The novel rearrangement of 1-acetyl-1-methylcyclohexa-2,5-diene

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Declaration

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Abstract

This thesis describes the results of the research into the novel rearrangement of 1-acetyl-1-methylcyclohexa-2,5-diene under basic conditions. The rearrangement involves the migration of an acetyl group around the cyclohexadiene ring. The rearrangement occurs *via* a cyclopropane intermediate, to produce a mixture of two isomers. The study involves calculations that evaluate the feasibility of the proposed mechanism. This is coupled with the experimental data for the rearrangement with a range of alkylating agents.

Chapter 1 presents a description of previous work carried out by the Elliott group and how the novel rearrangement of 1-acetyl-1-methylcyclohexa-2,5-diene was discovered. The proposed mechanism for the rearrangement is discussed which sets the stage for the work discussed in chapter 2.

Chapter 2 presents a review of Birch reduction chemistry. This was utilised as a synthetic route to produce 1-acetyl-1-methylcyclohexa-2,5-diene which is used as the starting material for rearrangement reactions.

Chapter 3 discusses the rearrangement reaction of 1-acetyl-1-methylcyclohexa-2,5-diene with a range of alkylating agents. It is followed by a computational study that evaluates the feasibility of the proposed mechanism.

Chapter 4 describes the brief evaluation of Na-SG as a method for partial reduction of aromatic compounds.

Acknowledgements

I would like to thank my supervisor, Dr Mark Elliott, for his support and guidance throughout my studies.

Thank you to the technicians and support staff at Cardiff University, who were always helpful and friendly.

I would also like to thank the members of the lab for their guidance, encouragement and friendship.

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Abbreviations

APCI	atmospehic pressure chemical ionisation
a.u.	atomic unit
BMEA	bis(methoxyethyl)amine
Bu	butyl
COSY	correlation spectroscopy
d	doublet
DBB	di-*tert*-butylbiphenyl
DCB	dichlorobenzene
DCM	dichloromethane
DFT	density functional theory
DNPH	2,4-dinitrophenyhydrazine
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
EDA	ethylenediamine
EDG	electron-donating group
EI	electron ionisation
ES	electrospray
Ether	diethyl ether
EtOAc	ethyl acetate
equiv.	equivalents
EWG	electron-withdrawing group
g	gram
HRMS	high resolution mass spectrometry
IR	infared
J	coupling constant
kJ	kilojoule
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
M	molar
MHz	megahertz
MTBE	methyl *tert*-butyl ether
m	multiplet

Me	methyl
MeTHF	2-methyl tetrahydrofuran
mg	milligram
mL	millilitre(s)
mmol	millimole(s)
NMR	nuclear magnetic resonance
m.p.	melting point
MS	mass spectrometry
Na-SG	sodium stabilised silica gel
Ph	phenyl
ppm	parts per million
q	quartet
r.t	room temperature
RHF	restricted Hartree-Fock
s	singlet
t	triplet
t-AmOH	*tert*-amyl alcohol
t-BuOK	potassium *tert*-butoxide
THF	tetrahydrofuran

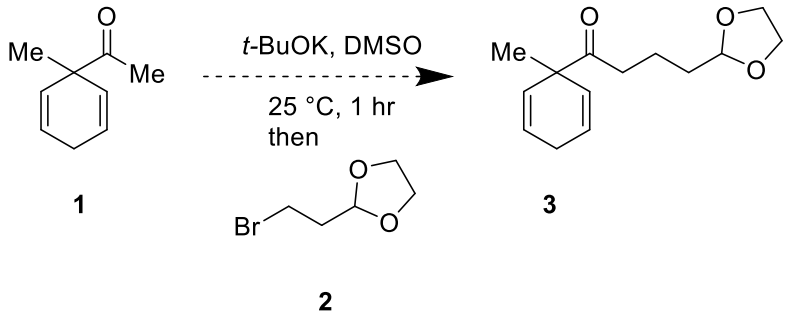
Chapter 1

Introduction

1.0 Introduction

1.1 Previous work by the Elliott group

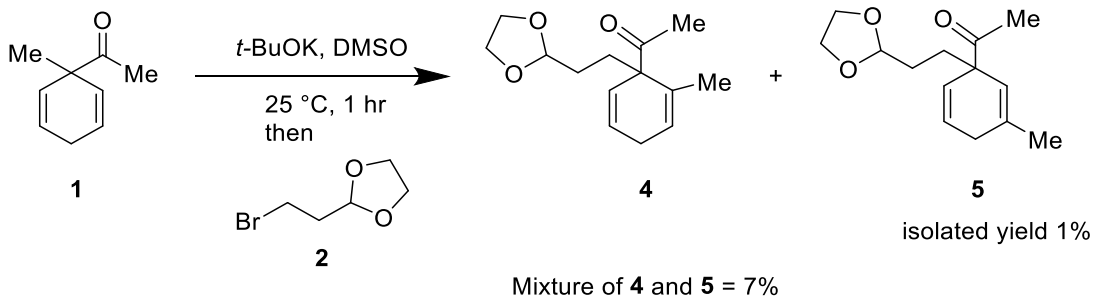
The Elliott group have previously investigated the alkylation of 1-acetyl-1-methylcyclohexa-2,5-diene **1**, with the hope to prepare a highly functionalised cyclohexadiene **3**.



Scheme 1: Desired outcome

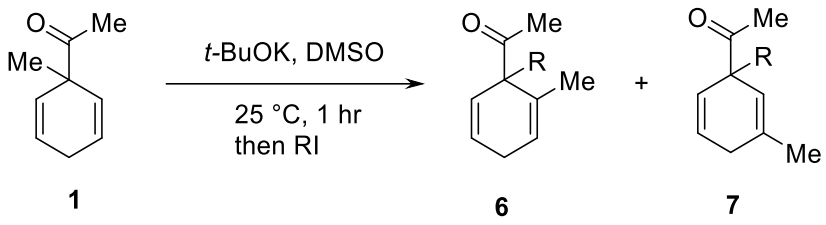
The reaction was performed under basic condition using potassium *t*-butoxide in DMSO followed by the addition of 2-(2-bromoethyl)-1,3-dioxolane **2**. Originally it was thought that the proton alpha to the carbonyl group would be deprotonated and alkylation would subsequently occur on the acetyl group.

Instead of producing the functionalised diene **3** pictured in **Scheme 1**, the reaction produced a mixture of two diene isomers **4** and **5** (**Scheme 2**).[1]



Scheme 2: The unexpected rearrangement and alkylation of 1-acetyl-1-methylcyclohexa-2,5-diene using 2-(2-bromoethyl)-1,3-dioxolane.[1]

The purification of the two isomers by column chromatography afforded compound **5** alone with a yield of (10 mg, 1%) and a 2:1 mixture of compounds **4** and **5** (65 mg, 7%). The initial expectation was for a deprotonation to occur alpha to the carbonyl group leading to formation of an enolate. Then a substitution reaction would proceed with a suitable halogenoalkane to form the desired alkylated product **3.** In practice two diene isomers **4** and **5** were observed in the ^{1}H NMR spectrum. The reason for this was not fully understood and it was therefore deemed necessary to carry out further investigation. The NMR spectra showed that the two diene isomers **4** and **5** were formed in a ratio of 1:2.7 respectively. The products were identified using NMR spectroscopy, including ^{1}H-^{1}H COSY. The goals of this project were to produce enough examples of this reaction and provide computational data to allow publication of this work.



Scheme 3: A generalised scheme for the rearrangement/alkylation of compound 1.

It was hoped that the computational data may offer some reasoning for the product ratios and confirm if the proposed mechanism was feasible (**Scheme 4**).

Compound **1** was produced using a Birch reduction-alkylation of acetophenone. This will be discussed on **Page 26**.

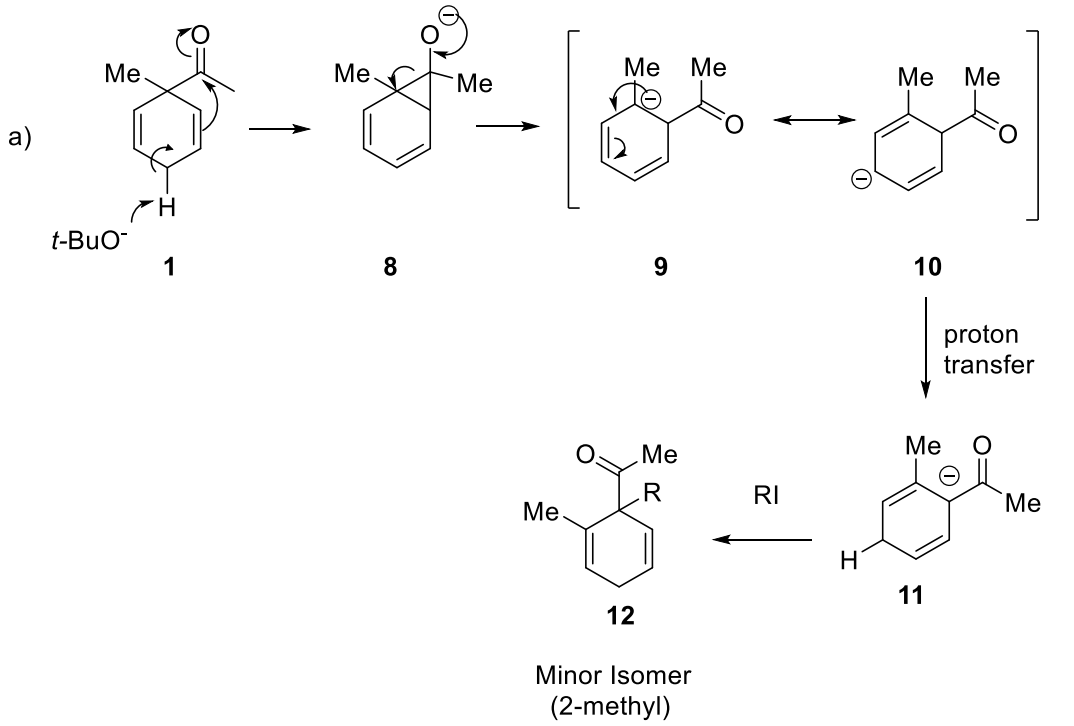
1.2 The proposed mechanism for the rearrangement of 1-acetyl-1-methylcyclohexa-2,5-diene under basic conditions

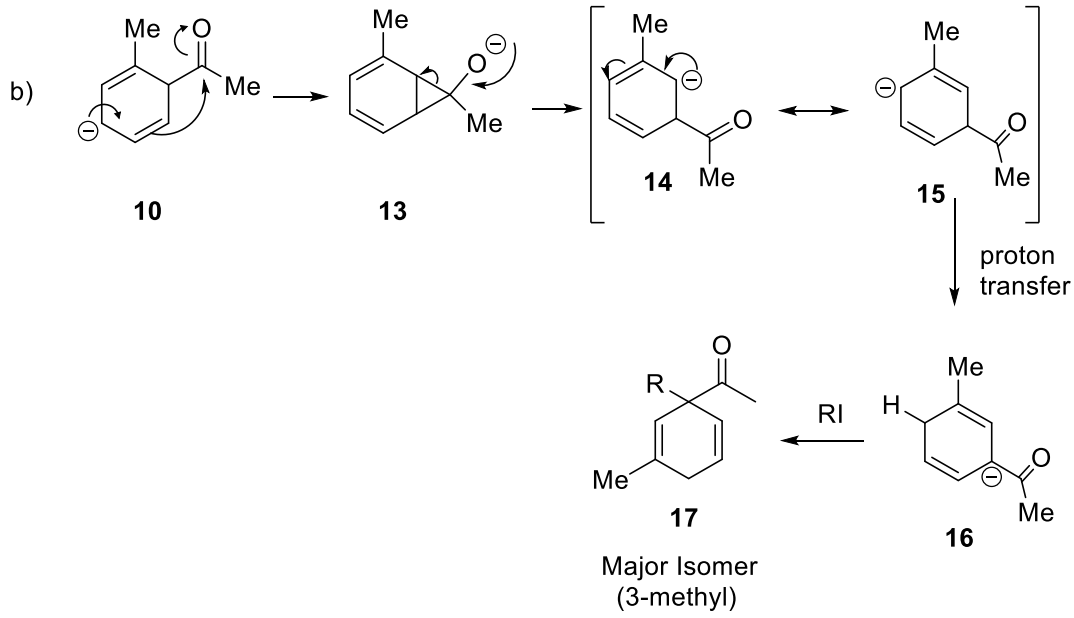
In the proposed mechanism, the first step is a deprotonation of C-4 of the parent diene **1** with *t*-BuOK. This leads to the rearrangement of the double bonds in the diene as cyclopropane intermediate **8** forms. If cyclopropane intermediate **8** was to undergo

cleavage of the original bond between the ring carbon and the carbonyl group, anion **10** would be formed. Anion **10** depicts the acetyl group having migrated one carbon around the diene ring. The negative charge is shifted from C-4 in anion **10** to C-1 in anion **11** in a proton transfer step as a result of a protonation/deprotonation occurring at opposite ends of the ring. The alkylation of **11** with a suitable halogenoalkane will produce the minor isomer **12**.

If diene anion **10** did not undergo alkylation and the negative charge was in position 2- or 6- then it could attack the carbonyl to form cyclopropane intermediate **13**. The cyclopropane bonds could then break in a similar fashion to the first cyclopropane. The acetyl group will have migrated around the ring as the previous diene carbon to carbonyl bond is broken to form **14**. The acetyl group will appear to have migrated around the ring by two carbons. A proton transfer step could occur to form diene anion **16** which could then be alkylated to form the major isomer **17**.

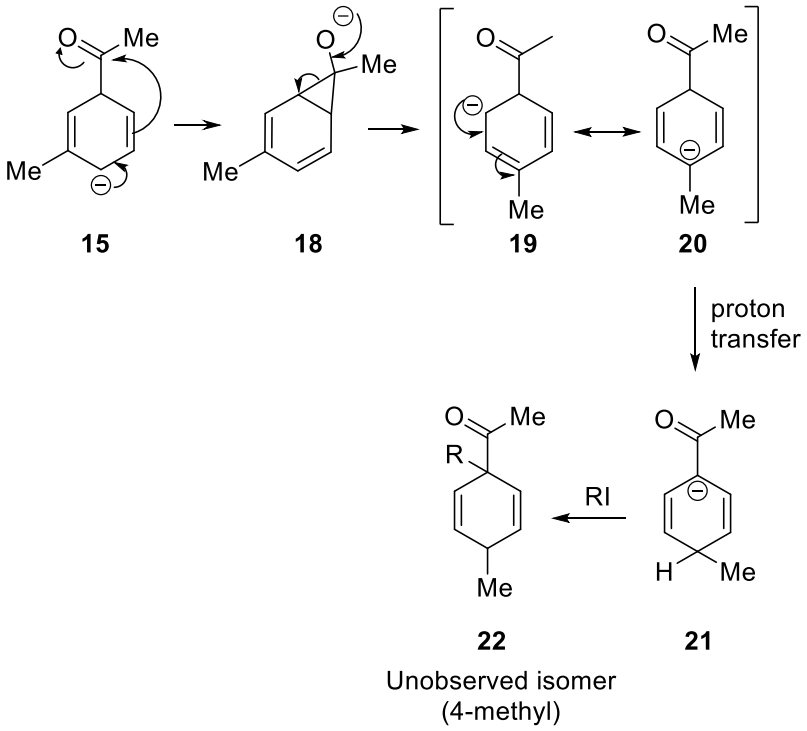
There is potential for a further migration (**Scheme 5**). This would occur in a similar fashion as above with the formation of a cyclopropane intermediate **18**. If the cyclopropane intermediate **18** was to collapse so the newly formed bond between the carbon on the cyclohexadiene and carbonyl bond remained, whilst the original bond between the cyclohexadiene and the acetyl group was broken, then the diene anion **20** would be formed. If **20** underwent a proton transfer due to a protonation/deprotonation occurring at opposite ends of the ring then **21** would form. Alkylation from a suitable halogenoalkane would produce the isomer **22**. The acetyl group will have migrated a total of three carbons around the ring from its original position in compound **1**.





Scheme 4: The proposed mechanism for the rearrangement of compound 1.

1.3 Formation of a potential third isomer, so far unobserved



Scheme 5: The proposed mechanism for the formation of a third isomer, not observed in the experimental results.

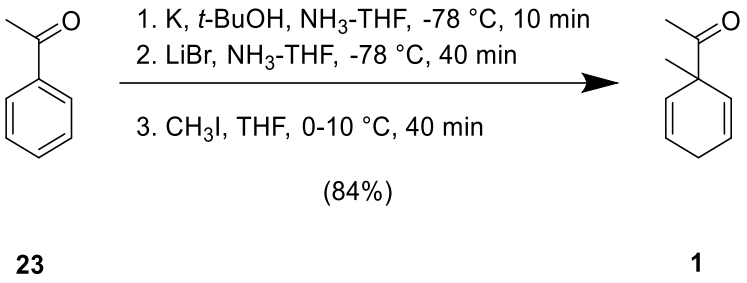
Chapter 2

The Birch reduction

2.0 The Birch reduction

2.1 Synthesis of 1 -acetyl-1-methylcyclohexa-2,5-diene

Compound **1** was produced by using the Birch reduction and methylation of acetophenone **23**. Narisada has reported an effective procedure for the reductive alkylation of acetophenone. The procedure details the *in situ* methylation of l-(cyclohexa-2,5-dienylidene)ethanolate to produce 1-acetyl-1-methylcyclohexa-2,5-diene **1** (84%).[2] The optimised conditions for this reaction are detailed below in **Scheme 6**. These conditions afforded the product in a good yield of 84%, along with some unreacted acetophenone, 1-phenyethyl alcohol and *dl*-2,3-diphenylbutane-2,3-diol.



Scheme 6: The reductive alkylation of acetophenone.

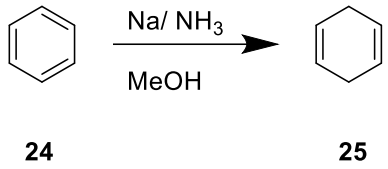
The addition of a lithium salt (either lithium iodide or lithium bromide) was noted as key in order to form a lithium enolate which was essential to achieve an alkylation.

2.2 Introducing the Birch reduction

The Birch reduction is a well-established procedure. Initially Kraus (1921) reported that sodium metal dissolved in liquid ammonia consists of metal atoms in equilibrium with metal cations and solvated electrons.[3,4,5] The reducing capabilities of the alkali metals dissolved in ammonia was originally investigated by Wooster and Godfrey in 1937.[6] The study observed the reduction of toluene using alkali metals dissolved in ammonia followed by the addition of water or another hydrolytic solvent. In this experiment, sodium or potassium metal was added portion-wise to toluene dissolved in liquid ammonia. In the absence of a proton source the deep blue colour persisted indefinitely. When the reaction was repeated with the addition of water, the reaction produced an unsaturated liquid with a boiling range of 110–115 °C. The unsaturated liquid was

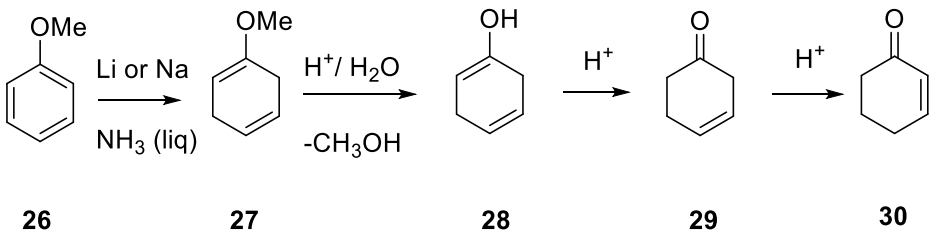
subjected to a series of chemical tests. The product was found to char with fuming sulfuric acid, react vigorously with bromine and decolourise bromine solution. The results suggested that toluene had been partially reduced.

Wooster went on to report the reduction of benzene **24** using sodium and methanol in 1938 (**Scheme 7**). Arthur Birch continued to develop the procedure and devised the Birch reduction that we are now familiar with today.



Scheme 7: The reduction of benzene by Wooster and Godfrey.[6]

Alkali metal-ammonia reduction chemistry founded the basis of research by Arthur Birch. The procedure was extensively developed to become the aptly named Birch reduction (reported in 1944).[5,7] Birch applied his method to partially reduce methoxytetralin and estrone methyl ether towards the end of the war whilst investigating the synthesis of cortical hormones.[7] Bizarrely, Birch was tasked with researching the female hormones and synthetic analogs because the RAF believed German fighter pilots were being supplied with cortical hormones. Thus Birch was tasked with finding a similar alternative for use by British pilots. Birch managed to successfully reduce a whole range of anisole derivatives.[5] Birch analysed the dihydro-derivatives by converting them into ketones through treatment with a mineral acid (**Scheme 8**).



Scheme 8: Birch reduction and acid hydrolysis of anisole.

The cyclohexanone compounds detailed in **Table 1** were then converted into 2,4-dinitrophenylhydrazone derivatives, except for 2-cyclohexenone which was converted into a semicarbazide derivative and analysed as such.

