

This list covers formal lectures and seminars; group meetings, problem seminars and similar activities are not included here.

Date	Lecturer	Title
5/10/00	Dr. A. Armstrong (Imperial College)	New Methods for Asymmetric Heteroatom Transfer
9/10/00	Dr. A. Sarkar (NCL, Pune)	Conformation and Reactivity of Fischer Carbene Complexes
10/10/00	Dr. J. Clayden (Manchester)	Stereocontrol and Synthesis with Rotationally Restricted Compounds
11/10/00	Dr. D. J. Evans (ANU)	Chaos, Lyapunov Exponents and Transport Coefficients
15/11/00	Dr. G. Stevenson (Merck)	The Treatment of Alzheimers Disease
22/11/00	Dr. C. Wallis (Glaxo Wellcome)	The Development of the Asthma Drug Ventolin
24/1/01	Prof. R. Taylor (York)	Adventures in Natural Product Synthesis
7/2/01	Dr. S. Bennett (Open University)	Widening the Appeal: The Role on Independent Learning in Chemistry
12/3/01	Dr. M. Willis (Bath)	New Routes for Old Cycles
21/3/01	First Memorial Lecture for T. J. Norwood	
1/10/01	Prof. K. C. Nicolau (U.S.A)	
4/10/01	Dr. P. O'Brien (York)	
14/10/01	Prof. V. C. Gibson (London)	
22/10/01	Dr. A. Hooper (Rothamstead)	
23/01/02	Prof. K. A. McLauchlan (Oxford)	
24/01/02	Dr. T. Donohoe (Oxford)	
14/03/02	Dr. B. Davies (Oxford)	
17/05/02	Prof. K. Uneyama (Okayama)	
13/06/02	Prof. T. Bach (Munich)	
3/10/02	Dr. Andrew D. Miller (London)	Adventures in chemical biology from Non-viral gene therapy to the chemistry of stress.
16/10/02	Dr. Timothy Wright (Sussex)	Theoretical and experimental studies of NO-containing complexes.

16/10/02	Dr. Patrick Perlmutter (Australia)	The nucleophilic addition/ ring closure approach to the synthesis of highly functional small molecules.
21/10/02	Professor Paul Raithby (Bath)	Adventures in organometallic polymer chemistry.
4/11/02	Professor R. Grubbes (U.S.A)	The application of olefins metathesis to the rapid synthesis of organic molecules.
4/11/02	Professor R. Sheldon (Delft)	Green catalytic oxidation of alcohols.
4/11/02	Professor Martin Wills (Warick)	Assymetric ketone reduccion.
4/11/02	Dr. David Davies (Leicester)	Design of Half-sandwich complexes as chiral lewis acid catalyst.
6/11/02	Dr. Andrew Cooper (Liverpool)	Materials synthesis using supercritical and dense solvent gas.
9/12/02	Professor Tod Marder (Durham)	The role of transition metal boryl complexes in catalysed borylations including rhorium catalysed C-H bond functionalisation.
23/01/03	Dr. Kevin Booker-Milburn (Bristol)	New radical and photochemical methods for target molecules synthesis.
10/02/03	Dr. Steve D. R. Christie (Loughborough)	Metal alkyne complexes in asymmetric synthesis.
17/02/03	Professor Vickie McKee (Loughborough)	Manipulating metal arrays within macrocycles.
26/02/03	Dr. Chris Richards (London)	Very active planar catalysts for asymmetric synthesis.
3/03/03	Dr. Cristopher M. Rayner (Leeds)	Exploiting the potential of carbon dioxide in synthetic organic chemistry.
7/05/03	Dr. John Snaith (Birmingham)	The stereoselective synthesis of piperidines
19/05/03	Dr. David Berrisford (U.M.I.S.T)	The interaction of non-protein ligands with complex viral RNAs-synthetic chemistry allied to structural biology.
28/05/03	Dr. Andrew Clark (Warick)	Synthesis of heterocycles using cooper and cerium-mediated radical cyclisation.
2/06/03	Dr. Sarah Heath (Manchester)	Shedding light on biological systems: the development of lanthanide probes.
9/06/03	Dr. Alan Spivey (London)	Catalytic asymmetric acylation- Studies towards the total synthesis of polyol sesquiterpenes.

Appendix 1D: Conference Attendance and Presentation of Posters.

Date(s)	Meeting/Conference	Place	Poster
18/01/01	Stereochemistry at Sheffield "Modern Aspects of Stereochemistry"	Sheffield	-
7/11/01	Astra Zeneca Symposium	Loughborough	-
18/12/01	Sheffield Stereochemistry Conference	Sheffield	-
25/03/02	2nd Bristol Synthesis Meeting 2002	Bristol	-
30/04/02	RSC Perkins Division East Midlands Section Young Members Symposium 2002.	Loughborough	-
6-8/09/02	RSC Bioorganic Chemistry Conference.	Leicester	-
18/09/02	RSC Carbohydrate Section Autumn Meeting 2002.	Reading	-
12-16/03/03	The First International Conference on Green & Sustainable Chemistry. Waseda University International Conference Center.	Tokyo (Japan)	P
14/04/03	3rd Bristol Synthesis Meeting.	Bristol	-
6/04/03	RSC East Midlands Meeting 2003	Sheffield	P

COMMUNICATION

ChemComm www.rsc.org/chemcomm

The regiospecific Fischer indole reaction in choline chloride·2$ZnCl_2$ with product isolation by direct sublimation from the ionic liquid†

Raul Calderon Morales, Vasuki Tambyrajah, Paul R. Jenkins,* David L. Davies and Andrew P. Abbott

The Green Chemistry Research Group, Department of Chemistry, University of Leicester, Leicester, UK LE1 7RH

Received (in Cambridge, UK) 26th October 2003, Accepted 21st November 2003
First published as an Advance Article on the web 12th December 2003

The Fischer indole synthesis occurs in high yield with one equivalent of the ionic liquid choline chloride·2$ZnCl_2$; exclusive formation of 2,3-disubstituted indoles is observed in the reaction of alkyl methyl ketones, and the products readily sublime directly from the ionic liquid.

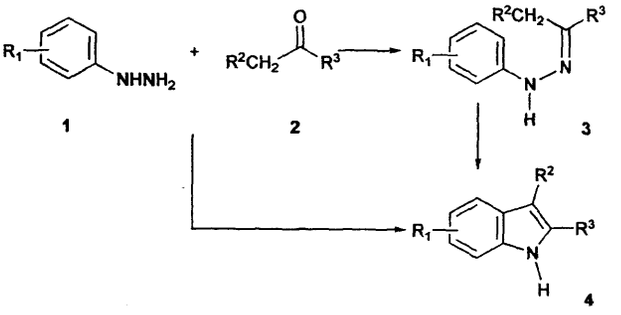
The alkylimidazolium–aluminium chloride mixtures have been studied extensively for use in acid catalysed reactions, particularly in Friedel–Crafts reactions.[1] However, chloroaluminate(III) ionic liquids are moisture sensitive and the product isolation from these liquids can be difficult. Similarly, ionic liquids formed using zinc chloride with pyridinium[2a] and imidazolium salts,[2b] have also been reported.

Recent studies at Leicester have demonstrated that quaternary ammonium salts may be used to produce moisture-stable Lewis acidic ionic liquids.[3] The combination of choline chloride, a cheap readily-available quaternary ammonium salt, and $ZnCl_2$ or $SnCl_2$ can be used as a Lewis acidic solvent for the Diels–Alder reaction.[4] More recently, the novel solvent properties of choline chloride–urea ionic liquids have been reported.[5]

In seeking new applications for the choline chloride·2$ZnCl_2$, some recent publications on the synthesis and reactions of heterocyclic compounds in ionic liquids have attracted our attention; these included the Bischler–Napieralski cyclisation,[6] the formation of 2-phenylimidazo[1,2-*a*]pyridine,[7] and the acylation[8] and electrophilic fluorination[9] of indoles. There was also one report of the Fischer indole synthesis in an ionic liquid using 1-butylpyridinium chloride–$AlCl_3$ (*n*-BPC-$AlCl_3$) ionic liquid.[10] This reaction is a good candidate for performing in ionic liquids as it is normally carried out in hot polyphosphoric acid, product isolation is by addition to water followed by filtration of the product, and disposal of the phosphoric acid residues can have a considerable environmental impact.

In our initial studies we prepared the phenylhydrazone of acetophenone and heated it with 3 eq. of the choline chloride·2$ZnCl_2$ ionic liquid for 4 h. Product isolation by addition of water and filtration of the product gave a 91% yield of 2-phenylindole **4aa** at 95 °C (Scheme 1). Yields were rather more modest with the phenylhydrazones of butanone and cyclohexanone, with 2,3-dimethylindole **4ab** (56%) and 1,2,3,4-tetrahydrocarbazole **4ac** (38%) as the products.

The isolated products of these reactions were finally purified by vacuum sublimation. It occurred to us that it may be possible to isolate the indole product directly from the ionic liquid by vacuum sublimation. Since an ionic liquid has little or no vapour pressure, then the vapour pressure of the solution of the indole product in the ionic liquid would be expected to be about the same as the vapour pressure of the indole itself. In the case of 2-phenylindole **4aa** a 91% yield of product could be obtained by direct vacuum sublimation of the ionic liquid reaction mixture. For 2,3-dimethylindole **4ab** a 56% yield was obtained using this method. In the reaction with the cyclohexanone hydrazone **3ac**, the product 1,2,3,4-tetrahydrocarbazole **4ac** was sublimed directly from the reaction without a vacuum and could be isolated by scraping it from the ionic liquid surface and from the glass of the reaction vessel. A key factor in determining the efficiency of the product sublimation is that we are going from a hydrazone which is basic to a product which is a weak base as the lone pair on the indole nitrogen is part of the aromatic system and not available for coordination to $ZnCl_2$.



Scheme 1

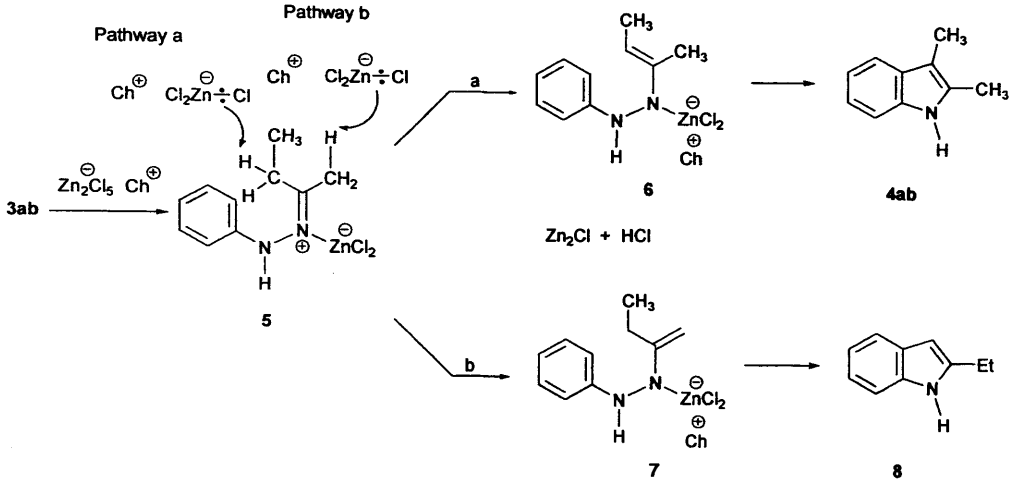
† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b313655h/

Table 1 One-pot reaction with product isolation by sublimation

Hydrazine R^1, **1**	Ketone **2**	Indole **4**	Ionic liquid (eq.)	Time/ h	*T*/°C	Yield (%)	Mp/°C Found	Mp/°C Reported
H, **1a**	Butanone **2b**	2,3-Dimethylindole **4ab**	3	1	95	80	105–107	107
2,5-Cl_2, **1b**	Butanone **2b**	4,7-Dichloro-2,3-dimethylindole **4bb**	3	4	95	72	89–90	90–91
4-Cl, **1c**	Butanone **2b**	5-Chloro-2,3-dimethylindole **4cb**	1	2	120	88	142–143	141–142
2-Me, **1d**	Butanone **2b**	2,3,7-Trimethylindole[a] **4db**	1	3	120	71	75–76	76–77
H, **1a**	2-Pentanone **2d**	3-Ethyl-2-methylindole **4ad**	3	4	95	48	43–44	44–45
4-Cl, **1c**	2-Pentanone **2d**	5-Chloro-3-ethyl-2-methylindole **4cd**	1	2	120	64	74–75	76
H, **1a**	Cyclohexanone **2c**	1,2,3,4-Tetrahydrocarbazole[a] **4ac**	3	4	95	82	117–119	118–119
2,5-Cl_2, **1b**	Cyclohexanone **2c**	5,8-Dichloro-1,2,3,4-tetrahydrocarbazole **4bc**	3	4	95	59	90–91	91–93
4-Cl, **1c**	Cyclohexanone **2c**	6-Chloro-1,2,3,4-tetrahydrocarbazole **4cc**	1	2	120	84	147–148	146–147
2-Me, **1d**	Cyclohexanone **2c**	8-Methyl-1,2,3,4-tetrahydrocarbazole[a] **4dc**	1	3	120	76	93–94	93–95

[a] Vacuum sublimation direct from the ionic liquid was incomplete, the unsublimed product was isolated by aqueous work-up and sublimation of the isolated product. Yields quoted are based on the total weight of the isolated product.

DOI: 10.1039/b313655h



Scheme 2

We further reasoned that it may be possible to carry out a series of reactions in the same ionic liquid. To this end when we had sublimed the 2-phenylindole **4aa** in 91% yield from the ionic liquid we added a further quantity of acetophenone hydrazone and carried out a second reaction. This time the yield was 72% and a third repetition gave a 34% yield. During the Fischer indole reaction 1 eq. of ammonia is produced which coordinates to $ZnCl_2$. In the repeated use of the choline chloride·$2ZnCl_2$ for a series of reactions ammonia will accumulate and reduce the efficiency of the reaction as observed by the fall in yield.

In seeking further improvements in the reaction we next attempted a one-pot conversion of the phenylhydrazine and the ketone to the indole. This worked well with yields in the range of 48–88%, Table 1.

Another important issue in the Fischer indole synthesis is the selectivity when an unsymmetrical dialkyl ketone is used. In previous studies on the Fischer indole synthesis[11] of the phenylhydrazone of butanone a 4 : 1 mixture of 2,3-dimethylindole **4ab** and 2-ethylindole **8** was obtained. In order to explain this selectivity we first have to consider the actual species present in the ionic liquid choline chloride·$2ZnCl_2$. The FAB mass spectrum of choline chloride·$2ZnCl_2$ shows the presence of $[ZnCl_3]^-$ (*m/z*, 171), $[Zn_2Cl_5]^-$ (*m/z*, 307) and $[Zn_3Cl_7]^-$ (*m/z*, 443).[3] We believe that these species arise from the following equilibria where Ch^+Cl^- is choline chloride.[12]

$$2ZnCl_2 + Ch^+Cl^- \rightleftharpoons Zn_2Cl_5^- + Ch^+ \quad (1)$$

$$2Zn_2Cl_5^- \rightleftharpoons ZnCl_3^- + Zn_3Cl_7^- \quad (2)$$

$$Zn_2Cl_5^- \rightleftharpoons ZnCl_2 + ZnCl_3^- \quad (3)$$

If we consider eqn. (3), the reaction of the hydrazone **3ab**, a Lewis base, with $Zn_2Cl_5^-$ will produce iminium cation **5** and $ZnCl_3^-$ (Scheme 2). $ZnCl_3^-$ can now act as a base and remove a proton in one of two ways. In pathway a, the proton is removed by $ZnCl_3^-$ to produce the zinc enamine **6**, which is the thermodynamic product, $ZnCl_2$ and HCl. Under the published reaction conditions[11] pathway b is also observed in which a proton is lost from the methyl group to give the less substituted zinc enamine **7**, which is the kinetic product. The reaction here is under kinetic control as there is no special stability of the iminium cation **5** and pathways a and b are irreversible processes leading to two products **4ab** and **8**. We propose that in the ionic liquid choline chloride·$2ZnCl_2$ the iminium cation is stabilised and pathway b becomes a reversible reaction hence the less substituted zinc enamine **7** can reprotonate, return to the iminium cation **5** and follow pathway a to the more stable zinc enamine **6** and hence form exclusively the 2,3-dimethylindole **4ab**. This explanation is bourne out by four examples using butanone and two using pentanone, in all cases a single indole arising from the more substituted enamine intermediate is observed, Table 1.

Finally we reduced the amount of ionic liquid used in the reaction to 1 eq. to obtain between 64 and 88% of directly sublimed product as shown in Table 1 for the synthesis of 5-chloro-2,3-dimethylindole **4cb** and 2,3,7-trimethylindole **4db**, 5-chloro-3-ethyl-2-methylindole **4cd**, and 6-chloro- and 8-methyl-1,2,3,4-tetrahydrocarbazole **4cc** and **4dc**.

In conclusion we have carried out the Fischer indole synthesis using 1 eq. of the ionic liquid choline chloride·$2ZnCl_2$ with direct product isolation by vacuum sublimation. In unsymmetrical cases regiospecific formation of a single product arising from the formation of the more substituted enamine intermediate is observed.

We are grateful to The University of Leicester and Scionix for fellowships to R.C.-M. and V.T.

Notes and references

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12 We have carried out a full electrochemical study of these equilibria including mole fraction measurements of the ions $ZnCl_3^-$, $Zn_2Cl_5^-$ and $Zn_2Cl_5^-$ using potentiometry. These results are the subject of a manuscript in preparation.