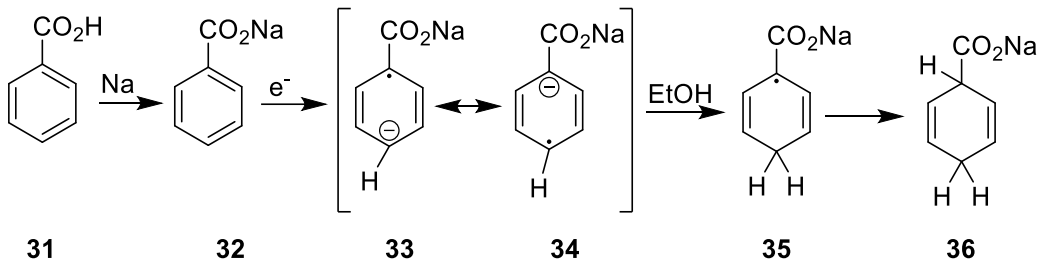
Starting compound	**Product from the Birch reduction and acid hydrolysis**	**Yield for the 2,4-dinitrophenyl hydrazone derivatives of the cyclohexenone.**
Anisole	2-Cyclohexenone	20%
2-Methylanisole	6-Methyl-2-cyclohexenone	12%
3-Methylanisole	3-Methyl-2-cyclohexenone	45%
3,4-Dimethylanisole	3,4-Dimethyl-2-cyclohexenone	35%
3,5-Dimethylanisole	3,5-Dimethyl-2-cyclohexenone	16%

Table 1: The Birch reduction of anisole analogs, yields are calculated from 2,4-dinitrophenylhydrazone and semicarbazide derivatives.[5]

The partial reduction of aromatic substrates can be a useful route for the synthesis of partially unsaturated cyclic compounds. The general procedure is achieved by dissolving alkali metals (usually Li, Na, K) in liquid ammonia solvent, with an alcohol (ethanol or *t*-butyl alcohol are common) as a proton source, and an inert co-solvent (*e.g.* diethyl ether, tetrahydrofuran) is usually required.[4]

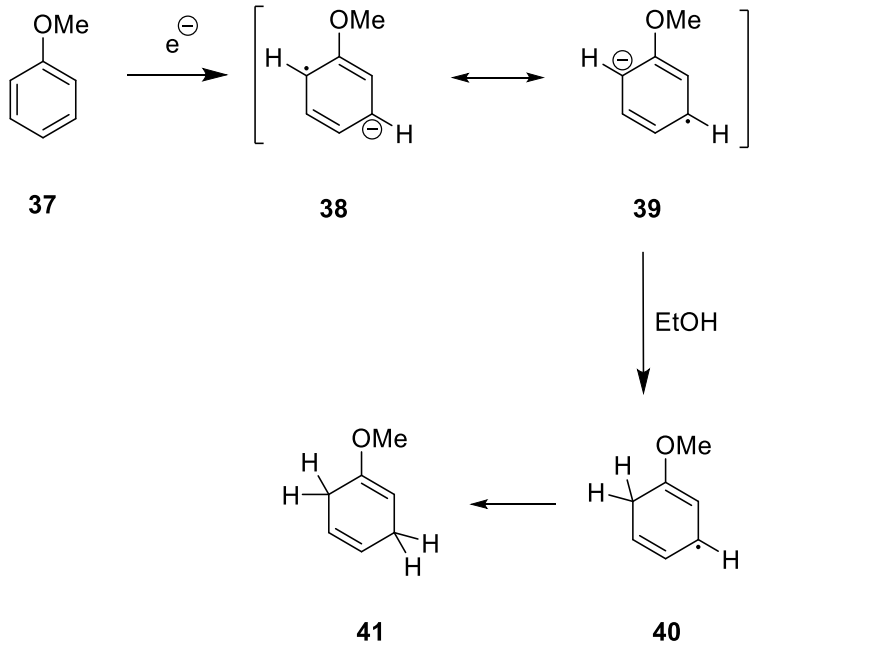
2.3 Regioselectivity of the Birch reduction

The functional groups attached to a mono-substituted aromatic compounds influence the regioselectivity of the Birch reduction. The resulting arrangement of the diene is dependent on whether the substituent group is electron-withdrawing or electron-donating. An electron-donating group (*e.g.* Alkyl, OMe, NR_2) will appear on an sp^2 hybridised carbon, whereas an electron-withdrawing group (*e.g.* C=O) will appear on an sp^3 hybridised carbon in the product.[4,8]



Scheme 9: The effect of an electron-withdrawing group on the regioselectivity of the double bonds.[4]

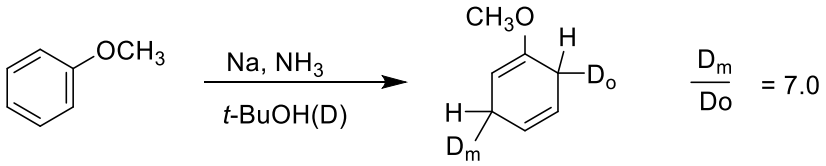
Electron-withdrawing groups stabilise the electron density at the *ipso* and *para* positions through conjugation and therefore a negative charge will be found at one of these positions.



Scheme 10: The effect of an electron-donating group on the regioselectivity of the Birch reduction.[4]

The negative charge is less destabilised by the electron donating (OMe) group when it is in the *ortho*/*meta* position. Zimmerman *et al.* investigated the mechanism of the Birch reduction and rationalised the steps using an isotopic labelling experiment. Using *t*-BuOH that contained a small amount of deuterated *t*-BuOD as a proton/deuterium

source, Zimmerman was able to support his notion of initial protonation of the carbon anion *ortho* to the methoxy group. The initial protonation should be more selective to becoming protonated than deuterated.[8]



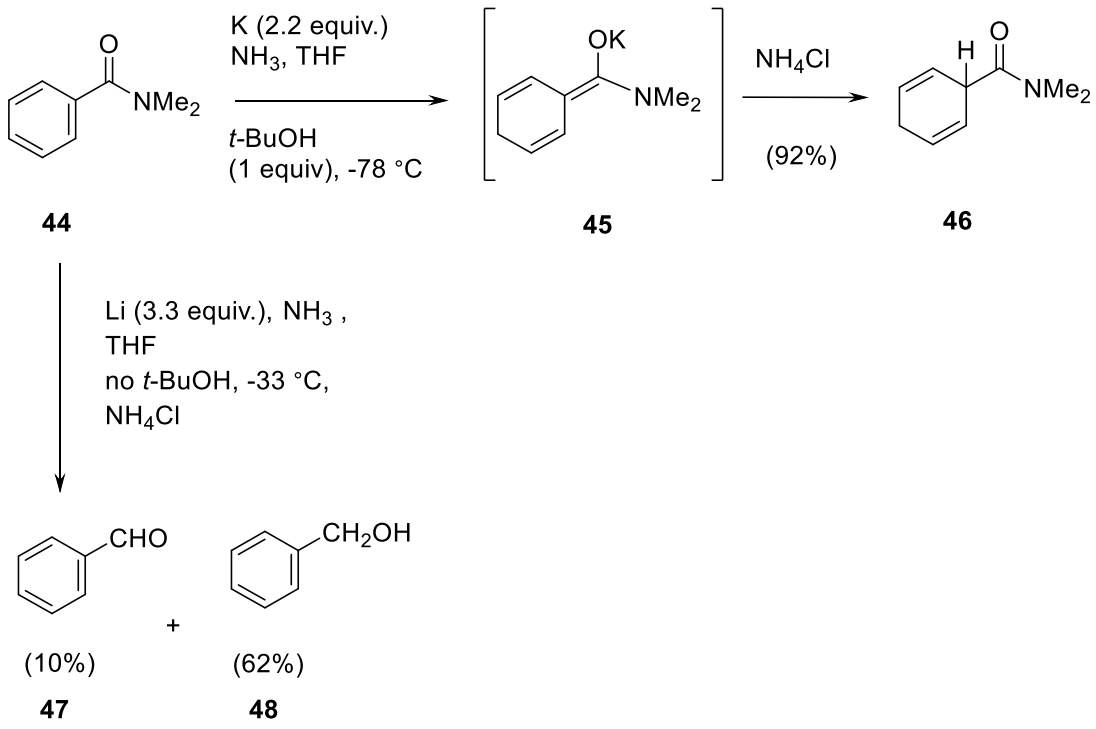
42 **43**

Scheme 11: Zimmerman: an isotopic study of anisole using *t*-BuOH(D).[8]

2.4 Reducing capabilities of the alkali metals

The Birch reduction can employ several alkali metals as a source of electrons. The metal that is used can have a profound effect on the outcome of the reduction. This is credited to the differences in their reduction potentials (Li = –2.99 V, Na = –2.59 V, K = –2.73 V, Ca = –2.39 V).[3] Careful consideration must be taken when assessing which alkali metal to use when reducing substituted aromatic rings.

Originally benzamide substrates were thought of as being inappropriate for a Birch reduction as it was believed that reduction of the amide would compete with the reduction of the aromatic ring. Schultz *et al.* discovered that adding potassium metal in NH_3-THF solution at –78 °C to *N,N*-dimethylbenzamide, followed by the addition of one equivalent of *t*-BuOH, resulted in the formation of diene **46** in good yield (92%). If lithium metal in NH_3-THF solution at –33 °C was used on the same substrate in the absence of *t*-butyl alcohol, the major products were benzaldehyde **47** (10%) and benzyl alcohol **48** (62%) (**Scheme 12**).[9]



Scheme 12: Reduction of *N,N*-dimethylbenzamide, showing reduction of the aromatic ring or reduction of the amide.[9]

Contradictory to the above reaction which favoured potassium metal, a study conducted by Wilds and Nelson reported that yields for the same compounds were greater when lithium was used instead of sodium.[10]

2.5 Preventing reduction of alkylating agents during a Birch reduction-alkylation

In order to avoid reducing the alkylating agents during a Birch alkylation, penta-1,3-diene (piperylene) may be added after the reduction of the conjugated ring. This helps to mop up excess solvated electrons/potassium. Lithium bromide may also be added to reduce the basicity of the anion. This allows an alkylating agent to be used that will otherwise be deprotonated in the presence of a strong base.[11] In certain cases when alkylating in the presence of acetyl groups on mono aromatics, the addition of lithium bromide is used to form a lithium enolate. A lithium enolate is easier to alkylate than sodium or potassium enolates.[12]

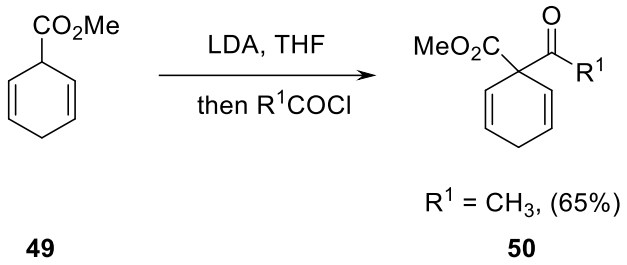
2.6 Hook and Mander's preferred Birch reduction conditions

Hook and Mander have summarised the key conditions for completing a Birch reduction.[12] The main points to consider are, that ammonia should ideally be freshly distilled and dry. This should alleviate the presence of any iron salts, formed in the ammonia cylinder, which may catalyse the unwanted formation of sodium amide.

Oxygen should be excluded from the reaction flask. This can be achieved by using an inert gas atmosphere (nitrogen is generally considered sufficient). The temperature of the reaction must be kept low in order to reduce any undesired side chain reactions. For the reduction of aromatic esters and ketones the temperature should be below –70 °C. Some metals are more selective than others. Generally, sodium and lithium are considered a good choice, with potassium less commonly used but favourable when certain substrates are used. The metal should be added in small portions to a mixture of the substrate dissolved in ammonia, co-solvent and alcohol at below –70 °C. Tetrahydrofuran is considered a convenient co-solvent for most reductions. A readily available proton source is also required. *t*-butyl alcohol and ethanol have been previously mentioned. Methanol and ethanol are preferential as they perform the protonation faster than the tertiary alcohols and therefore reduce the chance of undesired side chain reactions. After the addition of the alkali metal to the solution, a dark blue colour should persist for over 5 minutes to highlight the presence of solvated electrons. After the blue colour has persisted, penta-1,3-diene may be added, followed by an electrophile e.g. ammonium chloride to quench the reaction.

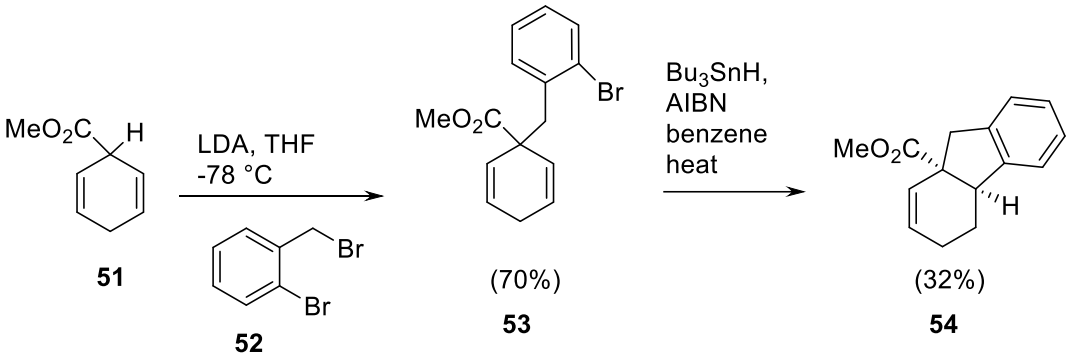
2.7 Substituting groups onto a cyclohexa-1,4 diene

Substituting groups onto a cyclohexadiene can be achieved under basic conditions, employing LDA dissolved in THF, followed by the addition of an acyl chloride. An example involving methyl cyclohexa-2,5-diene-1-carboxylate **49** under these conditions (**Scheme 13**). Initially the proton alpha to the ester is removed by LDA. The reaction proceeds using the nucleophilic tendency of the enolate. This performs a nucleophilic addition onto the acyl chloride to form the intermediate alkoxide. This is followed by the elimination of the chloride to give the product **50** (**Scheme 13**).[13]



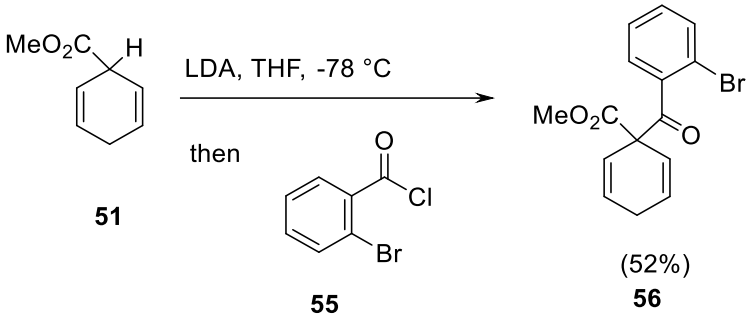
Scheme 13: Substituting an alkyl group onto a cyclohexadiene.[13]

Elliott and co-workers were able to perform an alkylation at the *ipso* position on methyl cyclohexa-2,5-diene-1-carboxylate **51** using 2-bromobenzyl bromide **52**. Treatment of **53** with tributyltin hydride under standard conditions gave **54** as the cyclised product (**Scheme 14**).



Scheme 14: Alkylation of cyclohexadiene 50 using with 2-bromobenzyl bromide and cyclisation.[14]

Attempts to deprotonate **51** and react it with 2-bromobenzaldehyde failed. However the acylation of methyl cyclohexa-2,5-diene-1-carboxylate **51** was achieved using 2-bromobenzoyl chloride **55**, to produce **56** (**Scheme 15**).



Scheme 15: Acylation of cyclohexadiene using with 2-bromobenzoyl chloride.[14]

Chapter 3

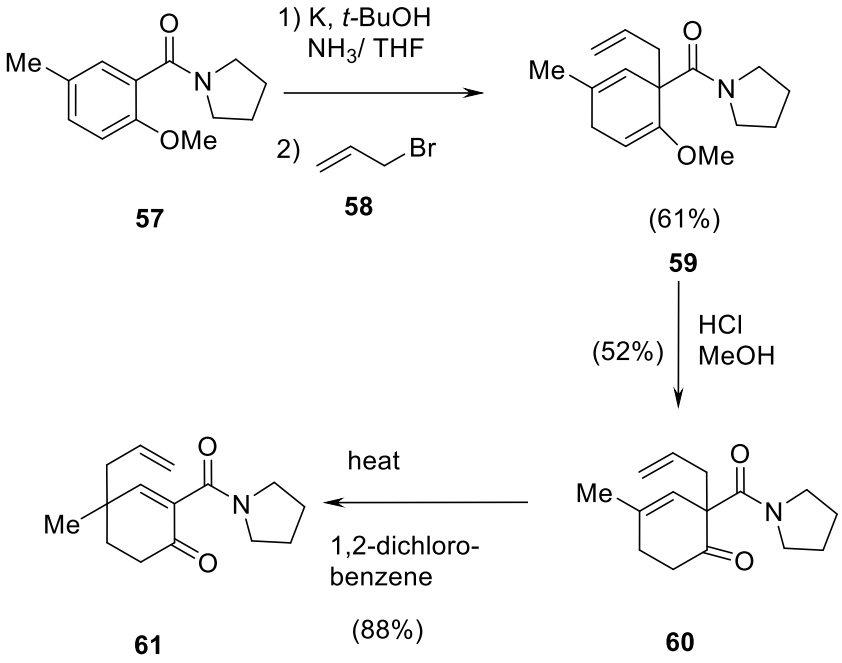
Rearrangement reactions of cyclohexadienes

3.0 Rearrangement reactions of cyclohexadienes

3.1 The Cope rearrangement

The Cope rearrangement consists of a [3,3]-sigmatropic rearrangement of a 1,5-diene to produce a thermodynamically more stable regioisomer.

Malachowski *et al.* investigated the Birch reduction-allylation and subsequent Cope rearrangement of *o*-anisic acid derivatives. The study provided the first example of a quaternary carbon synthesis onto a cycloalkenone ring by a Cope rearrangement.[15] The first stage involved the Birch reduction-alkylation of **57**, to produce diene **59**. The resulting cyclohexa-1,4-diene derivative **59** was hydrolysed to cyclohexanone **60** using hydrochloric acid and methanol. The product underwent a sigmatropic rearrangement when heated under reflux in 1,2-dichlorobenzene to produce **61** (**Scheme 16**).[15, 16]

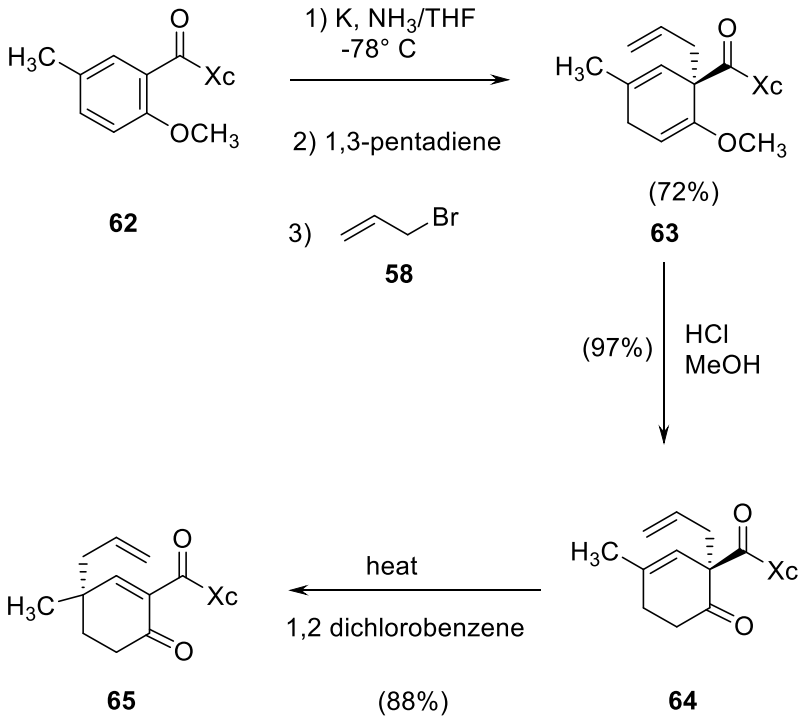


Scheme 16: Birch reduction–allylation and Cope rearrangement of *N*-pyrrolidinyl 2-methoxy-5-methylbenzamide.[15]

Malachowski *et al.* were able to apply the Birch-Cope rearrangement in a stereoselective synthesis. This involved producing compound **63** by a Birch reduction-alkylation achieving a yield of 72% and a diastereoselectivity of 110:1 in favour of the isomer with the *(R)* at the newly-formed quaternary centre as shown. Compound **63** was converted

into the Cope rearrangement substrate **64** by acid hydrolysis. Compound **64** required heating under reflux for 10 hours in 1,2-dichlorobenzene to achieve the sigmatropic rearrangement. The total synthesis from **62** to produce **65** had an overall yield of 60% (**Scheme 17**).[17]

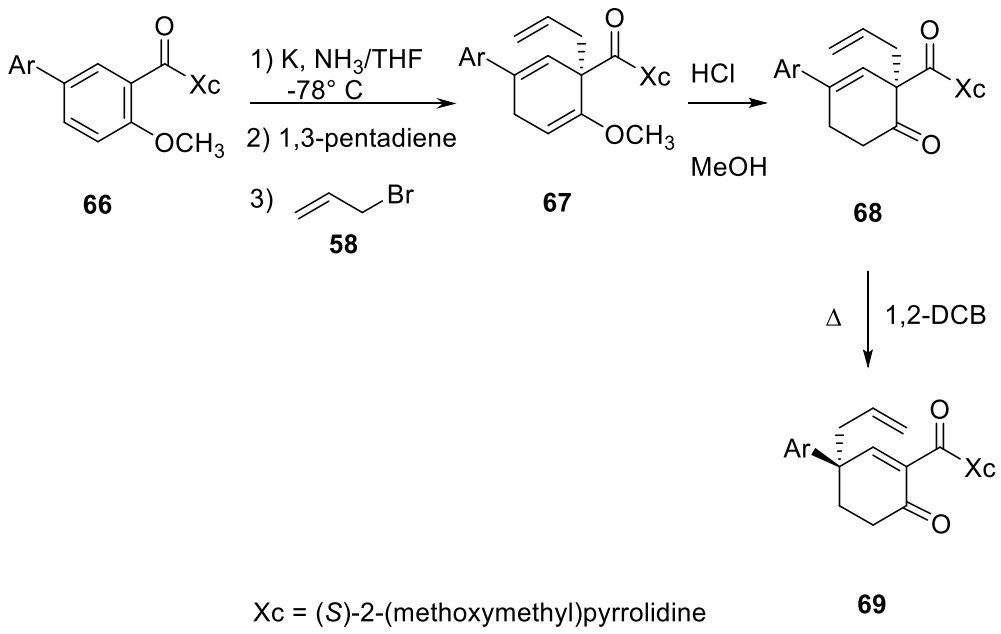
The results were analysed by gas chromatography and compared to a 1:1 diastereomeric mixture as a reference.



Scheme 17: Enantioselective Birch reduction-Cope rearrangement.[17]

3.2 The spontaneous Cope rearrangement

In a study by Paul, Malachowki and Lee an example of a spontaneous Cope rearrangement at room temperature was observed for one very unstable compound, **67a**.[18] The study featured the investigation of the Birch–Cope sequence for the formation of a quaternary centre on C-5 of 2-cyclohexen-1-one rings (**Scheme 18**).

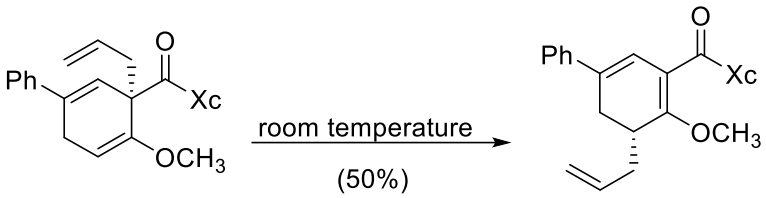


Scheme 18: C-5 Aryl derivatives in the Birch–Cope sequence.[18]

Ar	d.r.	Yield of 67 (%)	Yield of 68 (%)	Yield of 69 (%)
a: Ph	35:1	62	64	80
b: 4-$(CH_3O)C_6H_4$	50:1	58	89	80
c: 3,4-$(CH_3O)_2C_6H_3$	>99:<1	70	95	80
d: 2,3-$(CH_3O)_2C_6H_3$	>99:<1	70	96	50

Table 2: Yields for the C-5 Aryl derivatives in Birch–Cope sequence in Scheme 18

When compound **67a** was being stored it was discovered to have undergone a spontaneous Cope rearrangement to produce a new product **70**. The spontaneous rearrangement this time favoured the [3,3]-sigmatropic arrangement on the alternative side of the diene ring. **Scheme 19** below details the Cope rearrangement of compound **67a** at room temperature.



67a **70**

Xc= (*S*)-2-(methoxymethyl)pyrrolidine

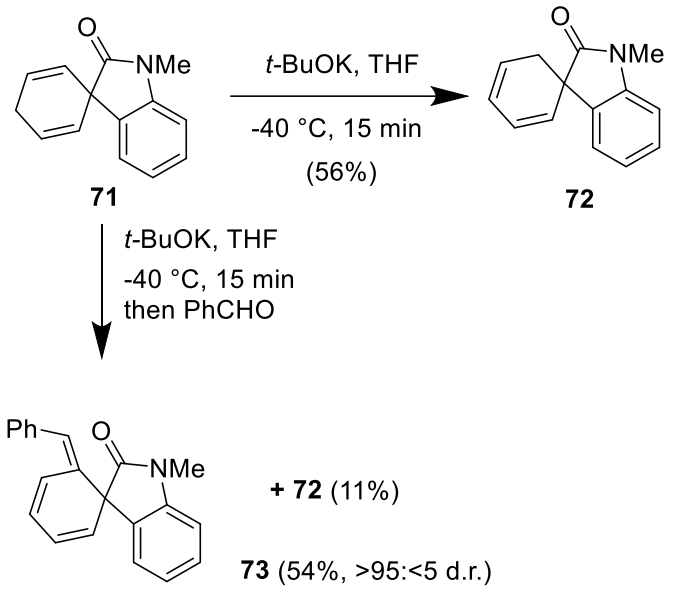
Scheme 19: Spontaneous Cope rearrangement.[18]

The other aryl derivatives detailed in **Table 2**, did not rearrange spontaneously.

3.3 The Landais rearrangement

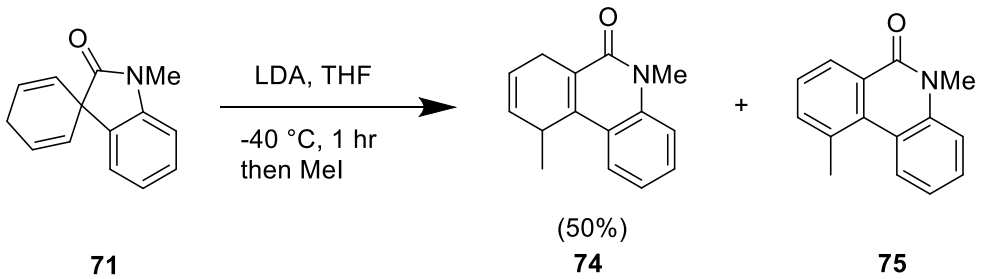
Landais *et al.* carried out some interesting research into the functionalisation and rearrangement of spirocyclohexadienyl oxindoles under basic conditions.[19] The study was conducted using experimental and theoretical techniques to rationalise the mechanism of the rearrangement. When *t*-BuOK was added to spirocyclohexadienyl oxindole **71** in THF and stirred for 15 minutes the diene system became dissymmetric to form **72**. Landais suggested that this had occurred through a deprotonation of **71** by *t*-BuOK, followed by the reprotonation with *t*-BuOH to form the isomerised product **72**.

Addition of benzaldehyde shortly after deprotonation gave a compound which was drawn as **73** along with a small amount of **72**. Compound **73** was described as a single (*Z*) isomer, however the structure drawn in the literature depicts the (*E*) isomer.



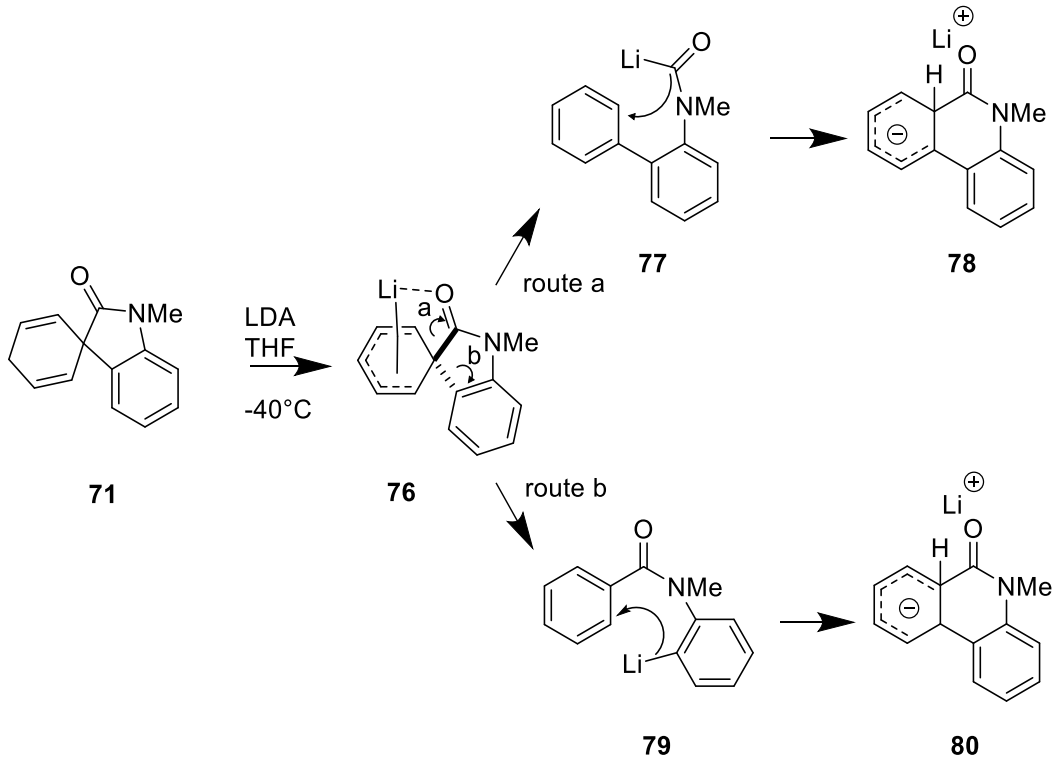
Scheme 20: Desymmetrisation of spirocyclohexadienyl oxindole 71 with *t*-BuOK.[19]

In a separate experiment, spirocyclohexadienyl oxindole **71** was treated with LDA at -78 °C followed by the addition of iodomethane. Under these conditions no rearrangement occurred. When the reaction of spirocyclohexadienyl oxindole **71** was repeated at a temperature of –40 °C with LDA and quenched with iodomethane a rearrangement and alkylation had occurred to produce a mixture of **74** and **75**.[19] Product **75** is the oxidation product of compound **74** after re-aromatisation.



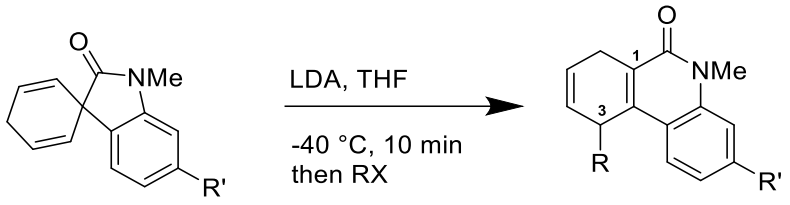
Scheme 21: Rearrangement of spriocyclohexadienyl oxindole 71 under basic conditions.[19]

The proposed mechanism for this rearrangement is detailed in **Scheme 22** below. It involves the coordination of a lithium ion to the amide group. This coordination influences the regioselectivity of the whole process.[19]



Scheme 22: The proposed mechanism by Landais for the rearrangement of spriocyclohexadienyl oxindole 71 under basic conditions.[19]

The optimisation process for this reaction demonstrated that LDA dissolved in THF at a temperature at –40 °C, followed by the addition of iodomethane after 10 minutes produced the highest yield. The optimised reaction conditions were able to produce **74** in a yield of over 90%. When a higher temperature or a longer reaction time was used, the yield of **74** decreased and more of compound **75** was produced. This has been attributed to the oxidative aromatisation of **74**. The optimised conditions were suitable for a range of alkylating agents; allyl bromide and chloro(methoxy)methane are just two examples. All of the alkylating agents used achieved a regioselective alkylation.

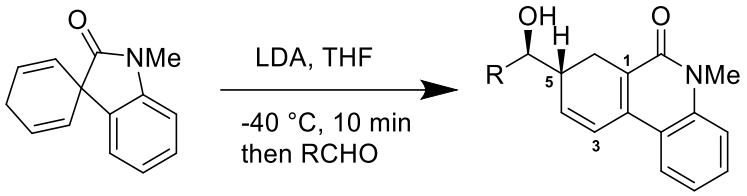


71 **81**

R'	RX	Product	Yield (%)
H	MeI	**81a**	67
H	AllylBr	**81b**	48
H	$MeOCH_2Cl$	**81c**	30

Table 3 Rearrangement of spriocyclohexadienyl oxindole 71 followed by the addition of alkylating agents.[19]

Landais *et al.* have noted that the yields for several of their products are not representative of the real efficiency of the process due to the tendency for the compounds to rearomatise. Interestingly when other electrophiles are used such as an aldehyde the regioselectivity of the reaction was different to that when a halogenoalkane was used in the quenching process. When a halogenoalkane was added the addition occurred at C-3 (**Table 3**). When an aldehyde was used as a quenching agent the aldehyde added at C-5 (**Table 4**).[19] X-ray diffraction studies of **82a** showed the reaction was stereoselective towards the *anti*-isomer, see alcohol **82**.



71 **82**

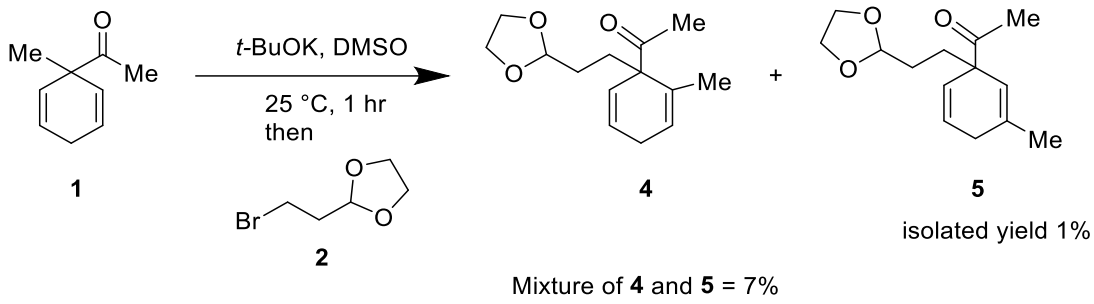
R	Product	d.r.	Yield (%)
Ph	**82a**	>95:<5	60
i-Pr	**82b**	85:15	63
t-Bu	**82c**	>95:<5	30

Table 4: Rearrangement of spriocyclohexadienyl oxindole 71 followed by the addition of an aldehyde.[19]

3.4 Results and Discussion

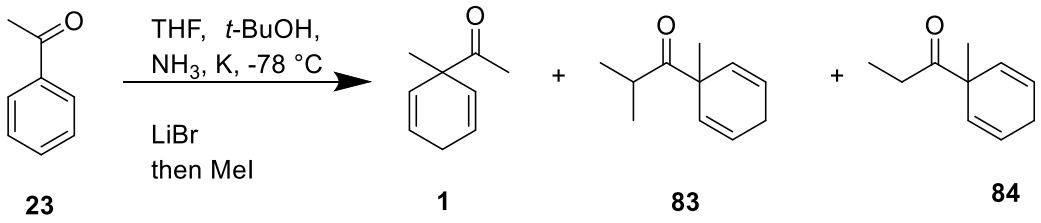
3.4.1 Experimental results

The overall aim of this project was to investigate the rearrangement below (**Scheme 2**) and to produce a selection of compounds produced by the rearrangement and alkylation of compound **1** under basic conditions.[1]



Scheme 2: The unexpected rearrangement and alkylation of 1-acetyl-1-methylcyclohexa-2,5-diene using 2-(2-bromoethyl)-1,3-dioxolane.[1]

The starting material **1** can be synthesised by a Birch reduction and alkylation. The Birch reduction and alkylation of acetophenone **23** has already been reported in the literature by Narisada.[2] This procedure was followed to repeatedly produce a good yield of the desired 1-acetyl-1-methylcyclohexa-2,5-diene **1** (**Scheme 23**). Diene **1** was easily isolated by column chromatography (22:1 hexane: ether) and achieved an isolated yield of between 30% and 70%.

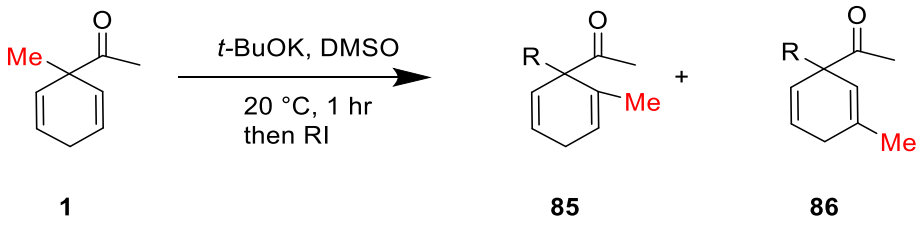


Scheme 23: The reductive alkylation of acetophenone to form the starting material compound 1

Generally the reaction temperature was kept at –78 °C. However when it was repeated at –30 °C it also produced an acceptable yield ~30–50%. When the higher temperature of –30°C was used the reaction produced a greater yield of undesired polysubstituted products. The two main side products of the reaction at –30 °C were **83** and **84**. To avoid producing these polysubstituted products it is advisable to maintain the temperature at –78 °C where possible. It was not unusual for a small amount of acetophenone **23** to remain unreacted.

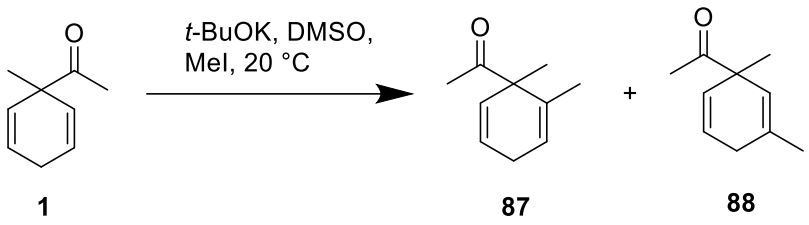
Upon addition of iodomethane as an alkylating agent, it was generally better to allow the ammonia to evaporate prior addition of iodomethane. The iodomethane was then added as a solution in THF. When the iodomethane was added *in situ* with the ammonia, a side product **83** became more prevalent. This may have been due to the additional mixing time as the ammonia required several hours to evaporate. Temperature may also have played a role, as the reaction was allowed to warm up following the addition of iodomethane to evaporate the ammonia under a flow of nitrogen.

The conditions for the rearrangement step involved the reaction of diene **1** with *t*-BuOK in DMSO followed by addition of a suitable alkylating agent. The reaction was expected to produce a mixture of diene isomers **85** and **86** with a range of different alkylating groups (R) (**Scheme 24**). For the context of the discussion, any reference to the minor isomer for discussion purposes refers to the methyl group *ortho* to the acetyl group forming diene **85**. Reference to the major isomer will involve the methyl group *meta* to the acetyl group to form diene **86** (**Scheme 24**).



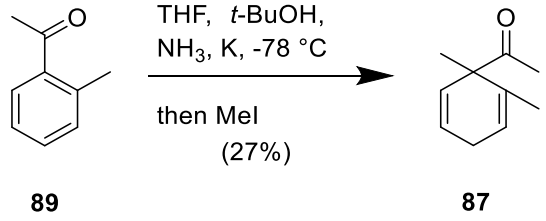
Scheme 24: The rearrangement and alkylation of compound 1.

To provide evidence for the products produced during the rearrangement reactions, it was decided that the products should be synthesised independently by an alternative reaction in order to characterise them. The rearrangement and alkylation where iodomethane was used to quench the reaction was chosen to analyse the products (R = Me). The rearrangement of diene **1** produced a mixture of dienes **87** and **88** (**Scheme 25**).



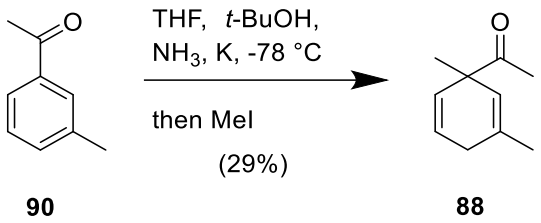
Scheme 25: The rearrangement and methylation of diene 1.

As mentioned above, it was decided that **87** and **88** should be produced independently to produce authentic samples for characterisation. Compound **87** was synthesised using the procedure detailed by Narisada.[2] Diene **87** was synthesised *via* a Birch reduction procedure from 2-methylacetophenone (**89**) in a yield of 27% (**Scheme 26**).



Scheme 26: The reductive alkylation of 2-methylacetophenone.

Diene **88** was also produced from the Birch reduction and methylation of 3-methylacetophenone **90** using the same procedure as detailed by Narisada, achieving a yield of 29% (**Scheme 27**).



Scheme 27: The reductive alkylation of 3-methylacetophenone.

A brief investigation directed at evaluating the rate of rearrangement and subsequent alkylation was conducted by varying the mixing time at various stages of the reaction. This was done to evaluate if the proportion of the isomers would change if the length of mixing with the alkylating agent was varied. If the rate of alkylation was slow then it could be expected that the dienes would further rearrange and more of the major isomer (*meta*) would be produced. Perhaps even the unobserved (*para*) isomer may have chance to form.

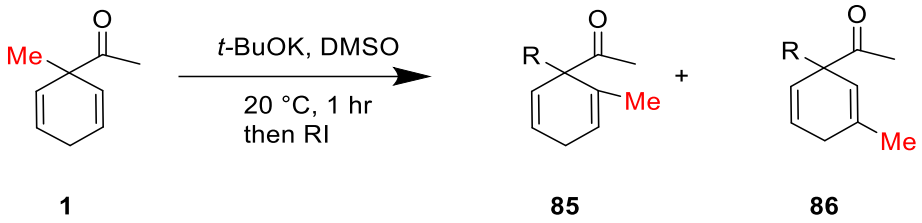
In reality the mixing time did not affect the proportion of the two isomers or lead to the formation of the *para* isomer. As these reactions did not produce a nice clean NMR spectrum of the crude reaction mixture it would be hard to totally discount the formation of the *para* isomer. The *para* isomer was never isolated, neither was there any a hint of another isomer being formed in any of the ^{1}H NMR spectra of crude reaction mixtures or for any of the reaction mixtures that were purified/partially purified.

There was a slight increase in the overall yield of the two isomers if the reaction was allowed to stir for 1 hour after addition of the alkylating agent as opposed to 5 minutes or several hours. When compound **1** was left to stir with *t*-BuOK in DMSO over several hours (before the addition of the alkylating agent) a slight increase in yield of the aromatic products was noticed. This can be attributed to the oxidative aromatisation of the diene **1**. It was also essential to ensure that the flask and solvent were flushed with nitrogen prior to the addition of the substrate. If this was not done, the reaction produced a mixture of aromatic compounds and unreacted diene **1**.

Table 5 below details the estimated yields of the minor and the major diene isomers present in the crude reaction mixtures. These were estimated from the ^{1}H NMR spectra of the crude reaction mixtures. Also present was a range of unidentified aromatic

compounds. The proportion of each product was estimated from the integration in the ^{1}H NMR spectrum.

The proportion of compounds **99** and **100** are not given as the ^{1}H NMR spectrum of the crude reaction mixture was messy in the diene region and therefore the ratios of the isomers could not be suitably concluded.



1 **85** **86**

Scheme 28: The rearrangement and alkylation of compound 1.

R group	Compound number for the minor isomer	Proportion of minor isomer in the crude mixture	Compound number for the minor isomer	Proportion of major isomer in the crude mixture	Unidentified aromatic compounds
Methyl	**87**	21%	**88**	35%	44%
Ethyl	**91**	20%	**92**	36%	44%
Butyl	**93**	14%	**94**	28%	58%
Heptyl	**95**	15%	**96**	27%	58%
Benzyl	**97**	9%	**98**	9%	82%
Allyl	**99**	n/a	**100**	n/a	n/a
Isopropyl	**101**	17%	**102**	30%	53%

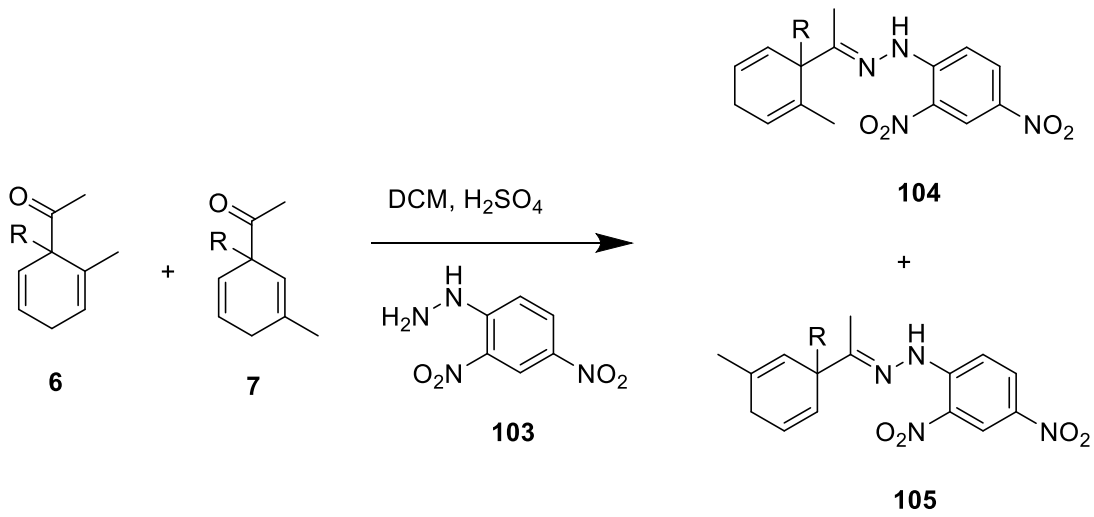
Table 5: Proportion of diene isomers as estimated from the ^{1}H NMR spectra of the crude reaction mixtures.