X-Ray Crystallography Data

(1S, 3S, 4S, 5R, 6S, 8R, 11R), (1R, 3R, 4R, 5S, 6R, 8S, 11S)-4-Bromo-benzoic acid-3-vinyl-tetracyclo[3.2.1.3^{1,8}.0^{7,11}]uncec-9-enyl ester (520).

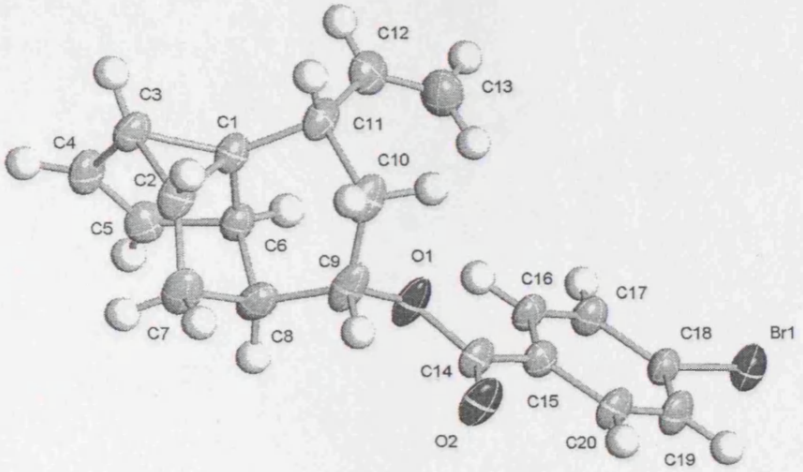
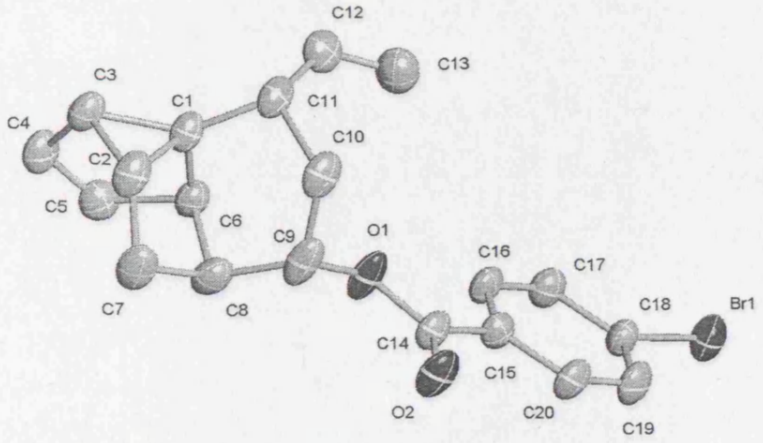


fig shows the atom label scheme and 50% displacement ellipsoids



as above but with H atoms omitted for clarity

(1S, 3S, 4S, 5R, 6S, 8R, 11R), (1R, 3R, 4R, 5S, 6R, 8S, 11S)-4-Bromo-benzoic acid-3-vinyl-tetracyclo[3.2.1.3^{1,8}.0^{7,11}]uncec-9-enyl ester (520).

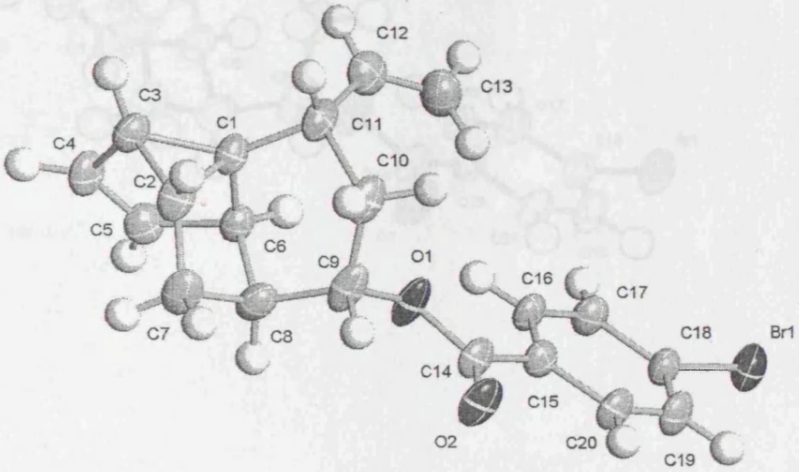
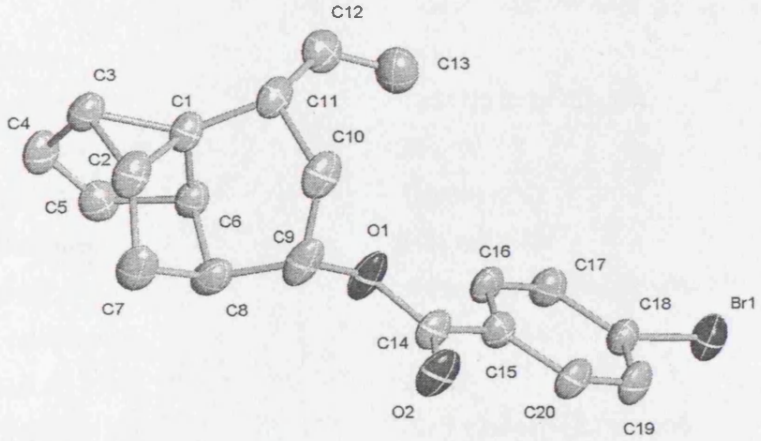


fig shows the atom label scheme and 50% displacement ellipsoids



as above but with H atoms omitted for clarity

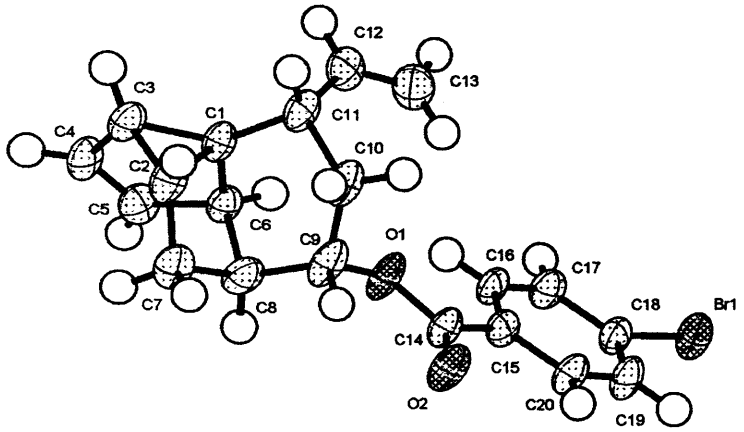

C12
C13
C3
C1
C11
C4
C10
C2
C5
C6
C9
O1
C16
C17
C18
Br1
C7
C8
C14
C15
O2
C20
C19

Table 1. Crystal data and structure refinement for 03123.

Identification code	03123	
Empirical formula	C20 H19 Br O2	
Formula weight	371.26	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.308(3) Å	α= 105.387(6)°.
	b = 9.390(4) Å	β= 100.332(6)°.
	c = 10.628(4) Å	γ = 91.481(7)°.
Volume	784.2(5) $Å^3$	
Z	2	
Density (calculated)	1.572 Mg/m^3	
Absorption coefficient	2.629 mm^{-1}	
F(000)	380	
Crystal size	0.36 x 0.09 x 0.04 mm^3	
Theta range for data collection	2.03 to 26.99°.	
Index ranges	-10<=h<=10, -11<=k<=11, -13<=l<=13	
Reflections collected	5322	
Independent reflections	3264 [R(int) = 0.0488]	
Completeness to theta = 26.99°	95.3 %	
Absorption correction	Empirical	
Max. and min. transmission	0.86 and 0.44	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3264 / 0 / 208	
Goodness-of-fit on F^2	0.939	
Final R indices [I>2sigma(I)]	R1 = 0.0644, wR2 = 0.1346	
R indices (all data)	R1 = 0.0984, wR2 = 0.1475	
Largest diff. peak and hole	0.812 and -0.651 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03123. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	4194(1)	1170(1)	3697(1)	47(1)
O(1)	8094(5)	6564(4)	8924(3)	45(1)
O(2)	9532(5)	6951(4)	7455(3)	47(1)
C(1)	7750(6)	8604(5)	12217(5)	32(1)
C(2)	9358(7)	9517(6)	12777(5)	41(1)
C(3)	8345(7)	9072(6)	13691(5)	37(1)
C(4)	8825(7)	7720(6)	14064(5)	40(1)
C(5)	8788(7)	6596(6)	13018(5)	39(1)
C(6)	8254(6)	7033(5)	11769(5)	32(1)
C(7)	10643(7)	8630(6)	12213(5)	44(1)
C(8)	9663(7)	7337(6)	11110(5)	41(1)
C(9)	8917(7)	7870(6)	9916(5)	45(2)
C(10)	7693(7)	9039(6)	10122(5)	41(1)
C(11)	6628(7)	9051(5)	11175(5)	38(1)
C(12)	5011(7)	8165(6)	10717(5)	43(1)
C(13)	4396(7)	7307(6)	9555(6)	51(2)
C(14)	8461(7)	6263(5)	7721(5)	34(1)
C(15)	7417(6)	5028(5)	6785(5)	32(1)
C(16)	6296(6)	4197(5)	7158(5)	34(1)
C(17)	5363(7)	3053(5)	6254(5)	36(1)
C(18)	5548(6)	2716(5)	4939(5)	34(1)
C(19)	6652(7)	3524(6)	4553(5)	42(1)
C(20)	7578(7)	4668(6)	5473(5)	37(1)

Table 3. Bond lengths [Å] and angles [°] for 03123.