The reactions in the table above were all successful and produced the two diene isomers in reasonable yield. These were observed in the ^{1}H NMR spectrum of the crude reaction mixtures along with a number of unidentified aromatic compounds.

Several problems were encountered during the purification of the crude reaction mixtures. When column chromatography was used the two diene isomers were difficult

to separate from each other and from a number of aromatic compounds. The isomers could not be separated to a high degree of purity. However, they could be partially purified so they were clearly observable but were never purified to a high enough standard for characterisation. Therefore the conclusion for this part of the study was that column chromatography was largely unsuccessful as a method of purification, achieving low yields and poor separation. A change of the purification technique was employed, utilising a classical method of preparing a 2,4-dinitrophenylhydrazone from the ketone in order to obtain a crystalline product. The reactions were repeated to obtain the crude reaction mixtures of the dienes. The crude reaction mixtures were then reacted with an excess of 2,4-dinitrophenylhydrazine in DCM with a few drops of concentrated sulfuric acid to catalyse the formation of the hydrazones.

The structures of the hydrazones are detailed in **Scheme 28**. It is assumed that the hydrazones are formed as the *E* isomers, although the actual geometry of these structures was not investigated during this study.



Scheme 29: Conversion of the diene isomers 6 and 7 into hydrazones.

The isomer that has an isopropyl group R was not purified as a hydrazone by column chromatography. Attempts to purify the ketone by column chromatography were carried out. The yield of the 2,4-dinitrophenylhydrazones in this case was very low. Compound **107** (R = Me) was only partially characterised in this example because ketone **88** (R = Me) was obtained from the Birch reduction in an independent synthesis and fully characterised.

R group	Compound number for the minor isomer	Compound number for the major isomer	% yield of the isolated major isomer
Methyl	**106**	**107**	12%
Ethyl	**108**	**109**	9%
Butyl	**110**	**111**	10%
Heptyl	**112**	**113**	18%
Benzyl	**114**	**115**	6%
Allyl	**116**	**117**	8%

Table 6: The yield of the purified major isomers as their 2,4-dinitrophenylhydrazone derivatives.

The aim of the project was adapted so that the diene isomers would be isolated by the recrystallisation of the 2,4-dinitrophenyhydrazone derivatives. The recrystallisation worked well for compound **107** (R = Me) and a good yield of the product was obtained (12%). The recrystallization procedure also worked to some degree for compounds **110** (R = Et) and **111** (R = Bu). However, when it came to purifying hydrazones **112** and **113** (R = heptyl) these didn't form a solid product; instead an orange oil was formed. This can be attributed to the addition of the bulkier heptyl group, this being less likely to pack efficiently to form a crystalline solid. The 2,4-dinitrophenylhydrazones **112** and **113** (R = heptyl) were unsuitable for recrystallisation. The 2,4-dinitrophenylhydrazones **112** and **113** were purified by column chromatography. The addition of the bulky 2,4-dinitrophenyl hydrazine group allowed the dienes to be purified and the major isomer **113** was separated.

Compound **107** (R = Me) was purified by recrystallisation as mentioned above. All other compounds in **Table 6** were purified as 2,4-dinitrophenylhydrazone derivatives by column chromatography. Only the major isomers were isolated after chromatography. Column chromatography of the 2,4-dinitrophenyhydrazones was much easier than the purification of the dienes as the parent ketones or the recrystallisation of the 2,4-dinitrophenylhydrazones.

It should be noted that the yields in **Table 6** represent the pure isolated products and therefore do not reflect the true potential of the reaction. A large portion of the products were not isolated pure enough for characterisation. The nature of the diene also lends itself to oxidative aromatisation and therefore unsurprisingly a lot of aromatic compounds were also present in the crude reaction mixture.

In order to establish the abundance of the two isomers, the integration in the ^{1}H NMR spectra of the crude reaction mixtures for the ketones was analysed.

The benzyl alkyl group distorts the average of the diene isomers and therefore the average was calculated excluding the 1:1 ratio on the assumption that it is an anomalous result. The measurements of the peak integrations reveal that on average the major isomer was 1.83 times more abundant than the minor isomer. **Figure 1** below shows the peaks in the NMR spectrum that were used during analysis of the peak integration ratios.

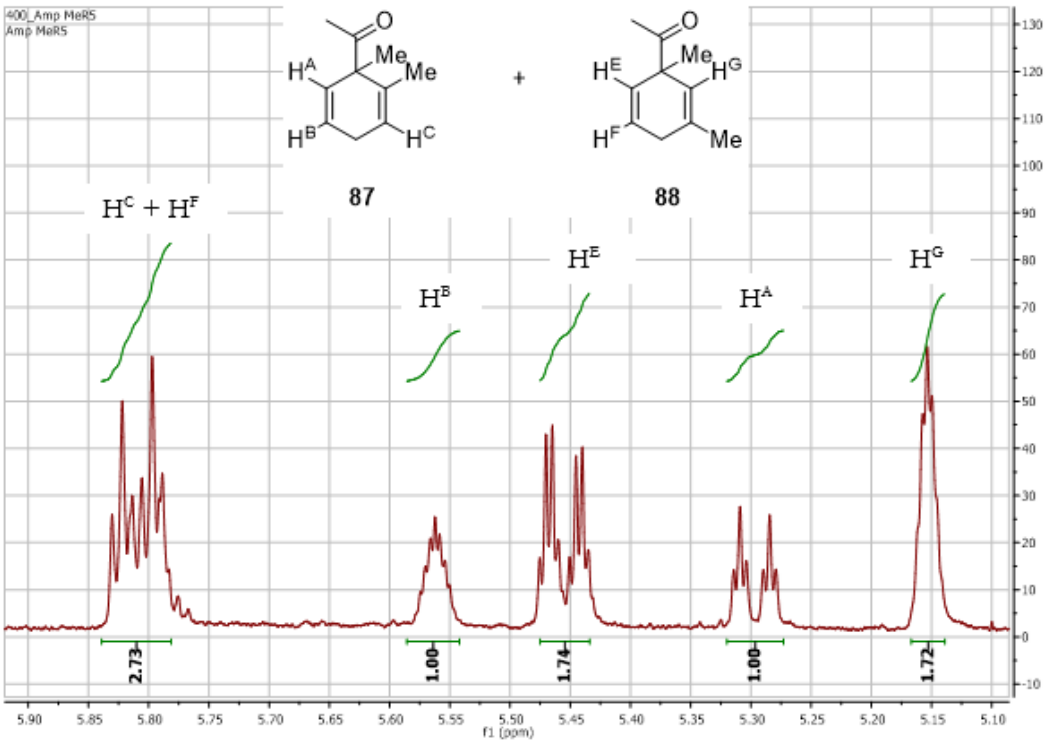


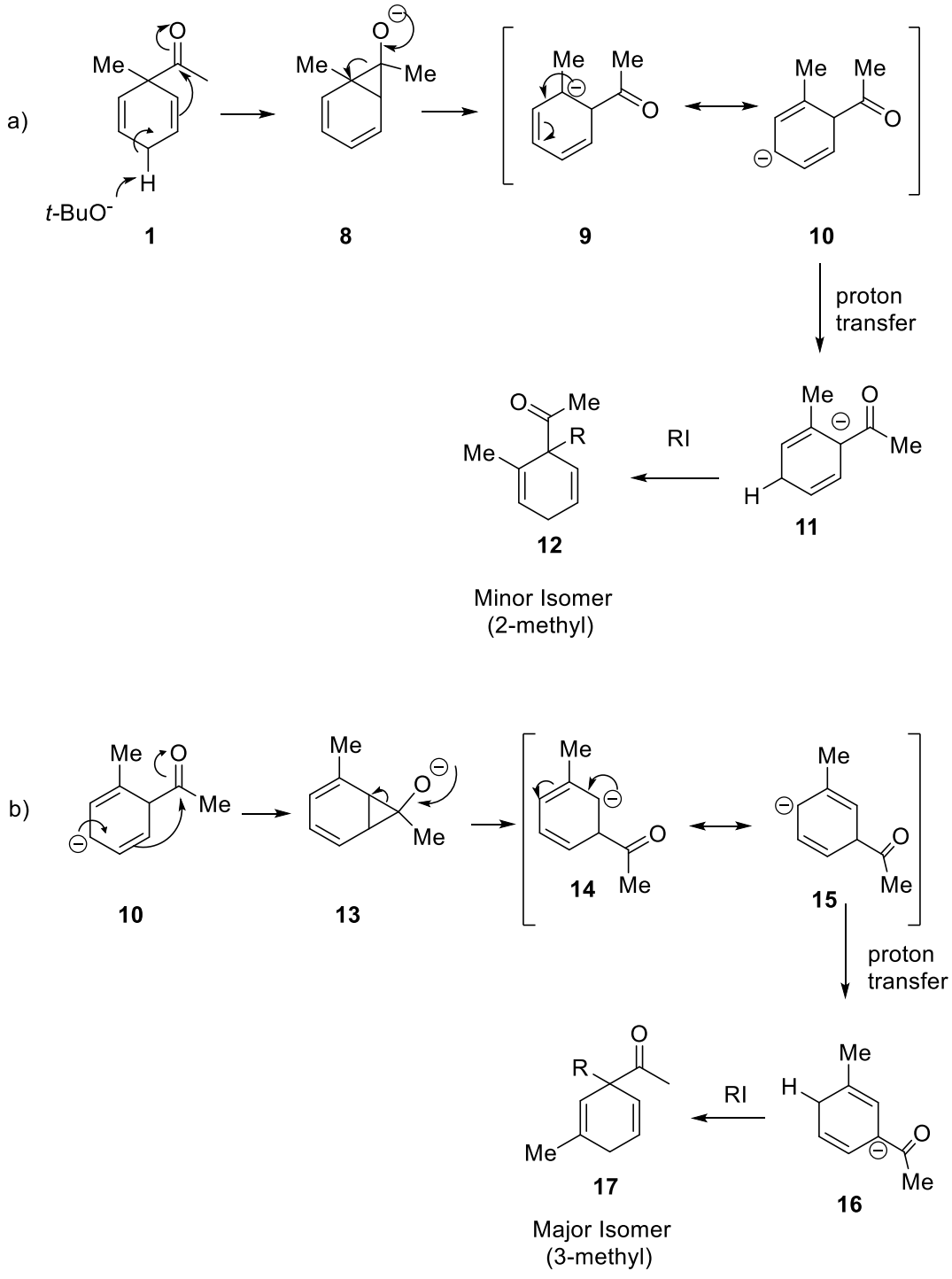
Figure 1: The peaks in the ^{1}H NMR spectrum for the diene isomers (R = Me) that are responsible for the major and minor diene products.

The major isomer was more abundant than the minor isomer in the majority of the rearrangements performed. The only example that shows a 1:1 ratio for the major to minor isomer arises when benzyl bromide was used as an alkylating agent to produce compounds **97** and **98**.

Alkylating group	**Ratio of major to minor isomers**
Methyl	1.73 : 1.00
Ethyl	1.85 : 1.00
Butyl	2.00 : 1.00
Heptyl	1.81 : 1.00
Benzyl	1.00 : 1.00
Isopropyl	1.84 : 1.00

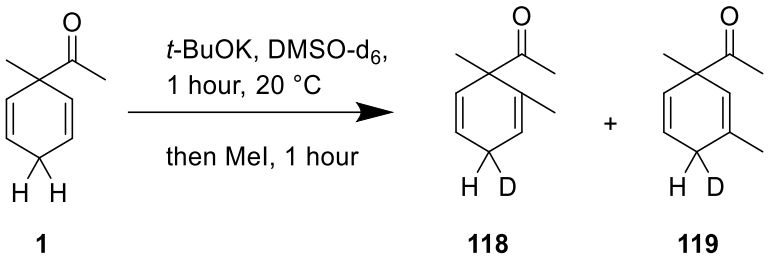
Table 7: Comparing the ratio of abundance for the two diene isomers.

In the proposed mechanism a proton transfer step is required. For example, diene **10** is converted into diene **11** through a proton transfer. Also, diene anion **15** has a proton transfer step as it is converted into diene **16**. There is some speculation about how this is achieved. This study does not offer any conclusive proof of the mechanism of this proton transfer step. Several mechanisms were considered, such as an intermolecular protonation/deprotonation between adjacent diene anions. One other suggestion was that perhaps the solvent plays some role in supplying the proton.



Scheme 30: The proposed mechanism for the rearrangement of compound 1.

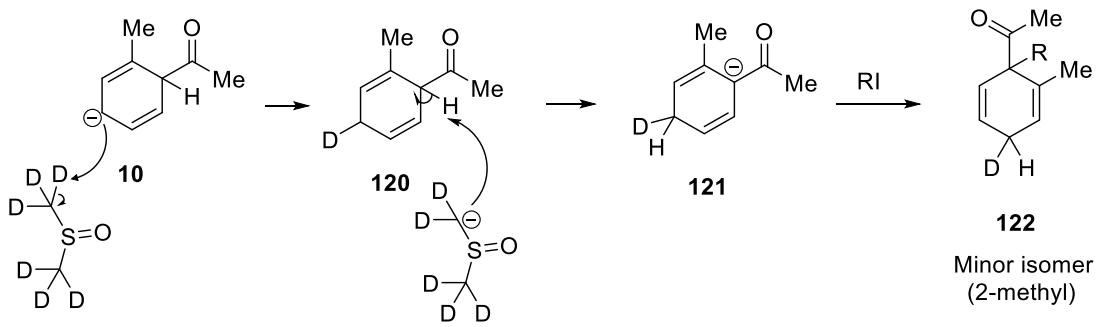
To establish whether the solvent plays a role in the proton transfer step, the rearrangement/alkylation of compound **1** was repeated in deuterated DMSO-d_6. The rearranged product showed deuteration at the *para* position.



Scheme 31: Rearrangement of compound 1 in DMSO-d_6.

The proton transfer step on **Scheme 30** shows the anion transferring from C-4 on diene anion **10** to give an anion alpha to the carbonyl group on diene anion **11**. As the previous structure **10** is a diene anion, it is very unlikely to form a di-anion which then becomes protonated. Therefore, it is more likely that the initial protonation of **11** occurs from one source followed by the more favourable deprotonation at the *ipso* positon (alpha to the carbonyl).

The source of the initial protonation at the *para* position has been attributed to coming from the solvent (DMSO). The NMR spectrum when d_6-DMSO was used showed that there was incorporation of deuterium at the *para* position. The NMR spectrum showed that the CH_2 peak in the ^1H NMR spectrum had decreased in integration by a third, with the resulting peak integration being 0.67 times the expected integration. In the ^{13}C NMR spectrum, there was a triplet signal in the region of the non-deuterated singlet CH_2 peak. The triplet is quite characteristic of a deuterated species due to deuterium nuclei possessing a spin of 1. This suggests that there is a solvent interaction that could be influencing the proton transfer step.



Scheme 32: Proposed mechanism for the proton source in the protonation step.

3.4.2 Computational study

A computational study was conducted to provide evidence for the proposed mechanism and whether it could explain why one isomer was more abundant. The computational study was performed to identify the energy barriers for the formation of the proposed intermediates and to find supporting evidence whether the intermediates were thermodynamically viable and if this could explain the abundance the different isomers.

Geometry optimisation calculations were performed using Spartan v5.0.1, student edition. Initial geometry optimisations were calculated for each of the structures at the Restricted Hartree-Fock (RHF) level with the basis set 6-31G* in a non-solvated gas phase model to generate an optimised structure. Structures generated using RHF calculations were re-optimised using density functional theory (DFT) using the standard B3LYP hybrid functional and the basis set 6-31G* in a non-solvated gas phase model. The results from the calculations are given as free energy values (in a. u.).

An energy profile calculation was performed at B3LYP with the basis set 6-31G* for the intermediate cyclopropane structures with bond constraints so that bond A was varied between 1.5 and 2.5 Å for the energy profile calculations.

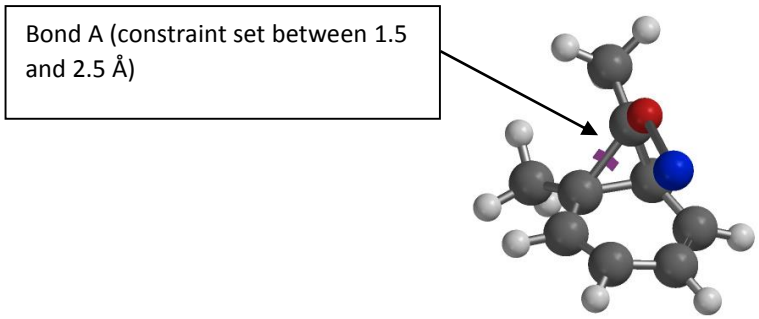


Figure 2: The search for the transition state, bond length A has constraints between 1.4 and 2.5 Å. Oxygen atom shown in red and the potassium ion shown in blue.

The energy profile showed a maximum energy point on the energy profile (**Figure 3**) when bond length A was 1.873 Å. This gives a starting point for identification of the transition state structure in **Figure 4**.

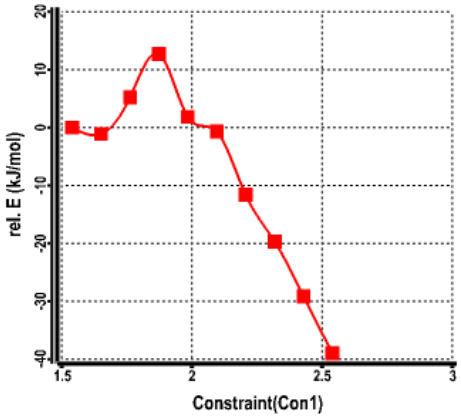


Figure 3: The energy profile of structure detailed in Figure 2.

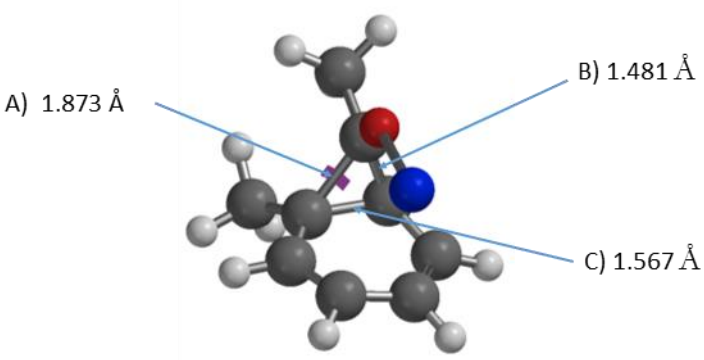


Figure 4: The structure determined from the maximum energy point on the energy profile diagram (Figure 3).

The transition states for cyclopropane closing/opening were calculated using the optimum bond lengths seen in **Figure 3 and 4**. This involved adding bond constraints to set the specified lengths for bond A. A single point calculation and frequency analysis of the structure was carried out to obtain Hessian data using the B3LYP hybrid functional with the 6-31G* basis set. From the set of Hessian data a transition state geometry calculation was performed using B3LYP with the basis set 6-31G*. It was essential to carry out the frequency calculations prior to the transition state geometry calculations. If the transition state geometry was ran without the Hessian data from the frequency analysis the calculation would fail. An error stating that the potassium element was 'un-parameterisable' would arise.

This is because there was a lack of parameters for potassium at that level of theory. After running a successful single-point energy calculation, the transition state geometry optimisation could be completed.

The transition state occurs as the bond closes to form the cyclopropane intermediate. The first transition state 'TS close' arises when the closing bond (**A**) has a length of 1.87 Å. As the bond closes even more, a cyclopropane intermediate forms with a bond length of ~1.54 Å. The cyclopropane undergoes a ring opening; here bond (**B**) lengthens to TS open with a bond length of ~1.87 Å. Bond (**B**) will then break as the cyclopropane structure opens. Once the bond opening is complete the acetyl group will have migrated one carbon around the ring.

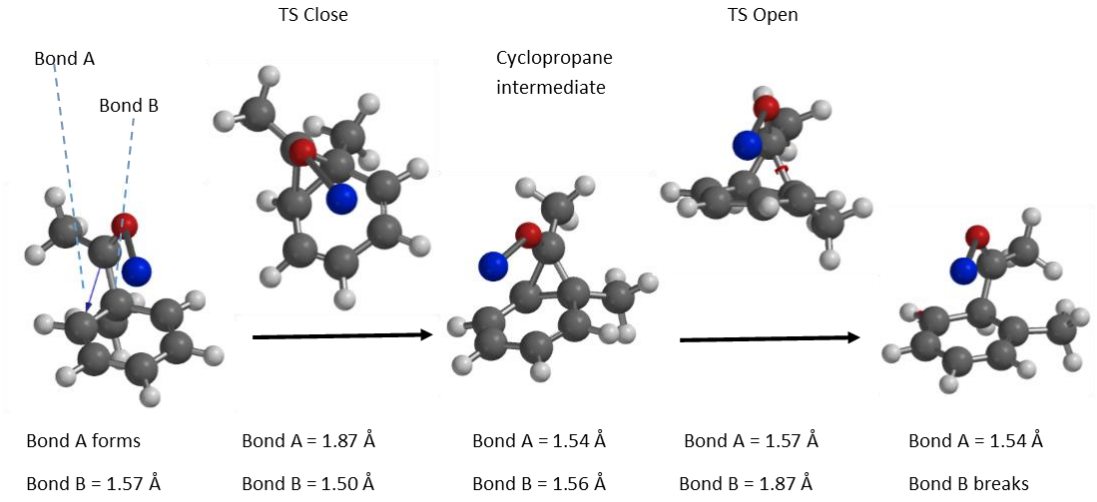


Figure 5: Formation of the transition state as the acetyl group migrates around the ring.

The arrangement of the dienes was assessed to see how the position of the carbonyl group in relationship to the diene ring affected the stability of the dienes. A series of calculations was performed to assess the orientation of the carbonyl group in the diene.

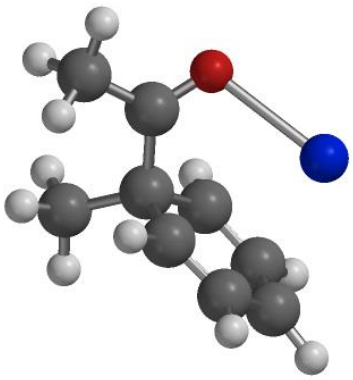


Figure 6: Diene anion with the oxygen (red) *endo.*

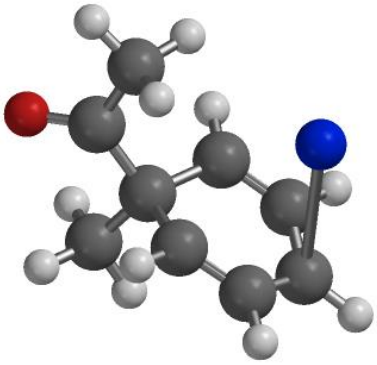


Figure 7: Diene anion with the oxygen (red) *exo.*

The table below shows the calculations for diene anions prior to protonation. These have been calculated with the carbonyl either *exo* or *endo* with respect to the diene ring.

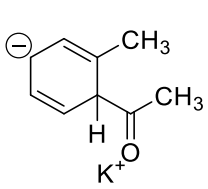
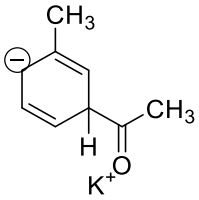
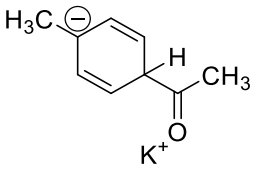
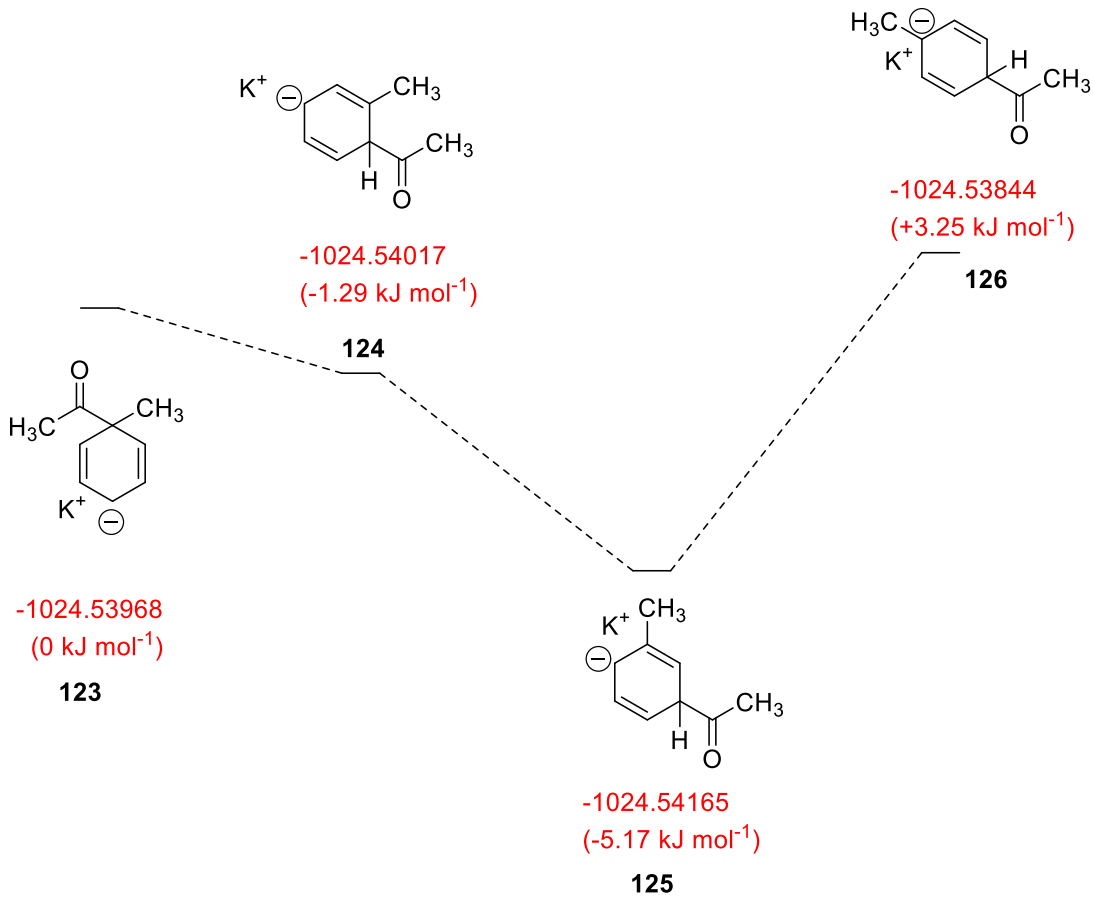
Position of oxygen relative to the diene ring.	 **10**	 **15**	 **20**
Exo	–1024.54017	–1024.54165	–1024.53844
Endo	–1024.56364	–1024.56314	–1024.55915
Δ in energy	61.6 kJmol^{-1}	56.4 kJmol^{-1}	54.4 kJmol^{-1}

Table 8: A comparison of the dienes with the oxygen *exo* and *endo*.

The above calculations show that the *endo* arrangement is always lower in energy than the *exo* arrangement. For example diene anion **10** (**Table 8**) in an *endo* arrangement is lower in energy by 0.02347 Hartrees or 61.6 kJmol^{-1} when compared to **10** in an *exo* arrangement. Therefore the majority of the calculations will be performed with the oxygen in an *endo* arrangement to the diene. A summary of the diene anions with the oxygen in an *exo* arrangement to the diene ring is detailed below (**Scheme 33**).

The calculations below show the stability of the diene anions with the oxygen *exo* to the ring. The values given in kJmol^{-1} are relative to the stability of the initial diene anion prior to rearrangement. The major isomer **125** is lower in energy than the minor isomer **124**. The unobserved *para* isomer **126** is higher in energy by 8.42 kJmol^{-1} compared to **125**. The difference in energy could account for why it is not observed as it is thermodynamically less favourable. The calculation supports the observation from the experimental chemistry of isomer **125** being more abundant than isomer **124** and suggests that the explanation for this may be due to the thermodynamics of the reaction. The calculations performed with the carbonyl in an *endo* arrangement have been identified as lower in energy and so will be more relevant than the *exo* calculations. The complete energy profile was calculated with the oxygen in an *endo* arrangement to the diene ring (**Scheme 34**).



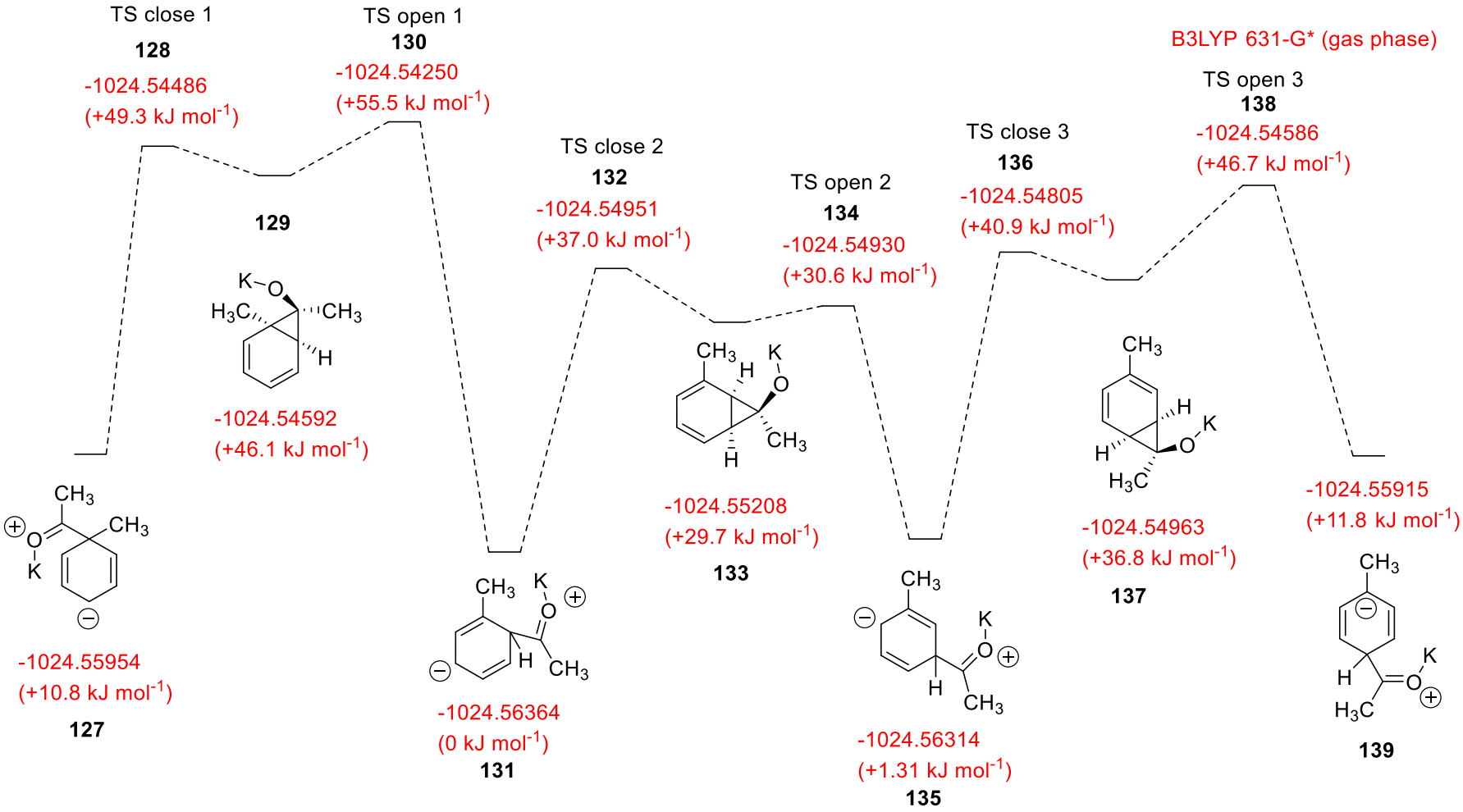
Scheme 33: A brief summary of the *exo* calculations.

The transition states for the bond-closing procedure as the cyclopropane intermediates are formed has been given the label TS close. The transition state for the bond opening as the acetyl group migrates one position around the ring has been given the label TS open.

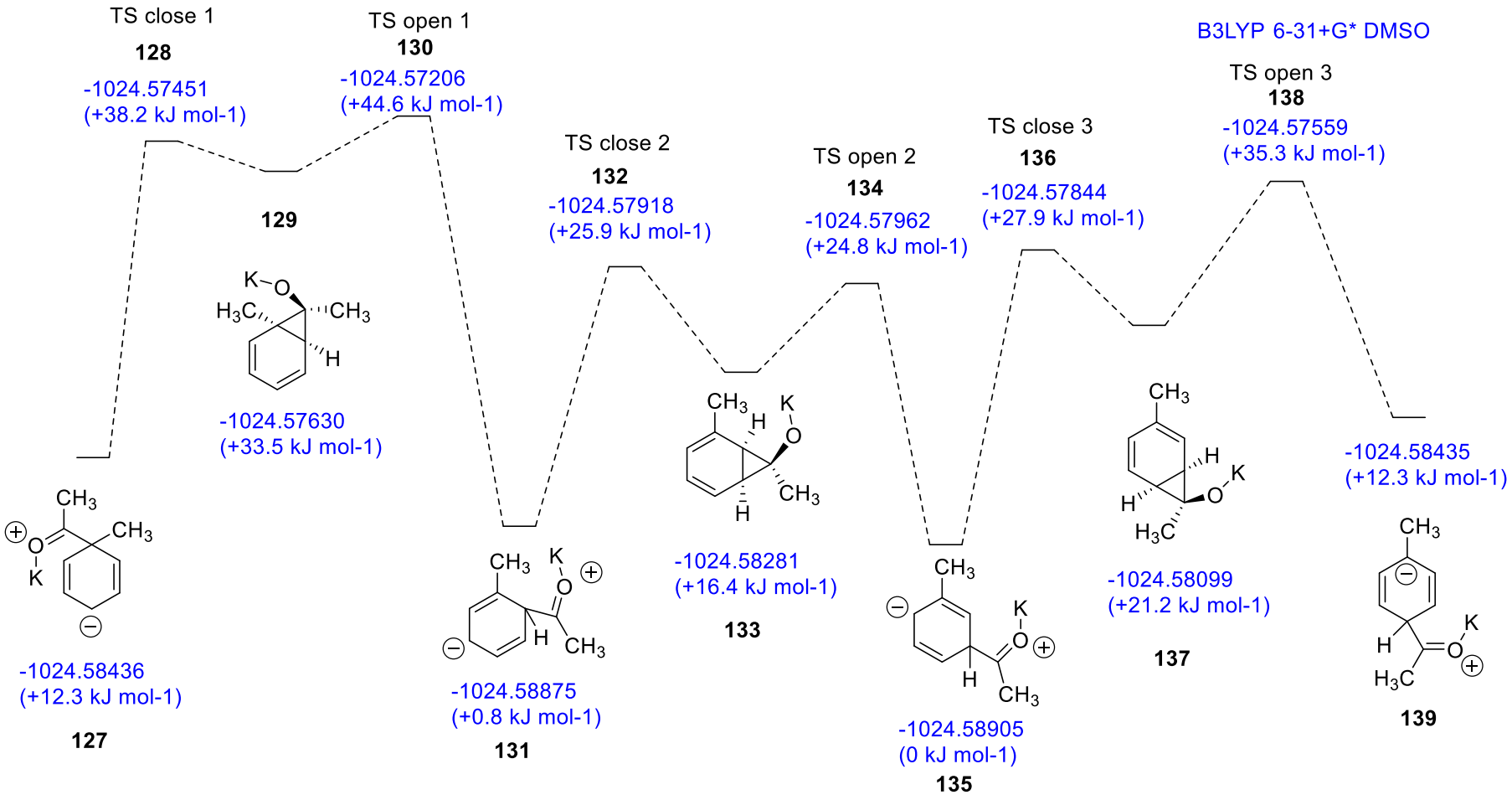
The summary of the *endo* calculations (**Scheme 34**) show that thermodynamically the two dienes **131** and **135** are the lowest in energy. Diene **131** is slightly lower in energy by 1.31 kJmol^{-1}. This is contradictory to the calculations performed in an *exo* arrangement. This suggests that isomer **131** should be more abundant since it is calculated to be lower in energy. However, this does not agree with the experimental observations. The energy profile is plotted relative to the lowest energy structure **131.** The other structures are calculated to show the difference in energy. Diene isomer **139** is calculated to be higher in energy than diene isomer **131** by 11.8 kJmol^{-1} and therefore is significantly less stable.

Hence, the difference in energy helps to explain why we do not see any of the *para* isomer in our experimental results. The difference in the experimental observations and the computational calculations in explaining the abundance of the isomers is contradictory. The difference between the experimental and the computational results could be attributed to the relatively low level of theory used, and particularly the fact that these are gas phase calculations, rather than using an appropriate solvent model.

Calculations performed in collaboration with Dr Elliott at 6-31+G* with addition of a DMSO solvent model yields the major isomer as lower in energy (**Scheme 35**).
The major diene anion **135** is now lower in energy by 0.8 kJ mol^{-1} than the minor diene anion **131.** The result of the theoretical study supports the experimental observations that the major isomer should be more abundant when calculated in a DMSO solvent model.



Scheme 34: The energy profile (kJ mol^{-1}) reaction pathway at B3LYP 6-31G* (DFT level) in a gas phase model in an *endo* arrangement.



Scheme 35: The energy profile (kJ mol^{-1}) reaction pathway at B3LYP 6-31+G* (DFT level) in a DMSO solvent model in an *endo* arrangement.

Below is a summary of the bond lengths for all of our calculations (**Table 9**). The cyclopropane transition states all have similar bond lengths. The transition states labelled TS all have a fairly consistent bond length for each structure, this shows that the original transition state was a good approximation.

Structure	**Compound number**	**Bond lengths**		
		A	**B**	**C**
diene anion *endo*	**127**	n/a	n/a	1.57
TS close 1 *endo*	**128**	1.79	1.56	1.50
1st cyclopropane *endo*	**129**	1.54	1.61	1.57
TS open 1 *endo*	**130**	1.57	1.87	1.48
methyl *ortho endo*	**131**	1.54	n/a	1.54
TS close 2 e*ndo*	**132**	1.88	1.55	1.49
2nd cyclopropane *endo*	**133**	1.55	1.55	1.55
TS open 2 *endo*	**134**	1.55	1.84	1.49
methyl m*eta* e*ndo*	**135**	1.54	n/a	1.54
TS close 3 *endo*	**136**	1.81	1.56	1.49
3rd cyclopropane *endo*	**137**	1.54	1.59	1.56
TS open 3 *endo*	**138**	1.56	1.85	1.49
methyl p*ara endo*	**139**	1.54	n/a	1.54

Table 9: Bond lengths from the *endo* calculations.

3.5 Conclusion

This study has shown that under basic conditions, 1-acetyl-1-methylcyclohexa-2,5-diene rearranges and is alkylated to produce a mixture of two dienes. The conditions are suitable for the *in situ* alkylation at the *ipso* position with a range of halogenoalkanes. The proposed mechanism of that involves the migration of an acetyl group around the ring is supported by a series of calculations. The results of the calculations support the formation of the major isomer in a higher abundance in line with the experimental results.

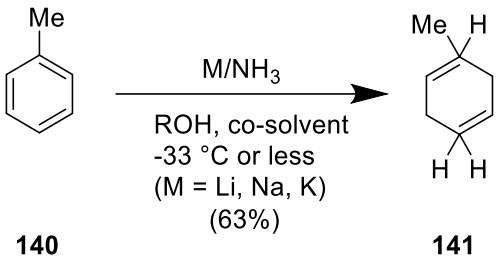
Chapter 4

The Birch reduction alternatives

4.0 Birch reduction alternatives

4.1 Na-SG reduction chemistry

Developments for Birch reduction chemistry focus on modifying the procedures to make them safer, greener and subsequently more commercially viable.



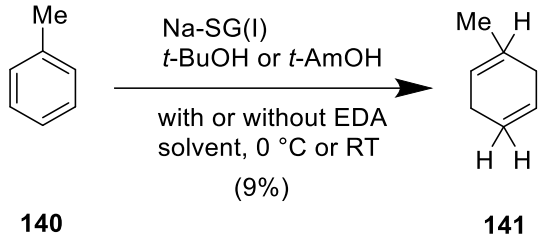
Scheme 36: **Common conditions for a Birch reduction of toluene.**[20]

Several attempts have been made to make reduction chemistry safer and easier. One approach was to incorporate alkali metals from the liquid metal phase into amorphous silica gel, and this was achieved with a loading of up to 60 mol %.[21,24]

By incorporating the parent metal into the porous silica it stabilises the reactive parent metal and reduces the hazards associated with the parent metal.

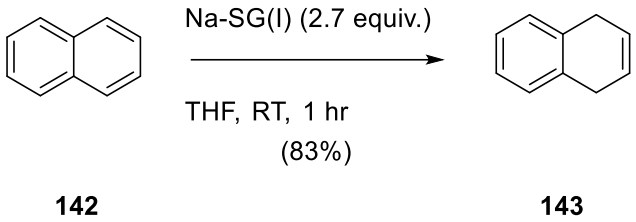
- Parent alkali metals are stabilised. This reduces fire hazard risks as it is no longer necessary to handle elemental alkali metals in the laboratory.
- Highly toxic liquid ammonia is not required as a solvent.
- Solvents such as THF or 2-MeTHF can be utilised.
- No need to cool reactions to cryogenic temperatures. Reactions can be carried out a 0 °C or room temperature.
- Can be easily quenched by addition of MeOH/water or even just water.[20]

Scheme 37 below shows the typical reaction conditions for carrying out a Birch-style reduction using Na-SG (sodium stabilised silica gel).



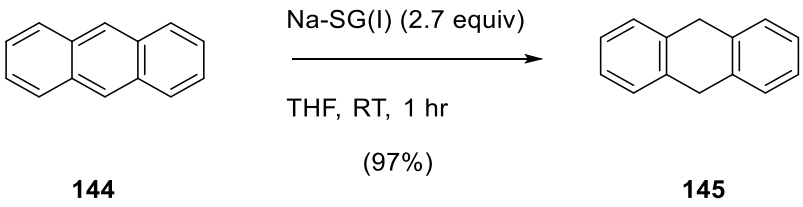
Scheme 37: Conditions for Na-SG(I) reduction of toluene.

There are several examples of aromatic substrates that have been partially reduced by using this method. Vogt has reported the reduction of naphthalene **142** into 1,4-dihydronaphthalene **143** with a yield of 83%.[22]



Scheme 38: The Na-SG(I) reduction of naphthalene.[22]

Anthracene **144** was reduced to 9,10-dihydroanthracene **145** with a yield of 94% using Na-SG(I) reduction at room temperature.

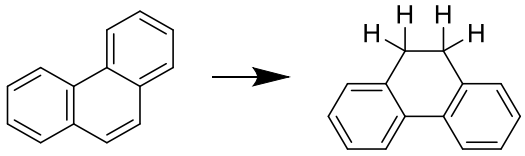


Scheme 39: The Na-SG(I) reduction of anthracene.[22]

The yields of aromatic substrates reduced using Na-SG(I) under ammonia-free conditions were compared with literature yields for the same compounds being reduced

using a sodium and liquid ammonia procedure. The general yields are comparable and in some cases show an improvement in the yield.

It been reported that Na-SG(I) conditions can produce comparable or higher yields than Birch conditions. There are some substrates *e.g.* isoquinoline that are not reduced as successfully when an alternative Na-SG(I) reduction is performed. The reduction of isoquinoline has a lower yield when Na-SG conditions are used when compared to the yield achieved by use of typical Birch reduction conditions, using sodium metal.[20]



146

Classical Birch Conditions

THF co solvent
Ammonia refluxing at -33 °C
Lithium metal (3.5 equivalents)
quenched with ethanol/water
57% yield

147

Na-SG(I) Reaction Conditions

THF solvent at 0 °C
Na-SG (I) (3.5 equivalents)
tert-Butanol (1.75 equivalents)
60% yield

Scheme 40: Comparison of classic Birch conditions for reduction of phenanthrene and alternative Na-SG reduction conditions.[20,23]

The procedure for a Na-SG(I) reduction that is detailed in the literature is a lot easier and more accessible than a Birch reduction method. The reaction can be carried out in a range of solvents and does not require ammonia or hazardous alkali metals.