Br(1)-C(18)	1.866(5)
O(1)-C(14)	1.327(6)
O(1)-C(9)	1.447(6)
O(2)-C(14)	1.202(6)
C(1)-C(11)	1.473(7)
C(1)-C(3)	1.495(6)
C(1)-C(2)	1.503(7)
C(1)-C(6)	1.519(7)
C(2)-C(7)	1.484(8)
C(2)-C(3)	1.522(7)
C(3)-C(4)	1.472(7)
C(4)-C(5)	1.310(7)
C(5)-C(6)	1.489(7)
C(6)-C(8)	1.525(7)
C(7)-C(8)	1.537(7)
C(8)-C(9)	1.521(8)
C(9)-C(10)	1.515(8)
C(10)-C(11)	1.544(7)
C(11)-C(12)	1.492(8)
C(12)-C(13)	1.288(7)
C(14)-C(15)	1.454(7)
C(15)-C(16)	1.376(7)
C(15)-C(20)	1.377(7)
C(16)-C(17)	1.349(7)
C(17)-C(18)	1.386(7)
C(18)-C(19)	1.360(7)
C(19)-C(20)	1.353(7)
C(14)-O(1)-C(9)	117.9(4)
C(11)-C(1)-C(3)	140.1(5)
C(11)-C(1)-C(2)	116.5(4)
C(3)-C(1)-C(2)	61.0(3)
C(11)-C(1)-C(6)	113.7(4)
C(3)-C(1)-C(6)	104.8(4)
C(2)-C(1)-C(6)	103.6(4)
C(7)-C(2)-C(1)	107.2(4)

C(7)-C(2)-C(3)	124.1(5)
C(1)-C(2)-C(3)	59.2(3)
C(4)-C(3)-C(1)	106.0(4)
C(4)-C(3)-C(2)	114.2(5)
C(1)-C(3)-C(2)	59.7(3)
C(5)-C(4)-C(3)	111.8(5)
C(4)-C(5)-C(6)	111.0(5)
C(5)-C(6)-C(1)	105.0(4)
C(5)-C(6)-C(8)	113.9(4)
C(1)-C(6)-C(8)	98.9(4)
C(2)-C(7)-C(8)	103.8(4)
C(9)-C(8)-C(6)	106.8(4)
C(9)-C(8)-C(7)	110.2(4)
C(6)-C(8)-C(7)	100.6(4)
O(1)-C(9)-C(10)	108.1(5)
O(1)-C(9)-C(8)	105.6(4)
C(10)-C(9)-C(8)	117.6(4)
C(9)-C(10)-C(11)	117.9(4)
C(1)-C(11)-C(12)	114.1(4)
C(1)-C(11)-C(10)	102.9(5)
C(12)-C(11)-C(10)	117.3(4)
C(13)-C(12)-C(11)	128.6(6)
O(2)-C(14)-O(1)	123.0(5)
O(2)-C(14)-C(15)	124.9(5)
O(1)-C(14)-C(15)	112.1(4)
C(16)-C(15)-C(20)	118.9(5)
C(16)-C(15)-C(14)	122.9(4)
C(20)-C(15)-C(14)	118.3(5)
C(17)-C(16)-C(15)	120.6(5)
C(16)-C(17)-C(18)	119.3(5)
C(19)-C(18)-C(17)	120.8(5)
C(19)-C(18)-Br(1)	120.7(4)
C(17)-C(18)-Br(1)	118.5(4)
C(20)-C(19)-C(18)	119.1(5)
C(19)-C(20)-C(15)	121.3(5)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03123. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	56(1)	52(1)	28(1)	7(1)	6(1)	-6(1)
O(1)	56(3)	52(2)	25(2)	4(2)	17(2)	-26(2)
O(2)	61(3)	51(2)	35(2)	14(2)	23(2)	-15(2)
C(1)	43(3)	31(2)	25(2)	11(2)	9(2)	-5(2)
C(2)	57(4)	39(3)	30(3)	14(2)	10(3)	-9(3)
C(3)	42(3)	43(3)	28(3)	11(2)	12(2)	-3(2)
C(4)	46(3)	52(3)	27(3)	20(2)	9(2)	-5(3)
C(5)	41(3)	45(3)	37(3)	21(2)	11(2)	-1(3)
C(6)	36(3)	37(3)	27(2)	11(2)	9(2)	-2(2)
C(7)	39(3)	57(3)	36(3)	14(3)	11(2)	-17(3)
C(8)	40(3)	48(3)	35(3)	8(2)	16(2)	-2(3)
C(9)	54(4)	50(3)	30(3)	7(2)	17(3)	-24(3)
C(10)	60(4)	39(3)	31(3)	17(2)	15(3)	-9(3)
C(11)	57(4)	34(3)	28(3)	14(2)	13(2)	4(2)
C(12)	50(4)	49(3)	38(3)	25(3)	10(3)	4(3)
C(13)	45(4)	63(4)	46(3)	18(3)	7(3)	-5(3)
C(14)	45(3)	39(3)	25(2)	15(2)	14(2)	-2(2)
C(15)	36(3)	40(3)	27(3)	16(2)	11(2)	1(2)
C(16)	40(3)	45(3)	22(2)	13(2)	13(2)	1(2)
C(17)	41(3)	41(3)	30(3)	13(2)	12(2)	-3(2)
C(18)	37(3)	42(3)	23(2)	9(2)	8(2)	2(2)
C(19)	53(4)	54(3)	23(3)	16(2)	13(2)	-2(3)
C(20)	49(3)	42(3)	26(3)	15(2)	17(2)	-2(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03123.

	x	y	z	U(eq)
H(2)	9377	10577	12760	49
H(3)	7780	9831	14274	44
H(4)	9125	7669	14956	48
H(5)	9065	5629	13052	47
H(6)	7352	6340	11134	39
H(7A)	11348	8264	12898	53
H(7B)	11340	9222	11843	53
H(8)	10317	6460	10867	49
H(9)	9828	8253	9565	53
H(10A)	6946	8926	9259	50
H(10B)	8306	10021	10364	50
H(11)	6406	10104	11558	45
H(12)	4347	8243	11369	51
H(13A)	4997	7179	8857	62
H(13B)	3342	6803	9396	62
H(16)	6177	4430	8061	41
H(17)	4588	2484	6515	43
H(19)	6772	3289	3651	50
H(20)	8354	5233	5209	44

(1R, 3S, 4S, 5S, 6R, 8S, 11S), (1S, 3R, 4R, 5R, 6S, 8R, 11R) 4-Bromo-benzoic acid-3-ethyl-tetracyclo[3.2.1.3^{1,8}.0^{7,11}]uncec-9-enyl ester (542).