The Na-SG silica gels can be handled in air, are easy to pour, easy to quench and can be packed into a column and so can be used in a flow system.

The alkali metal silica gels can be categorised into three categories denoted as stages 0, I and II, all appearing as shiny black powders. Stage 0 can be prepared by shaking a liquid Na_2K alloy with silica gel at room temperature for a few minutes. This is the most moisture and air sensitive of the M-SG samples (M = metal) and should be handled under an inert atmosphere. A Stage I M-SG can be prepared by either heating a stage 0 sample to 150 °C or by heating Na with silica gel to 165°C with continual agitation. A

stage II M-SG is produced by slowly heating sodium metal and silica gel up to 400 °C with intermittent agitation.[24] These M-SG samples are currently commercially available and are manufactured by SIGNa chemistry. Each stage of silica gel varies in their reactivity and reducing capabilities, stage 0 is the most reactive, followed by stage I and finally the least reactive Stage II.

Table 10 below shows the various stages of metal silica gels with the types of metals that can be used and current known applications.

Material	**Metals Used**	**Applications**
Stage 0 M-SG	liquid alloys (K_2, Na, Na_2K, *etc.*)	desulfurisation, polymer initiation, *etc.*
Stage I M-SG	liquid alloys and Na, K, Cs, Rb, *etc.*	Birch reduction, deprotections, Wurtz coupling, *etc.*
Stage II M-SG	liquid alloys and sodium	hydrogenation, solvent drying, *etc.*
Sodium silicide	sodium metal	hydrogen source, fuel cells, *etc.*

Table 10: Stages of sodium silica gel and their applications.[22]

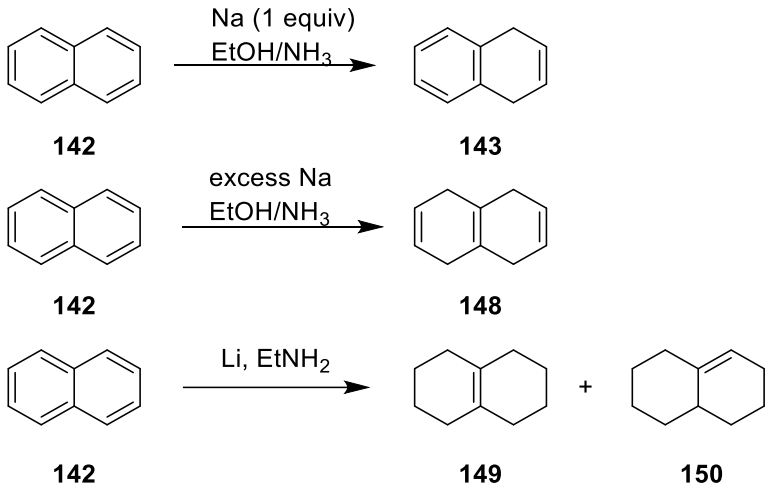
The stage I M-SG are available in several combinations of the parent metals, Na, Na_2K and K_2Na are all available and can be used for Birch reduction chemistry. The M-SG powders can be used with THF, Me-THF, MTBE, toluene, cyclohexane, heptane or dimethoxyethane as a solvent.

Constanzo *et al.* evaluated the reducing capabilities of Na-SG with a range of aromatic substrates. Some of the slower reactions required the addition of ethylenediamine (EDA). EDA is similarly used in the Benkeser reduction to facilitate the reaction. The EDA co-solvent was added in to the Na-SG reductions in molar equivalence with respect to sodium. In the Benkeser reaction, the conditions require a large excess of

ethylenediamine. The sodium silica gel reduction still employs an alcohol as a proton source, whereas the Benkeser reduction utilises a proton from the amine.

4.2 The Benkeser reduction

The Benkeser reduction uses low molecular weight amines, methyl-, ethyl-, propyl- or ethylenediamine as a solvent. The resulting compounds tend to be more extensively reduced than in the Birch reduction.[25] **Scheme 41** shows the comparison of the Birch reduction with and without an excess of sodium, compared to a Benkeser reduction of naphthalene.

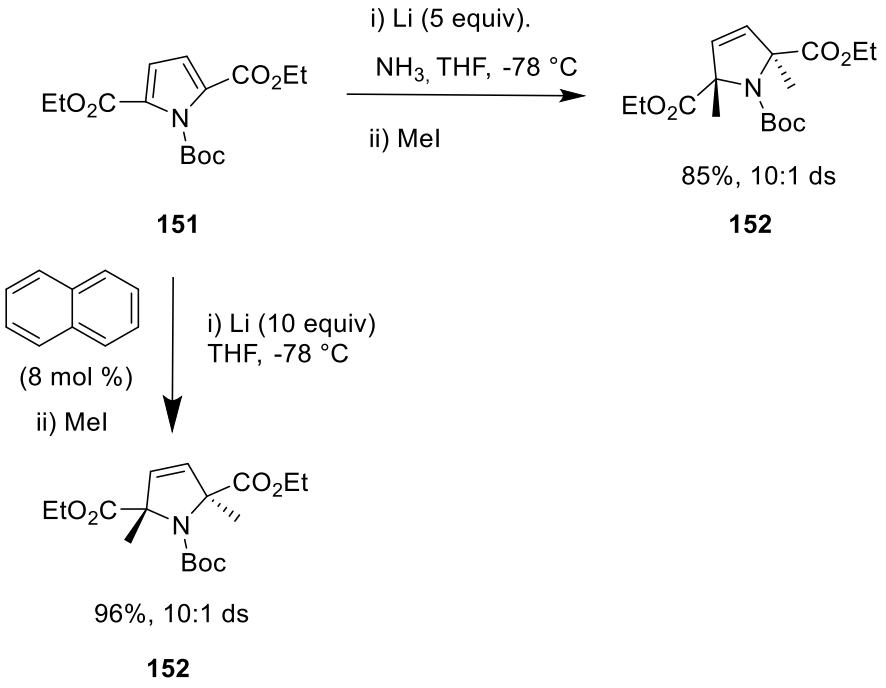


Scheme 41: Birch and Benkeser reduction of naphthalene.[25]

4.4 Donohoe's ammonia-free reduction of aromatic compounds

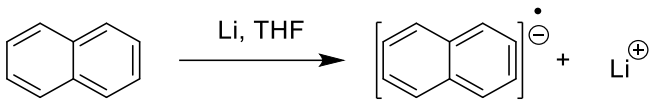
Donohoe *et al.* have reported another alternative to the Birch reduction procedure, achieving partial reduction of heterocycles in THF, using an amine as a proton source and naphthalene as an electron shuttle.[26] The lithium naphthalenide electron shuttle in essence replaces the solvated electrons that would normally associate themselves with the ammonia in the Birch reduction. The Li-Np is formed as a radical anion which reacts in a similar fashion as the NH_3-M radical anion generated in the Birch reduction. The ammonia-free conditions using lithium metal dissolved in THF could be used to reduce pyrroles and furans. The reduction could be followed by an *in situ* alkylation. This reduction method does not require ammonia which could make it favourable on a

large scale. It is also beneficial to consider its use in an academic establishment allowing a Birch-style reduction to be easily and safely undertaken in undergraduate laboratories.[27] Another benefit of an ammonia-free reduction is that the reaction can be quenched using sensitive electrophiles that could not be used in an ammonia-based reduction. **Scheme 42** below shows the comparison of reductive methylation of pyrrole **151** under Birch conditions and under Donohoe's ammonia-free conditions.



Scheme 42: Reductive methylation of diethyl pyrrole 2,5 dicarboxylate under standard Birch conditions and ammonia-free conditions.[26]

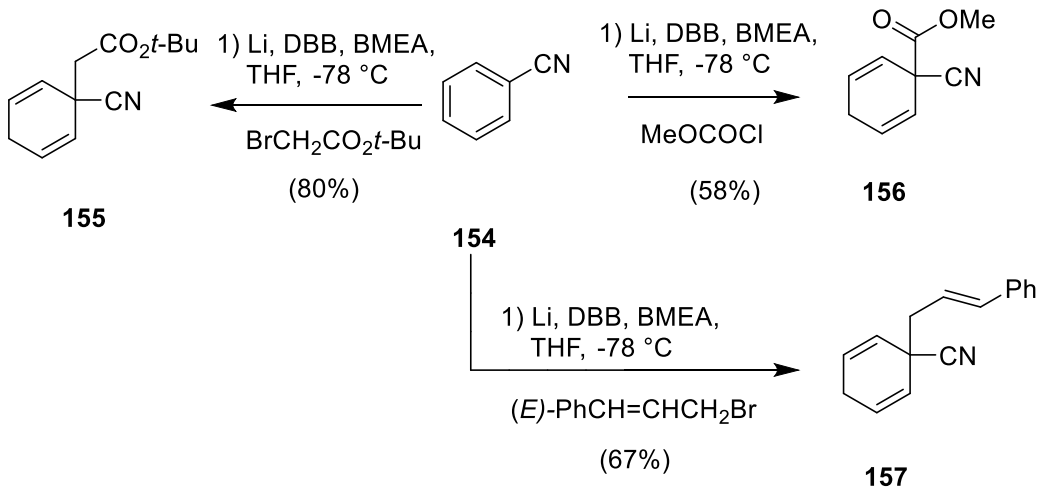
The yield and selectivity of the reduction under ammonia-free conditions was comparable to the yield and selectivity of the same reduction performed under conventional Birch conditions. This ammonia-free method employs lithium naphthalenide as the electron shuttle rather than the solvated electrons being loosely associated with ammonia, which are stabilised by the hydrogen bonds.[28] The electrons in this new regime are provided from lithium naphthalenide as shown in **Scheme 43** below.



142 153

Scheme 43: Lithium naphthalenide formation.[29]

Further development of ammonia-free reductions by Donohoe *et al.* found that lithium di-*tert*-butylbiphenyl was a better source of electrons than lithium naphthalenide **153**. A change in the electron shuttle to DBB increased yields and allowed new electrophiles such as diphenyl disulfide to be employed which had previously been unreported in Birch reduction chemistry.[29] The following conditions were used in the ammonia-free reductions: Li metal (4 equiv.), DBB (4 equiv.) and bis(methoxyethyl)amine (BMEA) (1.2 equiv.). By this method, Donohoe was able to reduce a series of hetero- and carboxylic aromatics, using LiDBB as a source of electrons and BMEA as proton source and THF as the solvent. A few examples of successful reductions carried out by Donohoe *et al.* using the lithium di-*tert*-butylbiphenyl as an electron shuttle are detailed below in **Scheme 44**.



Scheme 44: Donohoe *et al.* ammonia-free conditions.[29]

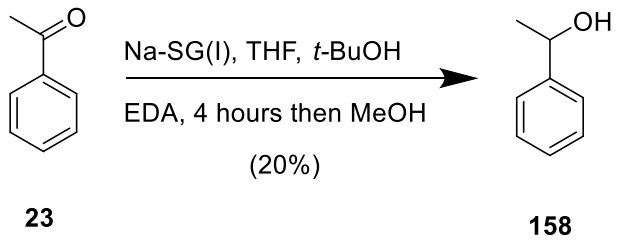
The examples in **Scheme 44** above show that the ammonia-free conditions are a lot more versatile than previously thought, with the application to the reduction of a whole range of aromatic systems.

4.4 Results and discussion

This section discusses the brief assessment of alternative Birch conditions with the aim of assessing the effectiveness of Na-SG(I) as a safer route and easier route to our starting diene **1**. There was a varying degree of success with this method. However, the aim of reducing a mono-substituted aromatic to a cyclohexadiene did not prove successful.

Acetophenone was mixed with sodium silica gel stage I (Na-SG(I)) dissolved in a THF and *t*-BuOK. The reaction was stirred at room temperature for 4 hours. The starting material remained unreacted. When the reaction was repeated with the addition of ethylenediamine, the reaction produced an aromatic product (**Scheme 45**).

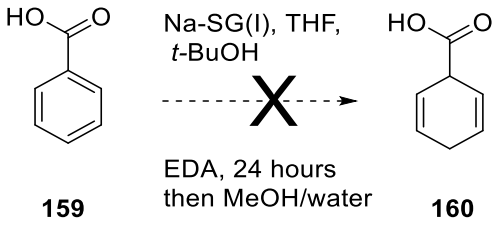
The ^{1}H NMR spectrum showed evidence of acetophenone having being converted to 1-phenylethanol in the ^{1}H NMR. This was identified by the appearance of a quartet at 4.75 ppm and a doublet at 1.34 ppm and three new peaks in the aromatic region. The ^{1}H NMR spectrum showed that the crude reaction mixture consisted of acetophenone and 1-phenylethanol in a ratio of 4:1 respectively.



Scheme 45: The reduction of acetophenone using Na-SG(I).

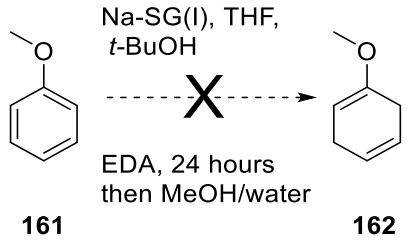
Several repeats of this reaction did not show any hint of cyclohexadiene compounds being synthesised.

Similar attempts to reduce a range of mono-aromatic compounds also proved unsuccessful. Attempts at reducing benzoic acid proved unsuccessful (**Scheme 46**). The reduction of benzoic acid produced a crude reaction mixture, of undistinguishable products. There were no peaks in the ^{1}H NMR spectrum that suggested a diene could have been formed. The majority of peaks in the ^{1}H NMR spectrum belonged to unreacted benzoic acid **159**.



Scheme 46: The attempted reduction of benzoic acid using Na-SG(I).

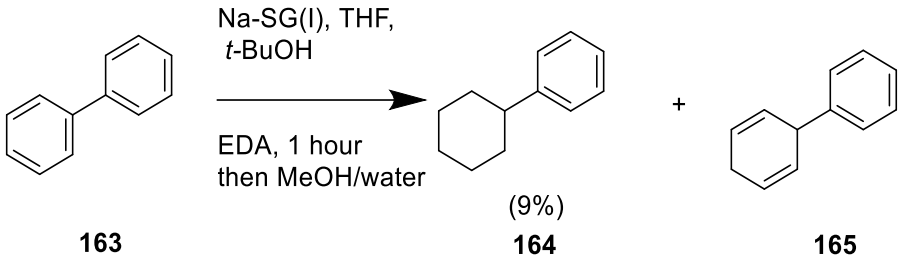
The attempted reduction of anisole was equally unexciting. No reduction occurred and anisole alone was recovered following the reaction. Anisole **161** did not react under Na-SG(I) conditions when stirred at room temperature for 4 hours or when stirred overnight at either 0 °C or room temperature (**Scheme 47**).



Scheme 47: The attempted reduction of anisole using Na-SG(I).

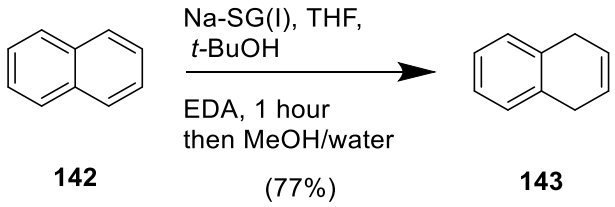
The most successful compounds for reduction by Na-SG(I) were cyclic compounds containing more than one aromatic ring. Naphthalene and biphenyl were reduced using Na-SG(I).

The reduction of biphenyl **163** produced compounds **164** and **165** in equal proportions in the ^{1}H NMR spectra of the crude reaction mixture. Compound **164** was easily isolated, albeit in a low yield (9%), by eluting with hexane on a silica column. Compound **165** was not isolated alone in this example.



Scheme 48: The reduction of biphenyl using Na-SG(I).

Naphthalene **142** was also reduced by a Na-SG (I) method and produced **143** alone in a good yield.



Scheme 49: The reduction of naphthalene using Na-SG(I).

The above reaction has already been reported in the literature. As the reduction of naphthalene performed well under Na-SG(I) conditions it was decided to try the reduction with *in situ* alkylation. Attempts to quench the above reaction with an alkylating agent (MeI) instead of MeOH/water were unsuccessful.

The stabilised alkali metals are a lot easier to handle than the standard Birch method as expected. However, they are not quite as effective at reducing monoaromatic compounds as existing Birch procedures.

Chapter 5

Experimental section

5.0 Experimental

5.1 General experimental points

All reagents were purchased from Sigma Aldrich, Tokyo Chemical Industry, Alfa-Aesar and Fischer and used as supplied unless otherwise stated. Sodium Silica Stage 1 gel (Na-SG(I)) ~35 wt. % Na-K loading as purchased from Sigma Aldrich.

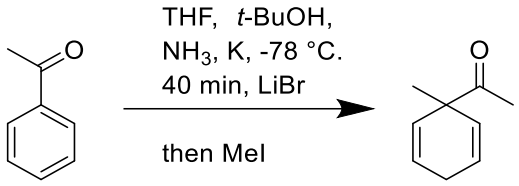
Anhydrous DMSO was purchased from Sigma-Aldrich. d_6-DMSO was purchased from Aldrich and dried for 24 hours over 3Å molecular sieves. THF was freshly distilled from sodium benzophenone ketyl prior to use.[30]

Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrometer. Mass spectra were recorded on a Fisions VG Platform II spectrometer and a Micromass Q-TOF Micro spectrometer. The NMR spectra were recorded on Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25 °C, or 250 MHz for ^{1}H and at 62 MHz for ^{13}C on a Bruker Avance DPX 250 or on a Bruker Avance 500 spectrometer operating at 500 MHz for ^{1}H and at 125 MHz for ^{13}C at 25 °C. All chemical shifts are reported in ppm relative to residual $CHCl_3$. Coupling constants (*J*) are reported in Hz.

Column chromatography was performed using flash chromatography with compressed air for pressure on Matrex Silica 60 Å (35–70 micron).[31]

5.2 Birch reduction

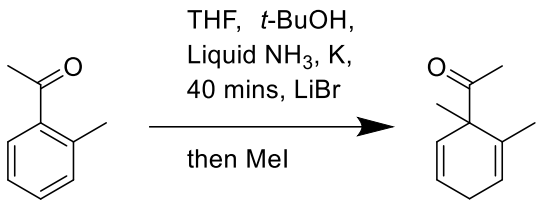
5.2.1 1-Acetyl-1-methylcyclohexa-2,5-diene (1)[2]



23 **1**

Acetophenone (4.9 mL, 41.6 mmol) was dissolved in THF (20 mL) and *t*-BuOH (4.8 mL, 50 mmol) was added. Liquid ammonia (140 mL) was condensed through a dry ice/acetone condenser to the THF solution and the solution cooled to -78 °C. Potassium metal (3.50 g, 90 mmol) was added in small portions until a permanent blue colour persisted for several minutes. The solution was stirred at -78 °C for 10 minutes. Anhydrous lithium bromide (8.00 g, 91.7 mmol) was added and the solution was stirred at -78 °C for 40 minutes. The ammonia was evaporated under a positive pressure of nitrogen over 3 hours. Iodomethane (5.2 mL, 83 mmol) in THF (5 mL) was added to the resulting paste and the solution stirred at 0 °C for 40 minutes. Saturated aqueous NaCl solution (20 mL) and ether (50 mL) were added. The two-phase solution was adjusted to pH 7.5 by careful addition of aqueous HCl (2 M). The ether layer was separated and the aqueous phase extracted with ether (3 x 50 mL portions). The organic extracts were combined and dried over $MgSO_4$. The solvent was evaporated under reduced pressure at 40 °C to yield a brown oil (5.62 g, 99%). The crude reaction mixture was purified by column chromatography on silica (20:1 hexane: diethyl ether) to give *the title compound* (2.23 g, 40%) as a colourless oil; $\nu_{max.}$ (neat) 1708, 1674, 1633 and 1603 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 5.84 (2H, dt, *J* 10.4, 3.4 Hz, CH=C<u>H</u>-CH_2), 5.49 (2H, dt, *J* 10.4, 2.0 Hz, C<u>H</u>=CH-CH_2), 2.73-2.78 (2H, m, CH_2), 2.10 (3H, s, CH_3) and 1.16 (3H, s, CH_3). Data in agreement with reference [2].

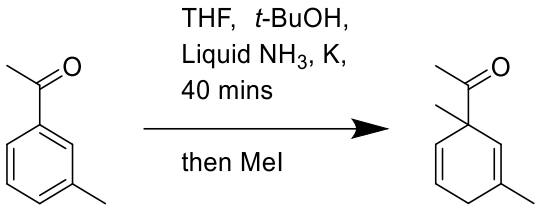
5.2.2 1-Acetyl-1,2-dimethylcyclohexa-2,5-diene (87)



89 **87**

2-Methylacetophenone (0.51 mL, 3.7 mmol) was dissolved in anhydrous THF (5 mL) under nitrogen. *t*-BuOH (0.41 mL, 4.4 mmol) was added and the solution cooled to -78 °C. Ammonia (20 mL) was added through a dry ice condenser. Pieces of potassium metal (0.31 g, 8 mmol) were added carefully to the solution until a permanent blue colour persisted. The solution was stirred at -78 °C for 10 minutes. Anhydrous lithium bromide (0.71 g, 8.16 mmol) was added portion wise and the solution was stirred at -78 °C for 40 minutes. The ammonia was evaporated under a positive pressure of nitrogen over 1 hour. A solution of iodomethane (0.46 mL, 7.38 mmol) in THF (5 mL) was added to the resultant orange slurry and the mixture was stirred at 0 °C for 40 minutes. The reaction was further evaporated under a positive pressure of nitrogen for 1 hour to ensure all the ammonia had evaporated. The solution was quenched with saturated aqueous NaCl solution (20 mL) and ether (20 mL). The two phases were adjusted to pH 7.5 with careful addition of aqueous HCl (2M). The ether layer was separated and the aqueous phase extracted with ether (3 x 20 mL portions). The ether extracts were combined and washed with brine (50 mL). The ether was evaporated under reduced pressure to yield the product as an orange oil (0.51 g, 91%). The product was purified by column chromatography eluting with hexane: diethyl ether (30:1) to give the *title compound* (0.15 g, 27 %) as a yellow oil (Found: MH^+, 151.1124. $C_{10}H_{15}O$ requires, 151.1123); $\nu_{max.}$ (neat) 3028, 2973, 2879, 2819, 1711, 1685, 1445, 1351, 1199, 1089, 952 and 705 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.87 (1H, dtd, *J* 9.9, 3.4, 1.4 Hz, CH=C<u>H</u>-CH_2), 5.65–5.61 (1H, m, C<u>H</u>=CH-CH_2), 5.36 (1H, dt, *J* 9.9, 2.1 Hz, C=C<u>H</u>-CH_2), 2.83–2.79 (2H, m, CH_2), 2.09 (3H, s, CH_3), 1.58 (3H, s, CH_3) and 1.21 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 210.2 (C=O), 138.9 (alkene C), 129.9 (CH), 125.5 (CH), 121.8 (CH), 54.7 (C), 27.1 (CH_2), 25.6 (CH_3), 21.5 (CH_3) and 19.6 (CH_3); *m/z* (APCI) 151 (MH+, 100%), 149 (9), 115 (73) and 83 (7).

5.2.3 1-Acetyl-1,3-dimethylcyclohexa-2,5-diene (88)

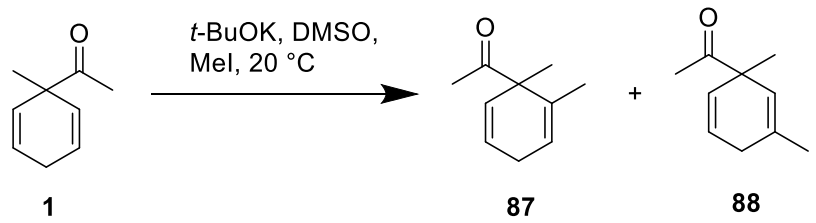


90 **88**

3-Methylacetophenone (0.51 mL, 3.7 mmol) was dissolved in anhydrous THF (5 mL) under nitrogen. *t*-BuOH (0.41 mL, 4.4 mmol) was added and the solution was cooled to -78 °C. Ammonia (20 mL) was added through a dry ice condenser. Pieces of potassium metal (0.31 g, 8 mmol) were added carefully to the solution until a permanent blue colour persisted. The solution was stirred for at -78 °C 10 minutes. Anhydrous lithium bromide (0.71 g, 8.16 mmol) was added portion wise and the solution was stirred at -78 °C for 40 minutes. The ammonia was evaporated under a positive pressure of nitrogen for over 1 hour. A solution of iodomethane (0.46 mL, 7.38 mmol) dissolved in THF (5 mL) was added to the resultant orange slurry and the mixture was stirred at 0 °C for 40 minutes. The reaction was flushed under a positive pressure of nitrogen for 1 hour to ensure all the ammonia had evaporated. The solution was quenched with saturated aqueous NaCl solution (20 mL) and ether (20 mL). The two phases were adjusted to pH 7.5 with careful addition of aqueous 2M HCl. The ether layer was separated and the aqueous phase separated with ether (3 x 20 mL portions). The ether extracts were combined and washed with brine. The ether was evaporated under reduced pressure to give an orange oil (0.54 g, 98%). The product was purified by column chromatography in hexane: diethyl ether (30:1) to give the *title compound* (0.16 g, 29%) as a yellow oil (Found: M^+, 150.1046. $C_{10}H_{14}O$ requires M, 150.1045); $\nu_{max.}$ (neat) 3024, 2971, 2927, 2868, 2814, 1709, 1446, 1421, 1380, 1351, 1283, 1203, 1088, 935, and 716 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.87 (1H, dt, *J* 10.0, 3.4 Hz, CH=C<u>H</u>-CH_2), 5.52 (1H, app. dq, *J* 10.0, 2.1 Hz, C<u>H</u>=CH-CH_2), 5.25–5.19 (1H, m, C-C<u>H</u>=C), 2.76–2.57 (2H, m, ring CH_2), 2.09 (3H, s, CH_3), 1.62 (3H, s, CH_3) and 1.18 (3H, s, CH_3); *m/z* (EI) 150 (M^+, 19%), 135 (53), 117 (7) and 89 (100).

5.3 Rearrangement chemistry

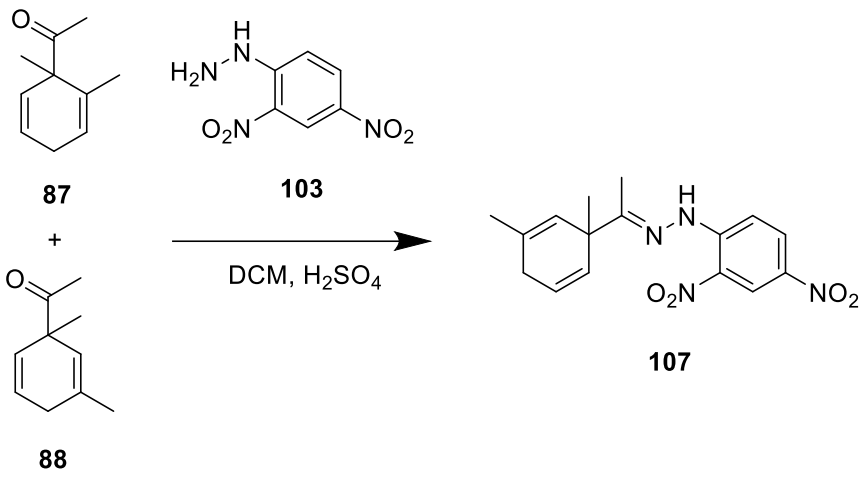
5.3.1 1-Acetyl-1,2-dimethylcyclohexa-2,5-diene (87) and 1-acetyl-1,3-dimethylcyclohexa-2,5-diene (88)



1 **87** **88**

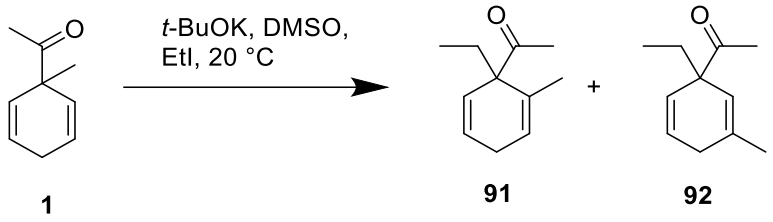
Diene **1** (0.50 g, 3.7 mmol) and *t*-BuOK (0.50 g, 4.4 mmol) were dissolved in anhydrous DMSO (5 mL) and stirred under nitrogen for 1 hour. Iodomethane (0.25 mL, 4.0 mmol) was added dropwise to the solution. The solution was stirred at 20 °C for 1 hour. The reaction mixture was quenched with water (20 mL) and extracted into ether (3 x 20 mL). The organic fractions were collected and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a mixture of the two regioisomers (0.39 g, 70%) as a yellow oil. The product was identified in the ^1H NMR of the crude reaction mixture. The product was purified after formation of the corresponding 2,4-dinitrophenylhydrazone (see below).

5.3.2 1-Acetyl-1,3-dimethylcyclohexa-2,5-diene 2,4-dinitrophenylhydrazone(107)



Ketones **87** and **88** (0.39 g, 2.6 mmol) were dissolved in dichloromethane (5 mL) and 2,4-dinitrophenylhydrazine (50% in water) (1.03 g, 2.6 mmol) was added. A few drops of concentrated sulfuric acid were added to catalyse the reaction. The reaction mixture was stirred at 20 °C for 1 hour. The reaction was washed with water (20 mL) and the product was extracted into dichloromethane (3 x 20 mL). The solvent was removed under reduced pressure to yield and orange solid (0.38 g). The product was dissolved in chloroform (5 mL) and filtered to remove the excess 2,4-dinitrophenylhydrazine. The orange filtrate was collected and evaporated under reduced pressure. The product was purified by column chromatography eluting with hexane to diethyl ether (22:1) to give compound **107** (0.15 g, 12%) as an orange solid, m.p. 95–97 °C; δ_H (400 MHz, $CDCl_3$) 11.01 (1H, NH), 9.14 (1H, d, *J* 2.6 Hz, aromatic CH), 8.32 (1H, dd, *J* 9.6, 2.6 Hz, aromatic CH), 7.99 (1 H, d, *J* 9.6 Hz, aromatic CH), 5.91 (1H, dt, *J* 10.0, 3.3 Hz, CH=C<u>H</u>-CH_2), 5.46 (1H, app. dq, *J* 10.0, 2.1 Hz, C<u>H</u>=CH-CH_2), 5.18–5.15 (1H, m, C-C<u>H</u>=C), 2.67–2.64 (2H, m, CH_2), 1.93 (3H, s, CH_3), 1.76 (3H, s, CH_3) and 1.39 (3H, s, CH_3).

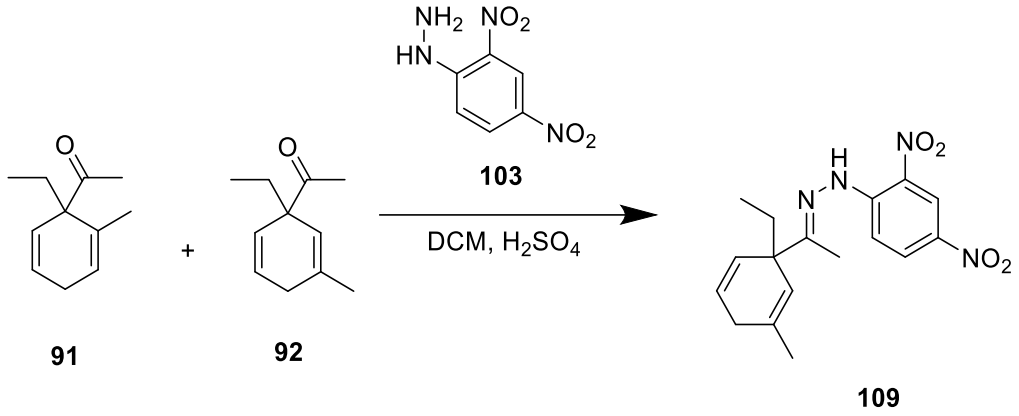
5.3.3 1-Acetyl-1-ethyl-2-methylcyclohexa-2,5-diene (91) and 1-acetyl-1-ethyl-3-methylcyclohexa-2,5-diene (92)



1 91 92

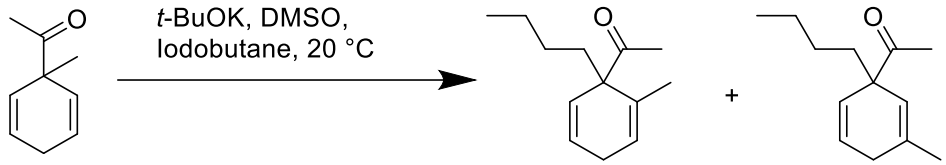
Compound **1** (0.50 g, 3.7 mmol) and *t*-BuOK (0.50 g, 4.4 mmol) were dissolved in DMSO (5 mL) and stirred under nitrogen for 1 hour. Iodoethane (0.32 mL, 4.0 mmol) was added and the solution was stirred at 20 °C for 1 hour. The reaction was quenched with water (20 mL) and extracted into ether (3 x 20 mL). The organic fractions were collected and dried over $MgSO_4$. The solvent was removed under reduced pressure to a give a mixture of the two regioisomers (0.54 g, 91%) as a yellow oil. The product was identified in the ^1H NMR of the crude reaction mixture. The product was purified after formation of the corresponding 2,4-dinitrophenylhydrazone (see below).

5.3.4 1-Acetyl-1-ethyl-3-methylcyclohexa-2,5-diene 2,4-dinitrophenylhydrazone (109)



Ketones **91** and **92** (0.54 g, 3.3 mmol) were dissolved in dichloromethane (5 mL) and 2,4-dinitrophenylhydrazine (50% in water) (1.30 g, 3.3 mmol) was added. A few drops of sulfuric acid were added as a catalyst and the reaction was stirred at 20 °C for 1 hour. The reaction mixture was washed with 1M HCl (50 mL) and extracted into DCM (3 x 20 mL) to yield orange solid (0.68 g). The product was purified by column chromatography in 15:1 hexane and diethyl ether to give the product **109** (0.10 g, 8.8%) as a yellow solid, m.p. 94–98 °C (Found: $[M–H]^-$, 343.1401. $C_{17}H_{19}N_4O_4$ requires M, 343.1406); $\nu_{max.}$ ($CHCl_3$) 3322, 2965, 1618, 1591, 1518, 1442, 1335, 1311 and 1278 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 11.02 (1H, s, NH), 9.14 (1H, d, *J* 2.6 Hz, aromatic CH), 8.31 (1H, dd, *J* 9.6, 2.6 Hz, aromatic CH), 7.97 (1H, d, *J* 9.6 Hz, aromatic CH), 6.00 (1 H, dt , *J* 9.9, 3.4 Hz, CH=C<u>H</u>-CH_2), 5.38 (1H, d, *J* 9.9 Hz, C<u>H</u>=CH-CH_2), 5.09-5.06 (1H, m, C-C<u>H</u>=C), 2.66–2.62 (2H, m, ring CH_2), 1.94 (3H, s, CH_3), 1.83 (2H, q, *J* 7.6 Hz, CH_2), 1.79 (3H, s, CH_3) and 0.82 (3H, t, *J* 7.6 Hz, CH_3); δ_C (101 MHz, $CDCl_3$) 161.4 (C), 145.6 (C), 137.7 (C), 134.7 (C), 132.0 (C), 130.0 (CH), 128.5 (CH), 127.0 (CH), 123.6 (CH), 123.2 (CH), 116.8 (CH), 50.9 (C), 31.2 (CH_2), 29.7 (CH_2), 23.4 (CH_3), 14.1 (CH_3) and 9.2 (CH_3); *m/z* (ES) 343 ($[M–H]^-$, 100%), 313 (12), 239 (8) and 159 (38).

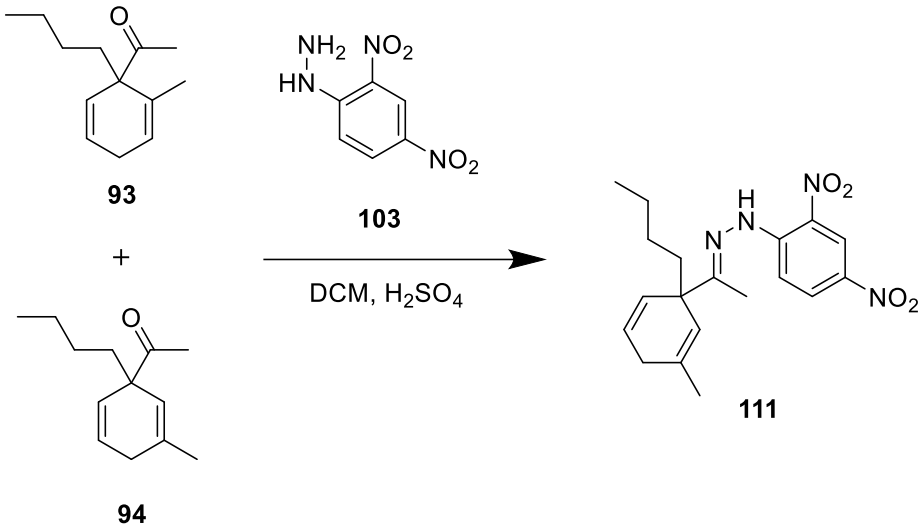
5.3.5 1-Acetyl-1-butyl-2-methylcyclohexa-2,5-diene (93) and 1-acetyl-1-butyl-3-methylcyclohexa-2,5-diene (94)



1 **93** **94**

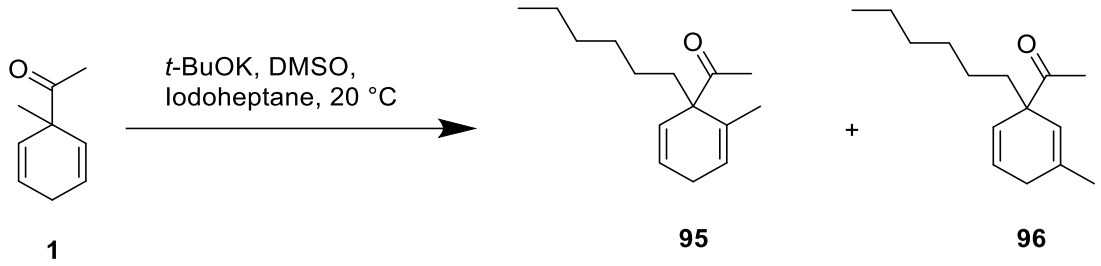
Compound **1** (0.50 g, 3.7 mmol) and *t*-BuOK (0.50 g, 4.4 mmol) were dissolved in DMSO (5 mL) and stirred under nitrogen for 1 hour. Iodobutane (0.45 mL, 4.0 mmol) was added and the solution was stirred at 20 °C for 1 hour. The reaction was quenched with water (20 mL) and extracted into ether (3 x 20 mL). The organic fractions were collected and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil (0.69 g, 99%). The product was observed in the ^1H NMR spectrum of the crude reaction mixture and purified after formation of the corresponding 2,4-dinitrophenylhydrazone (see below).

5.3.6 1-Acetyl-1-butyl-3-methylcyclohexa-2,5-diene 2,4-dinitrophenylhydrazone (111)



Ketones **93** and **94** (0.70 g, 3.95 mmol) were dissolved in dichloromethane (5 mL) and 2,4-dinitrophenylhydrazine (50% in water) (1.57 g, 3.95 mmol) was added. A few drops of sulfuric acid was added as a catalyst and the reaction was stirred at 20 °C for 1 hour. The reaction mixture was quenched with water (20 mL) and extracted into ether (3 x 20 mL). The organic fractions were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure to give an orange solid (0.70 g). The product was purified by column chromatography eluting with hexane to diethyl ether (22:1) to give compound **111** (0.14 g, 10%) as an orange solid, m.p. 98–100 °C (Found: $[M–H]^-$, 371.1709. $C_{19}H_{23}N_4O_4$ requires M, 371.1719); $\nu_{max.}$ ($CHCl_3$) 3324, 2947, 1624, 1592, 1519, 1500, 1418, 1361, 1337, 1310 and 1270 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.07 (1H, d, *J* 2.6 Hz, aromatic CH) , 8.25 (1H, dd, *J* 9.6, 2.6 Hz, aromatic CH), 7.89 (1H, d, *J* 9.6 Hz, aromatic CH), 5.90 (1H, dt, *J* 10.0, 3.4, CH=C<u>H</u>-CH_2), 5.35 (1H, app dq, *J* 10.0, 1.9 Hz, C<u>H</u>=CH-CH_2), 5.14–5.09 (1H, m, C-C<u>H</u>=C), 2.65–2.52 (2H, m, ring CH_2), 1.87 (3H, s, CH_3), 1.71 (2H, broad s, CH_2) 1.68 (3H, s, CH_3), 1.28 (2H, sextet, *J* 7.4 Hz, CH_2), 1.24–1.14 (2H, m, CH_2) and 0.90 (3H, t, *J* 7.4 Hz, CH_3); δ_C (101 MHz, $CDCl_3$) 161.5 (C), 145.7 (C), 137.7 (C), 134.2 (C), 132.5 (C), 130.1 (CH), 130.1 (C), 120.0 (CH), 126.6 (CH), 123.7 (CH), 116.8 (CH), 50.3 (q), 37.0 (CH_2), 31.2 (CH_2), 27.2 (CH_2), 23.5 (CH_2), 23.4 (CH_3), 14.4 (CH_3) and 14.0(CH_3). *m/z* (ES) 371 ($[M–H]^-$, 100%), 309 (6), 265 (9) and 161 (36).

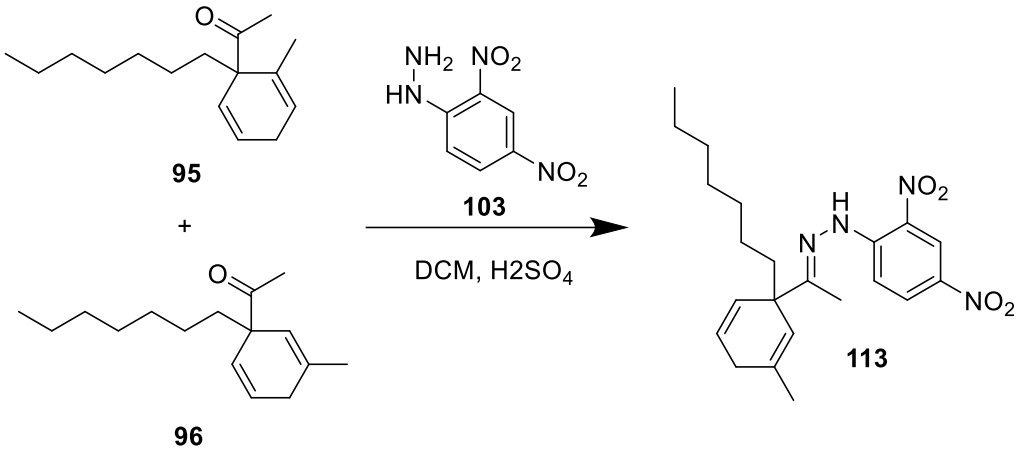
5.3.7 1-Acetyl-1-heptyl-2-methylcyclohexa-2,5-diene (95) and 1-acetyl-1-heptyl-3-methylcyclohexa-2,5-diene (96)



1 95 96

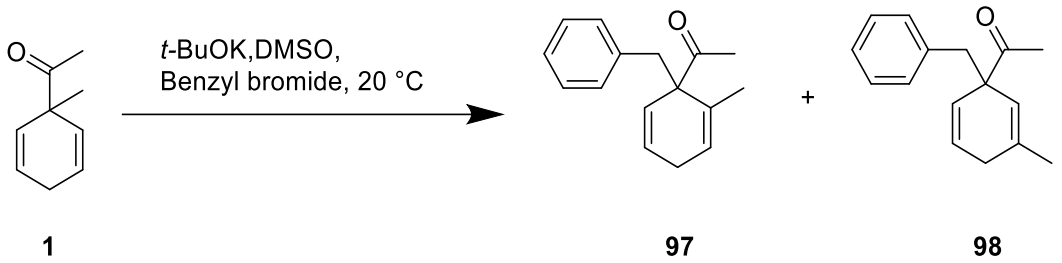
Diene **1** (0.5 g, 3.7 mmol) and t-BuOK (0.5 g, 4.4 mmol) were dissolved in DMSO (5 mL) and stirred under nitrogen for 1 hour. Iodoheptane (0.54 mL, 3.3 mmol) was added and stirred at 20 °C for1 hour. The reaction mixture was quenched with water (20 ml) and extracted into ether (3 x 20 ml). The organic fractions were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil (0.49 g, 76%). The product was identified in the ^1H NMR of the crude reaction mixture and purified after formation of the corresponding 2,4-dinitrophenylhydrazone (see below).