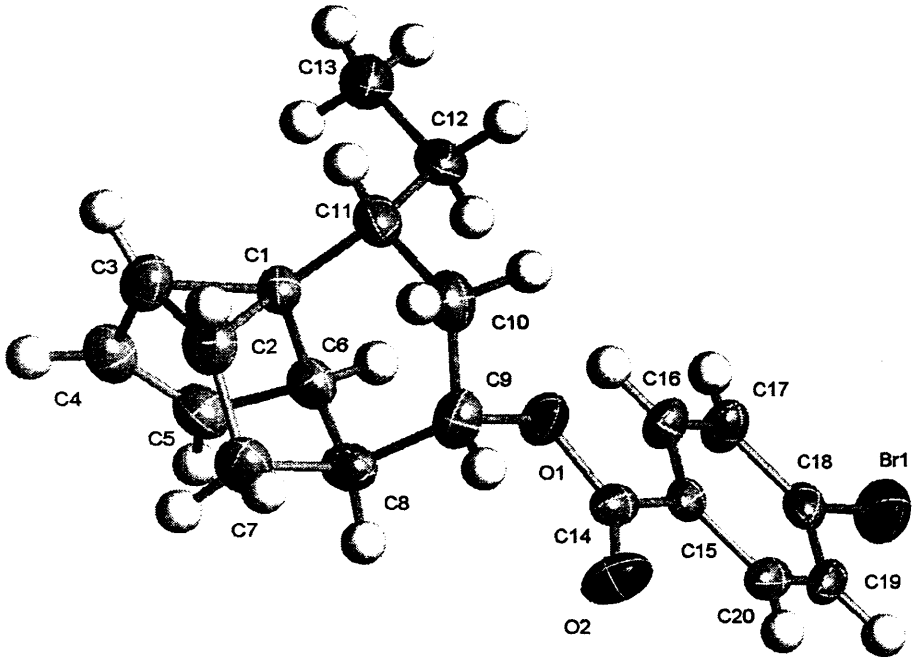
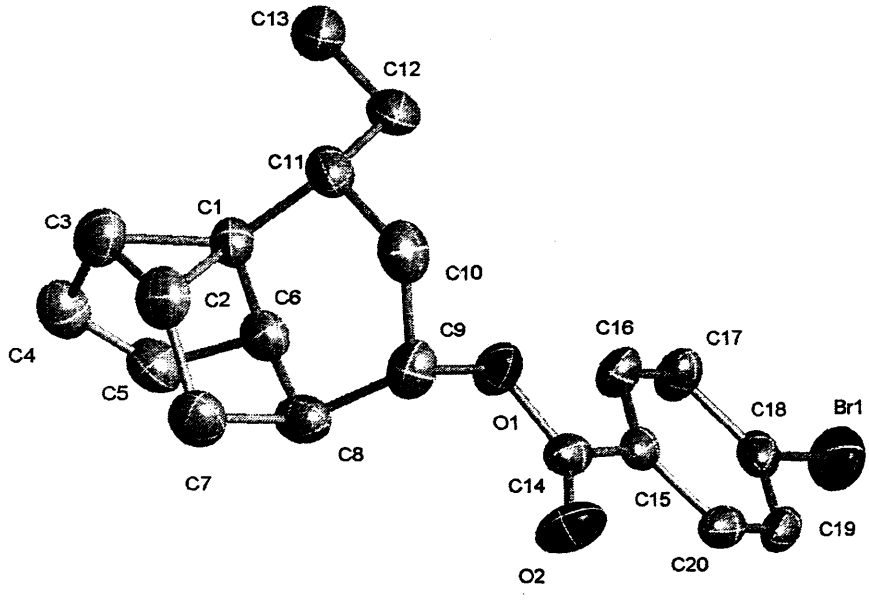


fig shows one of the two unique molecules in the asymmetric unit, the unique molecules exhibit minor orientation differences of the 5-membered rings and ethyl groups. The atom label scheme and 50% displacement ellipsoids are shown.



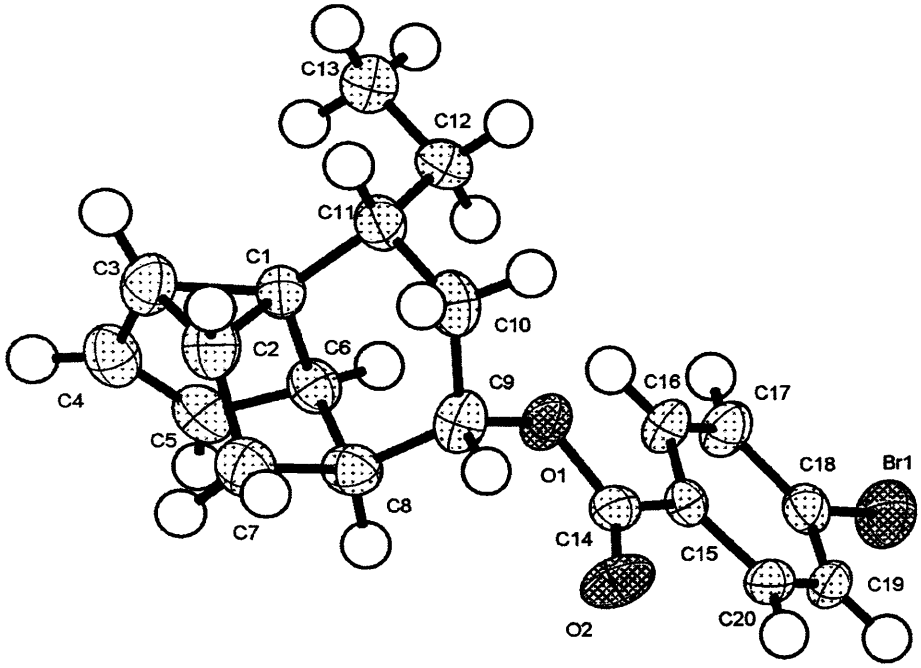

C13
C12
C11
C1
C3
C10
C2
C6
C9
C16
C17
C4
C5
O1
C18
Br1
C8
C14
C15
C19
C7
C20
O2

Table 1. Crystal data and structure refinement for 03145.

Identification code	03145	
Empirical formula	C20 H21 Br O2	
Formula weight	373.28	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.637(7) Å	α= 75.490(11)°.
	b = 11.279(8) Å	β= 79.573(12)°.
	c = 14.681(10) Å	γ = 75.354(11)°.
Volume	1636.7(19) $Å^3$	
Z	4	
Density (calculated)	1.515 Mg/m^3	
Absorption coefficient	2.519 mm^{-1}	
F(000)	768	
Crystal size	0.22 x 0.18 x 0.04 mm^3	
Theta range for data collection	1.44 to 26.00°.	
Index ranges	-13<=h<=12, -13<=k<=13, -18<=l<=18	
Reflections collected	12009	
Independent reflections	6236 [R(int) = 0.0450]	
Completeness to theta = 26.00°	96.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.86 and 0.52	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6236 / 0 / 417	
Goodness-of-fit on F^2	0.819	
Final R indices [I>2sigma(I)]	R1 = 0.0452, wR2 = 0.0826	
R indices (all data)	R1 = 0.0876, wR2 = 0.0905	
Largest diff. peak and hole	0.502 and -0.481 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03145. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	9527(1)	8153(1)	5024(1)	57(1)
O(1)	7412(2)	2801(2)	6581(2)	40(1)
O(2)	5883(3)	3804(2)	5649(2)	52(1)
C(1)	7476(4)	655(3)	8723(2)	33(1)
C(2)	6308(4)	113(4)	8924(3)	45(1)
C(3)	6992(4)	162(4)	9734(3)	45(1)
C(4)	6437(4)	1256(4)	10159(3)	44(1)
C(5)	6372(4)	2305(4)	9523(3)	44(1)
C(6)	6931(4)	2054(3)	8563(3)	36(1)
C(7)	5216(4)	1125(4)	8509(3)	50(1)
C(8)	5925(4)	2123(4)	7915(3)	41(1)
C(9)	6722(4)	1793(3)	7002(3)	40(1)
C(10)	7749(4)	583(4)	7103(3)	44(1)
C(11)	8497(4)	240(4)	7966(3)	41(1)
C(12)	9710(4)	748(4)	7811(3)	42(1)
C(13)	10420(4)	357(4)	8667(3)	52(1)
C(14)	6857(4)	3755(3)	5947(3)	33(1)
C(15)	7591(4)	4775(3)	5684(2)	30(1)
C(16)	8580(4)	4763(3)	6172(3)	36(1)
C(17)	9157(4)	5758(3)	5977(3)	39(1)
C(18)	8745(4)	6769(3)	5277(3)	35(1)
C(19)	7783(4)	6791(3)	4768(2)	36(1)
C(20)	7199(4)	5794(3)	4976(2)	34(1)
Br(1A)	-1552(1)	6533(1)	12436(1)	47(1)
O(1A)	1765(2)	6599(2)	8065(2)	34(1)
O(2A)	-236(2)	6882(3)	7693(2)	47(1)
C(1A)	4489(3)	7701(3)	6816(3)	32(1)
C(2A)	4354(4)	8023(3)	5782(3)	37(1)
C(3A)	5172(4)	8655(4)	6160(3)	44(1)
C(4A)	4493(4)	9865(4)	6376(3)	50(1)
C(5A)	3411(4)	9783(4)	6952(3)	42(1)
C(6A)	3226(3)	8473(3)	7232(3)	33(1)
C(7A)	2905(3)	8492(3)	5689(2)	36(1)

C(8A)	2282(3)	8164(3)	6715(2)	31(1)
C(9A)	2299(3)	6782(3)	7076(3)	32(1)
C(10A)	3635(4)	5896(3)	7028(3)	39(1)
C(11A)	4775(4)	6343(3)	7254(3)	39(1)
C(12A)	4930(4)	6002(4)	8292(3)	50(1)
C(13A)	6086(4)	6375(5)	8493(3)	74(2)
C(14A)	477(4)	6720(3)	8268(3)	34(1)
C(15A)	43(4)	6639(3)	9282(3)	30(1)
C(16A)	868(4)	6510(3)	9935(3)	39(1)
C(17A)	404(4)	6468(4)	10866(3)	42(1)
C(18A)	-904(4)	6553(3)	11157(3)	35(1)
C(19A)	-1738(4)	6664(3)	10532(3)	40(1)
C(20A)	-1258(4)	6712(3)	9594(3)	40(1)

Table 3. Bond lengths [Å] and angles [°] for 03145.

Br(1)-C(18)	1.877(4)
O(1)-C(14)	1.322(4)
O(1)-C(9)	1.455(4)
O(2)-C(14)	1.180(4)
C(1)-C(2)	1.471(5)
C(1)-C(11)	1.483(5)
C(1)-C(3)	1.494(5)
C(1)-C(6)	1.511(5)
C(2)-C(7)	1.504(5)
C(2)-C(3)	1.520(5)
C(3)-C(4)	1.465(5)
C(4)-C(5)	1.306(5)
C(5)-C(6)	1.493(5)
C(6)-C(8)	1.531(5)
C(7)-C(8)	1.514(5)
C(8)-C(9)	1.527(5)
C(9)-C(10)	1.511(5)
C(10)-C(11)	1.533(5)
C(11)-C(12)	1.499(5)
C(12)-C(13)	1.497(5)
C(14)-C(15)	1.485(5)
C(15)-C(16)	1.371(5)
C(15)-C(20)	1.376(5)
C(16)-C(17)	1.356(5)
C(17)-C(18)	1.368(5)
C(18)-C(19)	1.364(5)
C(19)-C(20)	1.362(5)
Br(1A)-C(18A)	1.876(4)
O(1A)-C(14A)	1.328(4)
O(1A)-C(9A)	1.444(4)
O(2A)-C(14A)	1.185(4)
C(1A)-C(11A)	1.481(5)
C(1A)-C(2A)	1.494(5)
C(1A)-C(3A)	1.495(5)
C(1A)-C(6A)	1.522(5)
C(2A)-C(3A)	1.504(5)

C(2A)-C(7A)	1.517(5)
C(3A)-C(4A)	1.455(5)
C(4A)-C(5A)	1.309(5)
C(5A)-C(6A)	1.484(5)
C(6A)-C(8A)	1.513(5)
C(7A)-C(8A)	1.526(5)
C(8A)-C(9A)	1.512(5)
C(9A)-C(10A)	1.518(5)
C(10A)-C(11A)	1.540(5)
C(11A)-C(12A)	1.505(5)
C(12A)-C(13A)	1.493(5)
C(14A)-C(15A)	1.465(5)
C(15A)-C(20A)	1.366(5)
C(15A)-C(16A)	1.371(5)
C(16A)-C(17A)	1.360(5)
C(17A)-C(18A)	1.366(5)
C(18A)-C(19A)	1.352(5)
C(19A)-C(20A)	1.371(5)

C(14)-O(1)-C(9)	118.1(3)
C(2)-C(1)-C(11)	116.3(3)
C(2)-C(1)-C(3)	61.7(2)
C(11)-C(1)-C(3)	138.7(3)
C(2)-C(1)-C(6)	104.2(3)
C(11)-C(1)-C(6)	115.0(3)
C(3)-C(1)-C(6)	104.5(3)
C(1)-C(2)-C(7)	106.8(3)
C(1)-C(2)-C(3)	59.9(2)
C(7)-C(2)-C(3)	125.0(4)
C(4)-C(3)-C(1)	106.5(3)
C(4)-C(3)-C(2)	114.7(3)
C(1)-C(3)-C(2)	58.4(2)
C(5)-C(4)-C(3)	111.7(4)
C(4)-C(5)-C(6)	110.7(4)
C(5)-C(6)-C(1)	105.4(3)
C(5)-C(6)-C(8)	115.4(3)
C(1)-C(6)-C(8)	97.2(3)
C(2)-C(7)-C(8)	102.9(3)

C(7)-C(8)-C(9)	114.2(3)
C(7)-C(8)-C(6)	100.6(3)
C(9)-C(8)-C(6)	105.7(3)
O(1)-C(9)-C(10)	106.7(3)
O(1)-C(9)-C(8)	105.9(3)
C(10)-C(9)-C(8)	116.8(3)
C(9)-C(10)-C(11)	116.4(3)
C(1)-C(11)-C(12)	115.4(3)
C(1)-C(11)-C(10)	103.1(3)
C(12)-C(11)-C(10)	115.0(3)
C(13)-C(12)-C(11)	112.7(3)
O(2)-C(14)-O(1)	124.2(4)
O(2)-C(14)-C(15)	124.4(4)
O(1)-C(14)-C(15)	111.4(3)
C(16)-C(15)-C(20)	119.7(4)
C(16)-C(15)-C(14)	121.7(3)
C(20)-C(15)-C(14)	118.5(3)
C(17)-C(16)-C(15)	120.7(3)
C(16)-C(17)-C(18)	118.8(4)
C(19)-C(18)-C(17)	121.6(3)
C(19)-C(18)-Br(1)	119.8(3)
C(17)-C(18)-Br(1)	118.7(3)
C(20)-C(19)-C(18)	119.2(3)
C(19)-C(20)-C(15)	120.0(4)
C(14A)-O(1A)-C(9A)	117.2(3)
C(11A)-C(1A)-C(2A)	115.5(3)
C(11A)-C(1A)-C(3A)	139.0(3)
C(2A)-C(1A)-C(3A)	60.4(2)
C(11A)-C(1A)-C(6A)	115.7(3)
C(2A)-C(1A)-C(6A)	102.6(3)
C(3A)-C(1A)-C(6A)	104.3(3)
C(1A)-C(2A)-C(3A)	59.8(2)
C(1A)-C(2A)-C(7A)	107.3(3)
C(3A)-C(2A)-C(7A)	125.6(3)
C(4A)-C(3A)-C(1A)	106.5(3)
C(4A)-C(3A)-C(2A)	114.7(3)
C(1A)-C(3A)-C(2A)	59.8(2)
C(5A)-C(4A)-C(3A)	111.5(4)

C(4A)-C(5A)-C(6A)	111.3(4)
C(5A)-C(6A)-C(8A)	116.2(3)
C(5A)-C(6A)-C(1A)	104.7(3)
C(8A)-C(6A)-C(1A)	98.3(3)
C(2A)-C(7A)-C(8A)	102.1(3)
C(9A)-C(8A)-C(6A)	107.0(3)
C(9A)-C(8A)-C(7A)	113.7(3)
C(6A)-C(8A)-C(7A)	101.0(3)
O(1A)-C(9A)-C(8A)	107.6(3)
O(1A)-C(9A)-C(10A)	106.2(3)
C(8A)-C(9A)-C(10A)	116.2(3)
C(9A)-C(10A)-C(11A)	116.6(3)
C(1A)-C(11A)-C(12A)	116.2(3)
C(1A)-C(11A)-C(10A)	102.9(3)
C(12A)-C(11A)-C(10A)	113.4(3)
C(13A)-C(12A)-C(11A)	112.7(4)
O(2A)-C(14A)-O(1A)	123.9(4)
O(2A)-C(14A)-C(15A)	124.1(4)
O(1A)-C(14A)-C(15A)	112.0(3)
C(20A)-C(15A)-C(16A)	118.2(4)
C(20A)-C(15A)-C(14A)	118.2(4)
C(16A)-C(15A)-C(14A)	123.7(4)
C(17A)-C(16A)-C(15A)	121.0(4)
C(16A)-C(17A)-C(18A)	119.5(4)
C(19A)-C(18A)-C(17A)	120.7(4)
C(19A)-C(18A)-Br(1A)	119.7(3)
C(17A)-C(18A)-Br(1A)	119.6(3)
C(18A)-C(19A)-C(20A)	119.1(4)
C(15A)-C(20A)-C(19A)	121.4(4)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03145. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	63(1)	46(1)	58(1)	3(1)	-4(1)	-23(1)
O(1)	40(2)	42(2)	37(2)	6(1)	-10(1)	-18(1)
O(2)	52(2)	45(2)	64(2)	-5(1)	-32(2)	-8(2)
C(1)	37(2)	31(2)	30(2)	-7(2)	0(2)	-9(2)
C(2)	53(3)	41(3)	45(3)	-8(2)	-1(2)	-24(2)
C(3)	47(3)	48(3)	40(3)	1(2)	-6(2)	-19(2)
C(4)	42(3)	59(3)	37(3)	-15(2)	-1(2)	-18(2)
C(5)	40(3)	45(3)	47(3)	-17(2)	2(2)	-10(2)
C(6)	35(2)	37(2)	38(2)	-9(2)	-1(2)	-12(2)
C(7)	41(3)	61(3)	48(3)	-7(2)	-5(2)	-17(2)
C(8)	34(2)	38(2)	50(3)	-7(2)	-4(2)	-9(2)
C(9)	51(3)	40(2)	36(2)	-5(2)	-8(2)	-21(2)
C(10)	53(3)	49(3)	37(2)	-16(2)	2(2)	-19(2)
C(11)	42(3)	40(2)	38(2)	-8(2)	4(2)	-7(2)
C(12)	36(3)	41(2)	43(3)	-10(2)	1(2)	-1(2)
C(13)	51(3)	51(3)	46(3)	-3(2)	-1(2)	-5(2)
C(14)	33(2)	36(2)	29(2)	-12(2)	-6(2)	2(2)
C(15)	32(2)	33(2)	21(2)	-9(2)	2(2)	-1(2)
C(16)	43(3)	36(2)	27(2)	0(2)	-10(2)	-10(2)
C(17)	42(3)	45(3)	32(2)	0(2)	-13(2)	-15(2)
C(18)	37(2)	31(2)	33(2)	-7(2)	4(2)	-4(2)
C(19)	43(3)	34(2)	23(2)	-1(2)	-4(2)	2(2)
C(20)	35(2)	38(2)	26(2)	-11(2)	-8(2)	2(2)
Br(1A)	58(1)	49(1)	36(1)	-11(1)	4(1)	-19(1)
O(1A)	31(2)	41(2)	32(2)	-6(1)	-3(1)	-12(1)
O(2A)	34(2)	78(2)	32(2)	-15(2)	-3(1)	-16(2)
C(1A)	23(2)	40(2)	36(2)	-14(2)	4(2)	-10(2)
C(2A)	37(3)	44(2)	31(2)	-16(2)	7(2)	-13(2)
C(3A)	33(2)	58(3)	45(3)	-19(2)	9(2)	-18(2)
C(4A)	54(3)	54(3)	51(3)	-13(2)	1(2)	-34(2)
C(5A)	46(3)	40(2)	46(3)	-16(2)	2(2)	-19(2)
C(6A)	31(2)	41(2)	29(2)	-11(2)	3(2)	-13(2)
C(7A)	40(3)	38(2)	30(2)	-9(2)	-5(2)	-11(2)

C(8A)	29(2)	33(2)	32(2)	-12(2)	-3(2)	-3(2)
C(9A)	31(2)	38(2)	33(2)	-16(2)	-3(2)	-8(2)
C(10A)	44(3)	37(2)	36(2)	-10(2)	1(2)	-8(2)
C(11A)	30(2)	46(3)	39(2)	-16(2)	-4(2)	0(2)
C(12A)	42(3)	56(3)	48(3)	-11(2)	-10(2)	-2(2)
C(13A)	44(3)	123(5)	61(3)	-32(3)	-11(3)	-15(3)
C(14A)	36(3)	29(2)	38(3)	-9(2)	-4(2)	-9(2)
C(15A)	32(2)	28(2)	32(2)	-6(2)	-5(2)	-9(2)
C(16A)	34(2)	52(3)	36(3)	-15(2)	2(2)	-16(2)
C(17A)	37(3)	57(3)	40(3)	-17(2)	-8(2)	-15(2)
C(18A)	44(3)	27(2)	32(2)	-6(2)	-2(2)	-10(2)
C(19A)	28(2)	43(3)	45(3)	-9(2)	1(2)	-7(2)
C(20A)	33(3)	49(3)	40(3)	-10(2)	-6(2)	-10(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03145.

	x	y	z	U(eq)
H(2)	6428	-730	8777	54
H(3)	7499	-626	10106	55
H(4)	6159	1208	10818	53
H(5)	6017	3116	9652	52
H(6)	7607	2549	8240	44
H(7A)	4567	1450	9013	60
H(7B)	4766	815	8112	60
H(8)	5323	2969	7793	49
H(9)	6111	1783	6562	48
H(10A)	8394	634	6524	53
H(10B)	7319	-109	7131	53
H(11)	8764	-696	8142	50
H(12A)	10305	453	7273	50
H(12B)	9467	1676	7638	50
H(13D)	9848	676	9196	78
H(13E)	11210	699	8525	78
H(13F)	10665	-561	8841	78
H(16)	8864	4051	6651	43
H(17)	9835	5752	6321	47
H(19)	7523	7493	4275	44
H(20)	6521	5803	4632	40
H(2A)	4844	7379	5411	44
H(3A)	6148	8457	6009	53
H(4A)	4798	10619	6129	60
H(5A)	2820	10473	7165	50
H(6A)	3048	8185	7935	40
H(7A1)	2622	8053	5282	43
H(7A2)	2688	9407	5428	43
H(8A)	1380	8691	6816	37
H(9A)	1724	6537	6718	39
H(10C)	3863	5724	6382	47
H(10D)	3563	5090	7476	47

H(11A)	5603	5938	6903	46
H(12C)	4128	6418	8648	60
H(12D)	5027	5084	8522	60
H(13A)	6886	5952	8154	111
H(13B)	6142	6133	9176	111
H(13C)	5988	7286	8280	111
H(16A)	1778	6450	9734	47
H(17A)	986	6380	11311	51
H(19A)	-2645	6708	10739	48
H(20A)	-1844	6797	9152	48

(1S, 3S, 4S, 5R, 6S, 8R, 11R), (1R, 3R, 4R, 5S, 6R, 8S, 11S)-4-Bromo-benzoic acid-3-vinyl-tetracyclo[3.2.1.3^{1,8}.0^{7,11}]uncec-9-enyl ester (520).

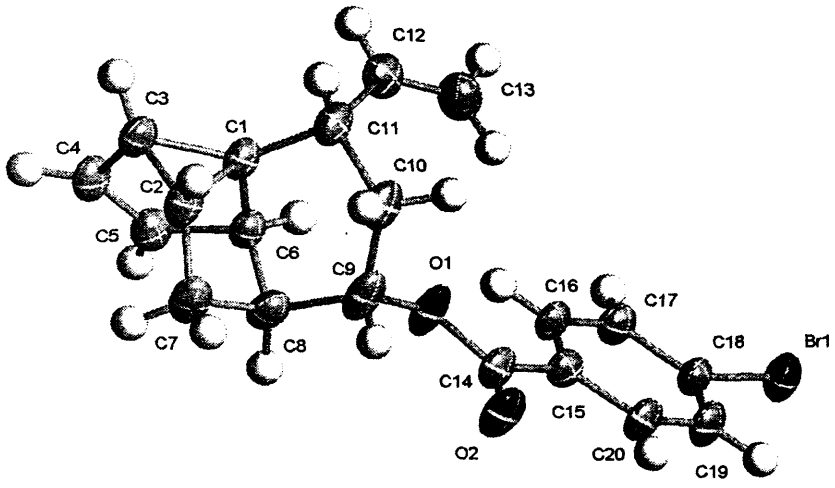
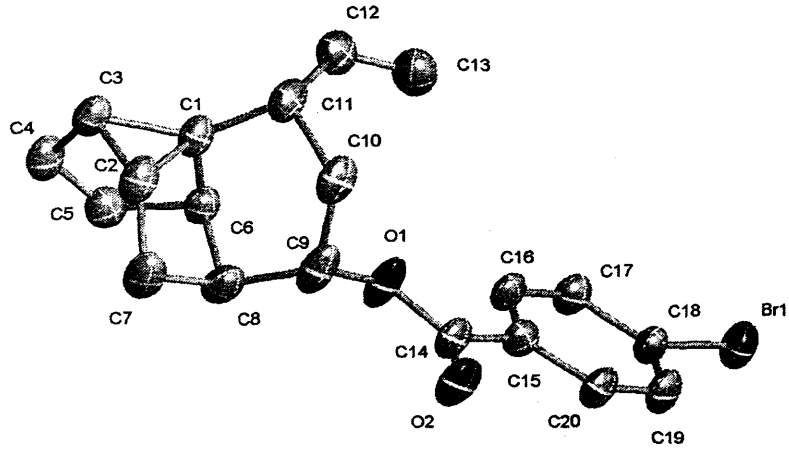


fig shows the atom label scheme and 50% displacement ellipsoids



as above but with H atoms omitted for clarity

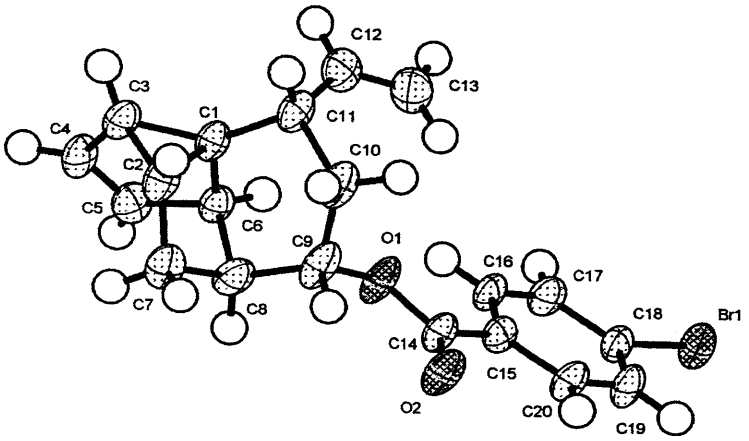

C12
C13
C3
C1
C11
C4
C10
C2
C5
C6
C9
O1
C16
C17
C7
C8
C18
Br1
C14
C15
O2
C20
C19

Table 1. Crystal data and structure refinement for 03123.

Identification code	03123	
Empirical formula	C20 H19 Br O2	
Formula weight	371.26	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.308(3) Å	α= 105.387(6)°.
	b = 9.390(4) Å	β= 100.332(6)°.
	c = 10.628(4) Å	γ = 91.481(7)°.
Volume	784.2(5) $Å^3$	
Z	2	
Density (calculated)	1.572 Mg/m^3	
Absorption coefficient	2.629 mm^{-1}	
F(000)	380	
Crystal size	0.36 x 0.09 x 0.04 mm^3	
Theta range for data collection	2.03 to 26.99°.	
Index ranges	-10<=h<=10, -11<=k<=11, -13<=l<=13	
Reflections collected	5322	
Independent reflections	3264 [R(int) = 0.0488]	
Completeness to theta = 26.99°	95.3 %	
Absorption correction	Empirical	
Max. and min. transmission	0.86 and 0.44	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3264 / 0 / 208	
Goodness-of-fit on F^2	0.939	
Final R indices [I>2sigma(I)]	R1 = 0.0644, wR2 = 0.1346	
R indices (all data)	R1 = 0.0984, wR2 = 0.1475	
Largest diff. peak and hole	0.812 and -0.651 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03123. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	4194(1)	1170(1)	3697(1)	47(1)
O(1)	8094(5)	6564(4)	8924(3)	45(1)
O(2)	9532(5)	6951(4)	7455(3)	47(1)
C(1)	7750(6)	8604(5)	12217(5)	32(1)
C(2)	9358(7)	9517(6)	12777(5)	41(1)
C(3)	8345(7)	9072(6)	13691(5)	37(1)
C(4)	8825(7)	7720(6)	14064(5)	40(1)
C(5)	8788(7)	6596(6)	13018(5)	39(1)
C(6)	8254(6)	7033(5)	11769(5)	32(1)
C(7)	10643(7)	8630(6)	12213(5)	44(1)
C(8)	9663(7)	7337(6)	11110(5)	41(1)
C(9)	8917(7)	7870(6)	9916(5)	45(2)
C(10)	7693(7)	9039(6)	10122(5)	41(1)
C(11)	6628(7)	9051(5)	11175(5)	38(1)
C(12)	5011(7)	8165(6)	10717(5)	43(1)
C(13)	4396(7)	7307(6)	9555(6)	51(2)
C(14)	8461(7)	6263(5)	7721(5)	34(1)
C(15)	7417(6)	5028(5)	6785(5)	32(1)
C(16)	6296(6)	4197(5)	7158(5)	34(1)
C(17)	5363(7)	3053(5)	6254(5)	36(1)
C(18)	5548(6)	2716(5)	4939(5)	34(1)
C(19)	6652(7)	3524(6)	4553(5)	42(1)
C(20)	7578(7)	4668(6)	5473(5)	37(1)

Table 3. Bond lengths [Å] and angles [°] for 03123.

Br(1)-C(18)	1.866(5)
O(1)-C(14)	1.327(6)
O(1)-C(9)	1.447(6)
O(2)-C(14)	1.202(6)
C(1)-C(11)	1.473(7)
C(1)-C(3)	1.495(6)
C(1)-C(2)	1.503(7)
C(1)-C(6)	1.519(7)
C(2)-C(7)	1.484(8)
C(2)-C(3)	1.522(7)
C(3)-C(4)	1.472(7)
C(4)-C(5)	1.310(7)
C(5)-C(6)	1.489(7)
C(6)-C(8)	1.525(7)
C(7)-C(8)	1.537(7)
C(8)-C(9)	1.521(8)
C(9)-C(10)	1.515(8)
C(10)-C(11)	1.544(7)
C(11)-C(12)	1.492(8)
C(12)-C(13)	1.288(7)
C(14)-C(15)	1.454(7)
C(15)-C(16)	1.376(7)
C(15)-C(20)	1.377(7)
C(16)-C(17)	1.349(7)
C(17)-C(18)	1.386(7)
C(18)-C(19)	1.360(7)
C(19)-C(20)	1.353(7)
C(14)-O(1)-C(9)	117.9(4)
C(11)-C(1)-C(3)	140.1(5)
C(11)-C(1)-C(2)	116.5(4)
C(3)-C(1)-C(2)	61.0(3)
C(11)-C(1)-C(6)	113.7(4)
C(3)-C(1)-C(6)	104.8(4)
C(2)-C(1)-C(6)	103.6(4)
C(7)-C(2)-C(1)	107.2(4)

C(7)-C(2)-C(3)	124.1(5)
C(1)-C(2)-C(3)	59.2(3)
C(4)-C(3)-C(1)	106.0(4)
C(4)-C(3)-C(2)	114.2(5)
C(1)-C(3)-C(2)	59.7(3)
C(5)-C(4)-C(3)	111.8(5)
C(4)-C(5)-C(6)	111.0(5)
C(5)-C(6)-C(1)	105.0(4)
C(5)-C(6)-C(8)	113.9(4)
C(1)-C(6)-C(8)	98.9(4)
C(2)-C(7)-C(8)	103.8(4)
C(9)-C(8)-C(6)	106.8(4)
C(9)-C(8)-C(7)	110.2(4)
C(6)-C(8)-C(7)	100.6(4)
O(1)-C(9)-C(10)	108.1(5)
O(1)-C(9)-C(8)	105.6(4)
C(10)-C(9)-C(8)	117.6(4)
C(9)-C(10)-C(11)	117.9(4)
C(1)-C(11)-C(12)	114.1(4)
C(1)-C(11)-C(10)	102.9(5)
C(12)-C(11)-C(10)	117.3(4)
C(13)-C(12)-C(11)	128.6(6)
O(2)-C(14)-O(1)	123.0(5)
O(2)-C(14)-C(15)	124.9(5)
O(1)-C(14)-C(15)	112.1(4)
C(16)-C(15)-C(20)	118.9(5)
C(16)-C(15)-C(14)	122.9(4)
C(20)-C(15)-C(14)	118.3(5)
C(17)-C(16)-C(15)	120.6(5)
C(16)-C(17)-C(18)	119.3(5)
C(19)-C(18)-C(17)	120.8(5)
C(19)-C(18)-Br(1)	120.7(4)
C(17)-C(18)-Br(1)	118.5(4)
C(20)-C(19)-C(18)	119.1(5)
C(19)-C(20)-C(15)	121.3(5)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03123. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	56(1)	52(1)	28(1)	7(1)	6(1)	-6(1)
O(1)	56(3)	52(2)	25(2)	4(2)	17(2)	-26(2)
O(2)	61(3)	51(2)	35(2)	14(2)	23(2)	-15(2)
C(1)	43(3)	31(2)	25(2)	11(2)	9(2)	-5(2)
C(2)	57(4)	39(3)	30(3)	14(2)	10(3)	-9(3)
C(3)	42(3)	43(3)	28(3)	11(2)	12(2)	-3(2)
C(4)	46(3)	52(3)	27(3)	20(2)	9(2)	-5(3)
C(5)	41(3)	45(3)	37(3)	21(2)	11(2)	-1(3)
C(6)	36(3)	37(3)	27(2)	11(2)	9(2)	-2(2)
C(7)	39(3)	57(3)	36(3)	14(3)	11(2)	-17(3)
C(8)	40(3)	48(3)	35(3)	8(2)	16(2)	-2(3)
C(9)	54(4)	50(3)	30(3)	7(2)	17(3)	-24(3)
C(10)	60(4)	39(3)	31(3)	17(2)	15(3)	-9(3)
C(11)	57(4)	34(3)	28(3)	14(2)	13(2)	4(2)
C(12)	50(4)	49(3)	38(3)	25(3)	10(3)	4(3)
C(13)	45(4)	63(4)	46(3)	18(3)	7(3)	-5(3)
C(14)	45(3)	39(3)	25(2)	15(2)	14(2)	-2(2)
C(15)	36(3)	40(3)	27(3)	16(2)	11(2)	1(2)
C(16)	40(3)	45(3)	22(2)	13(2)	13(2)	1(2)
C(17)	41(3)	41(3)	30(3)	13(2)	12(2)	-3(2)
C(18)	37(3)	42(3)	23(2)	9(2)	8(2)	2(2)
C(19)	53(4)	54(3)	23(3)	16(2)	13(2)	-2(3)
C(20)	49(3)	42(3)	26(3)	15(2)	17(2)	-2(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03123.

	x	y	z	U(eq)
H(2)	9377	10577	12760	49
H(3)	7780	9831	14274	44
H(4)	9125	7669	14956	48
H(5)	9065	5629	13052	47
H(6)	7352	6340	11134	39
H(7A)	11348	8264	12898	53
H(7B)	11340	9222	11843	53
H(8)	10317	6460	10867	49
H(9)	9828	8253	9565	53
H(10A)	6946	8926	9259	50
H(10B)	8306	10021	10364	50
H(11)	6406	10104	11558	45
H(12)	4347	8243	11369	51
H(13A)	4997	7179	8857	62
H(13B)	3342	6803	9396	62
H(16)	6177	4430	8061	41
H(17)	4588	2484	6515	43
H(19)	6772	3289	3651	50
H(20)	8354	5233	5209	44