5.3.8 1-Acetyl-1-heptyl-3-methylcyclohexa-2,5-diene 2,4-dinitrophenylhydrazone (113)



Ketones **95** and **96** (0.49 g, 2.2 mmol) were dissolved in dichloromethane (5 ml), 2,4-dinitrophenylhydrazine (50% in water) (0.87 g, 4.4 mmol) was added. A few drops of sulfuric acid were added as a catalyst and reaction stirred at 20 °C for 1 hour. The reaction was quenched with water (20 mL) and extracted into ether (3 x 20 mL). The organic fractions were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure to give compound **113** (0.21 g, 18%) as a yellow solid, m.p. 66–68 °C (Found: $[M–H]^-$, 413.2169. $C_{22}H_{29}N_4O_4$ requires M, 413.2189); $\nu_{max.}$ ($CHCl_3$) 3326, 2952, 1626, 1593, 1520, 1420, 1310 and 1278 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.06 (1H, d, *J* 2.6 Hz, aromatic CH), 8.26 (1H, dd, *J* 9.6, 2.6 Hz, aromatic CH), 7.89 (1H, d, *J* 9.6 Hz, aromatic CH), 5.90 (1H, dt, *J* 10.0, 3.4 Hz, CH=C<u>H</u>-CH_2), 5.35 (1H, app. dq, *J* 10.0, 2.1 Hz, C<u>H</u>=CH-CH_2), 5.06–5.03 (1H, m, C-C<u>H</u>=C), 2.65–2.62 (2H, m, ring CH_2), 1.87 (3H, s, CH_3), 1.71 (3H, s, CH_3), 1.17–1.27 (12H, m, alkane chain) and 0.82 (3H, t, *J* 6.6 Hz, CH_3); δ_C (101 MHz, $CDCl_3$) 161.5 (C=N), 145.7 (C), 137.8 (C), 134.1 (C), 130.1 (CH), 129.2 (C), 129.0 (CH) 126.6 (CH), 123.7 (CH), 123.7 (CH), 116.8 (CH), 50.4 (C), 37.3 (CH_2), 32.1 (CH_2), 31.2 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 25.0 (CH_2), 23.4 (CH_3), 22.8 (CH_2), 14.3 (CH_3) and 14.1 (CH_3); *m/z* (ES) 413 ($[M–H]^-$, 62%), 299 (100), 239 (10) and 166 (82).

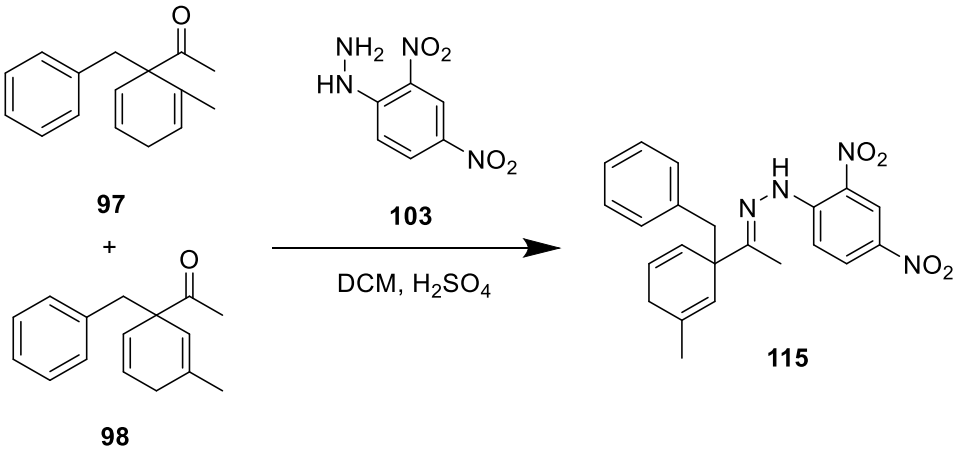
5.3.9 1-Acetyl-1-benzyl-2-methylcyclohexa-2,5-diene (97) and 1-acetyl-1-benzyl-3-methylcyclohexa-2,5-diene (98)



1 **97** **98**

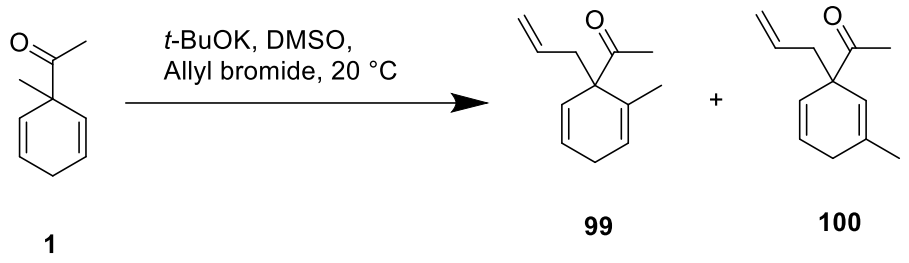
Compound **1** (0.50 g, 3.7 mmol) and *t*-BuOK (0.5 g, 4.4 mmol) were dissolved in DMSO (5 mL) and stirred under nitrogen for 1 hour. Benzyl bromide (0.48 mL, 4.0 mmol) was added and the reaction was stirred at 20 °C for 1 hour. The reaction was quenched with water (20 mL) and extracted into ether (3 x 20 mL). The organic fractions were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil (0.74 g, 90%). The product was observed in the ^1H NMR of the crude reaction mixture and purified after formation of the corresponding 2,4-dinitrophenylhydrazone (see below).

5.3.10 1-Acetyl-1-benzyl-3-methylcyclohexa-2,5-diene 2,4-dinitrophenylhydrazone (115)



Ketones **97** and **98** (0.395 mL, 4.0 mmol) were dissolved in dichloromethane (5 mL) and 2,4-dinitrophenylhydrazine (50% in water) (1.80 g, 9.0 mmol) was added. A few drops of sulfuric acid was added as a catalyst and the reaction was stirred at 20 °C for 1 hour. The reaction was quenched with water (20 mL) and extracted into ether (3 x 20 mL). The organic fractions were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure to give an orange solid (0.74 g). The product was purified by column chromatography eluting with hexane and diethyl ether (22:1) to give an orange solid **115** (0.078 g, 6%), m.p. 174–176 °C (Found: $[M–H]^-$, 405.1564. $C_{22}H_{21}N_4O_4$ requires M, 405.1563); $\nu_{max.}$ ($CHCl_3$) 2920, 2850, 1615, 1516, 1452, 1420, 1335, 1311 and 1278 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.07 (1H, d, *J* 1.5 Hz, aromatic CH), 8.25 (1H, d, *J* 8.2 Hz, aromatic CH), 7.94 (1H, d, *J* 9.6 Hz, aromatic CH), 7.19–6.99 (5H aromatic), 5.75 (1H, d, *J* 9.6 Hz, CH=C<u>H</u>-CH_2), 5.43 (1H, d, *J* 9.6 Hz, C<u>H</u>=CH-CH_2), 5.16 (1H, s, C-C<u>H</u>=C), 3.08 (2H,s, CH_2), 2.40–2.38 (2H, m, ring CH_2), 1.93 (3H, s, CH_3) and 1.59 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 161.1 (C=N), 145.7 (C), 138.3 (C), 137.9 (C), 135.0 (C), 131.0 (CH), 130.2 (CH), 129.3 (C), 128.1 (CH), 127. (CH), 127.4 (CH), 125.9 (CH), 123.7 (CH), 123.0 (CH), 116.8 (CH), 51.6 (C), 43.7 (CH_2), 30.7 (CH_2), 23.2 (CH_3) and 14.5 (CH_3); *m/z* (ES) 405 ($[M-H]^-$, 100%), 313 (8) and 161 (58).

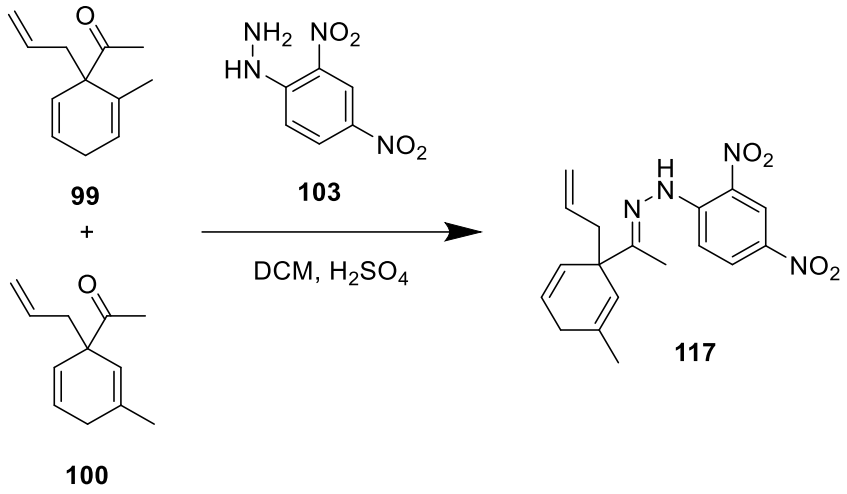
5.3.11 1-Acetyl-1-allyl-2-methylcyclohexa-2,5-diene (99) and 1-acetyl-1-allyl-3-methylcyclohexa-2,5-diene (100)



1 99 100

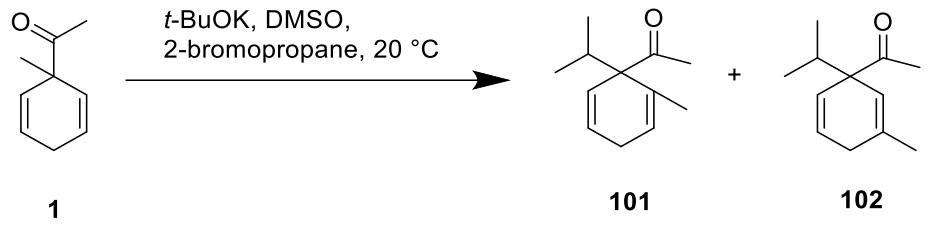
Compound **1** (0.5 g, 3.7 mmol) and *t*-BuOK (0.5 g, 4.4 mmol) were dissolved in DMSO (5 mL) and stirred under nitrogen for 1 hour. Allyl Bromide (0.35 mL, 3.7 mmol) was added and the reaction was stirred at 20 °C for 1 hour. The reaction was quenched with water (20 mL) and extracted into ether (3 x 20 mL). The organic fractions were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil (0.49 g, 75%). The product was identified in the ^1H NMR of the crude reaction mixture and purified after formation of the corresponding 2,4-dinitrophenylhydrazone (see below).

5.3.12 1-Acetyl-1-allyl-3-methylcyclohexa-2,5-diene 2,4-dinitrophenylhydrazone (117)



Ketones **99** and **100** (0.49 g, 2.8 mmol) were dissolved in dichloromethane (5 mL) and 2,4-dinitrophenylhydrazine (50% in water) (0.91 g, 4.6 mmol) was added. A few drops of sulfuric acid were added as a catalyst and reaction stirred at 20 °C for 1 hour. The reaction was quenched with water (20 mL) and extracted into ether (3 x 20 mL). The organic fractions were collected and dried over $MgSO_4$. The solvent was removed under reduced pressure to give compound **117** (0.076 g, 8%) as a yellow solid, m.p. 108–112 °C (Found: $[M–H]^-$, 355.1403. $C_{18}H_{19}N_4O_4$ requires M, 355.1406); $\nu_{max.}$ ($CHCl_3$) 3425, 2917, 1617, 1540, 1517, 1419, 1336, 1312 and 1280 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.05 (1H, d, *J* 2.8, aromatic CH), 8.25 (1H, dd, *J* 9.6, 2.8 Hz, aromatic CH), 7.90 (1H, d, *J* 9.6, aromatic CH), 5.98 (1H, app. dt, *J* 10.0, 3.4 Hz, ring CH=C<u>H</u>-CH_2), 5.75 (1H, ddt, *J* 17.1, 10.0, 7.2 Hz, allyl H_2C=C<u>H</u>-CH_2), 5.44 (1H, app. dq, *J* 10.0, 2.0 Hz, ring C<u>H</u>=CH-CH_2), 5.16–5.14 (1H, m, ring CH), 5.09–5.00 (2H, m, allyl =CH_2), 2.65–2.58 (2H, m, ring CH_2), 2.53 (2H, d, *J* 7.2 Hz, CH_2), 1.87 (3H, s, CH_3) and 1.71 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 160.6 (C), 145.6 (C), 137.9 (C), 135.3 (CH), 134.5 (C), 130.1 (CH), 129.3 (C), 128.6 (CH), 126.8 (CH), 123.6 (CH), 123.3 (CH), 117.1 (CH_2), 116.8 (CH), 50.0 (C), 42.1 (CH_2), 31.1 (CH_2), 23.4 (CH_3) and 14.0 (CH_3); *m/z* (ES) 355 ($[M–H]^-$, 100%), 311 (22), 265 (25) and 161 (88).

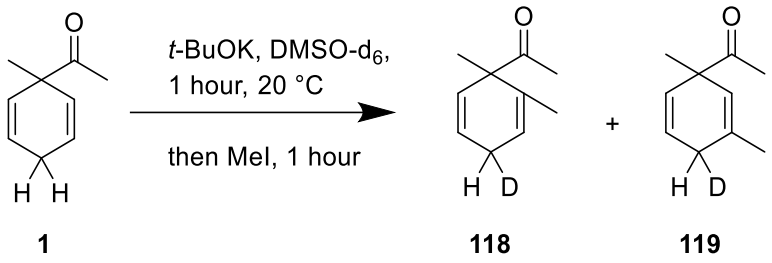
5.3.13 2-Acetyl-1-isopropyl-2-methylcyclohexa-2,5-diene (101) and 1-acetyl-1-isopropyl-3-methylcyclohexa-2,5-diene (102)



1 101 102

Compound **1** (0.5 g, 3.7 mmol) and *t*-BuOK (0.5 g, 4.4 mmol) were dissolved in DMSO (5 mL) and stirred under nitrogen for 1 hour. 2-Bromopropane (3.8 mL, 4.0 mmol) was added and the reaction stirred at 20 °C for 1 hour. The reaction was quenched with water (20 mL) and extracted into ether (3 x 20 mL). The organic fractions were collected and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil (0.40 g, 75%). The product was purified by column chromatography in hexane:diethyl ether (40:1) to produce compound **102** (0.022 g, 4%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 5.88 (1H, dt, *J* 10.2, 3.4 Hz, CH=C<u>H</u>-CH_2), 5.53 (1H, dq, *J* 10.2, 2.1 Hz, C<u>H</u>=CH-CH_2), 5.22–5.19 (1H, m, C-C<u>H</u>=C), 2.48–2.44 (2H, m, ring CH_2), 2.02 (3H, s, CH_3), 2.18–2.08 (1H, sep, *J* 6.9 CH), 1.70 (3H, s, CH_3), 0.79 (3H, d, *J* 6.9 Hz, CH(C<u>H</u>$_3$)) and 0.77 (3H, d, *J* 6.9 Hz, CH(C<u>H</u>$_3$)).

5.3.14 C-4 deuterated 1-acetyl-1,2-dimethylcyclohexa-2,5-diene (118) and C-4 deuterated 1-acetyl-1,3-dimethylcyclohexa-2,5-diene (119)



1 **118** **119**

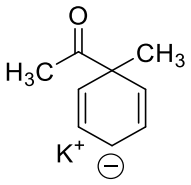
Compound **1** (0.40 g, 2.94 mmol) was dissolved in anhydrous d_6 DMSO (5 mL) with *t*-BuOK (0.40 g, 3.5 mmol) and stirred at 20 °C under nitrogen for 1 hour. Iodomethane (0.20 mL, 3.2 mmol) was added dropwise to the solution and the reaction mixture was stirred at 20 °C for 1 hour. The reaction was quenched with water (20 mL) and extracted into ether (3 x 20 mL portions). The ether extracts were combined, washed with brine (50 mL) and dried over $MgS0_4$. The solvent was removed under reduced pressure to produce yellow oil (0.42 g, 96%). The product was purified by column chromatography eluting with hexane: ether (100:1) to yield compound **119** (0.010 g, 2.4%) as a clear oil; δ_H (250 MHz, $CDCl_3$) 5.82 (1H, dd, *J* 10.0, 3.4 Hz, CH=C<u>H</u>-CH_2), 5.45 (1H, dt, *J* 10.0, 2.1 Hz, C<u>H</u>=CH-CH_2), 5.13 (1H, m, C-C<u>H</u>=C), 2.59–2.50 (1H, m, partially deuterated ring CH_2), 1.68 (3H, s, CH_3), 1.52 (3H, s, CH_3) and 1.10 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) δ 210.5 (C), 132.9 (C), 129.2 (CH), 125.4 (CH), 123.9 (CH), 52.5 (C), 30.9 (CH_2), 26.2 (CH_3), 24.1 (CH_3) and 23.3 (CH_3).

5.4 Computational results

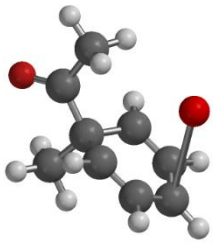
Density function theory, B3LYP, basis set 6-31G*, gas phase model.

5.4.1 Summary of *exo* calculations

Diene anion *exo* (123)



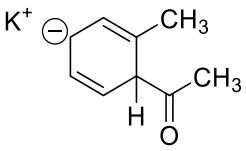
123



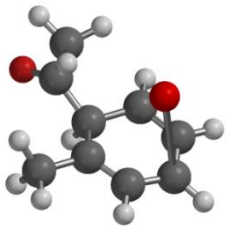
Free energy = –1024.53968 H

	X, Y, Z (Å)		
C	-1.264056	1.090284	-1.208979
H	-1.783444	1.245453	-2.157496
C	-0.020494	0.486464	-1.234310
H	0.451397	0.277018	-2.193920
C	0.893154	0.562676	-0.000663
C	-0.019525	0.487695	1.233809
H	0.453014	0.278801	2.193221
C	-1.263258	1.091313	1.208788
H	-1.781998	1.247347	2.157565
C	1.894340	-0.610810	0.000219
C	1.353898	-2.045824	-0.002700
H	0.735024	-2.221966	-0.892539
H	2.196114	-2.741623	-0.008741
H	0.743449	-2.228040	0.891830
C	1.699849	1.885579	-0.001610
H	2.340359	1.959290	-0.888416
H	2.340861	1.960360	0.884715
H	0.998205	2.724937	-0.001967
C	-1.923169	1.436910	0.000004
H	-2.870664	1.966431	0.000181
O	3.099338	-0.438930	0.003349
K	-1.932708	-1.434857	0.001127

Methyl *ortho exo* (124)



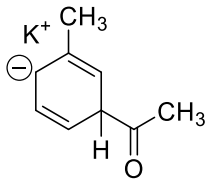
124



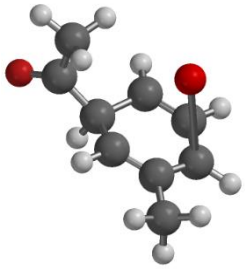
Free energy = –1024.54017 H

	X, Y, Z (Å)		
C	-1.554950	0.034218	-1.613319
H	-2.187372	-0.434344	-2.370743
C	-0.221335	-0.328212	-1.563114
H	0.183277	-0.961726	-2.351204
C	0.781396	0.497341	-0.755835
C	0.063328	1.177363	0.420513
C	-1.281849	1.466315	0.315739
H	-1.712306	2.132617	1.067940
C	1.982711	-0.355976	-0.314120
C	1.740767	-1.545571	0.621584
H	1.115817	-2.297759	0.121817
H	2.699746	-1.998436	0.882713
H	1.236237	-1.218394	1.541368
C	-2.143135	0.923981	-0.681373
H	-3.173105	1.252497	-0.774684
O	3.110914	-0.124008	-0.706065
K	-1.568840	-1.356331	0.893391
H	1.272328	1.272519	-1.388793
C	0.949130	1.908775	1.400127
H	1.610246	2.616474	0.870718
H	1.619202	1.246626	1.968230
H	0.360200	2.482867	2.125508

Methyl *meta exo* (125)



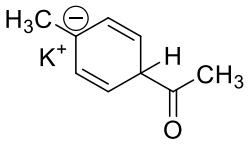
125



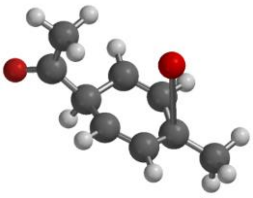
Free energy = –1024.54165 H

	X, Y, Z (Å)		
C	-0.913877	-0.106654	-1.847370
H	-1.223822	-0.602337	-2.770282
C	0.432849	-0.079274	-1.542060
H	1.155468	-0.433069	-2.275851
C	0.937637	0.861110	-0.444760
C	-0.157983	0.993883	0.615792
C	-1.496326	0.949919	0.267241
C	2.275804	0.394085	0.140005
C	2.326985	-0.931997	0.903031
H	2.062189	-1.763383	0.235057
H	3.338278	-1.091561	1.283459
H	1.619031	-0.919096	1.742690
C	-1.914828	0.405807	-0.982724
H	-2.959084	0.429036	-1.281203
O	3.293895	1.046788	0.001741
K	-0.887080	-1.881434	0.410723
H	1.197240	1.854644	-0.870813
H	0.119547	1.465520	1.558835
C	-2.544707	1.453271	1.240562
H	-2.122705	1.635053	2.235258
H	-3.387730	0.755922	1.343304
H	-2.968389	2.401322	0.883594

Methyl *para exo* (126)



126

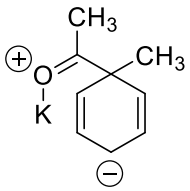


Free energy = –1024.53844 H

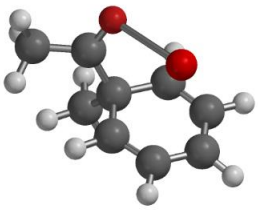
	X, Y, Z (Å)		
C	-1.186315	0.623335	-1.199757
H	-1.725503	0.544519	-2.148216
C	0.195853	0.550639	-1.228450
H	0.707000	0.526504	-2.189691
C	0.997379	0.980282	0.001075
C	0.195556	0.547743	1.229341
H	0.706341	0.521590	2.190737
C	-1.186644	0.620876	1.200493
H	-1.725984	0.540010	2.148717
C	2.424055	0.419406	0.000284
C	2.627346	-1.096296	0.001535
H	2.167078	-1.546316	-0.888407
H	3.697422	-1.316173	0.003524
H	2.163480	-1.545541	0.889946
C	-1.942093	0.703453	0.000403
O	3.393290	1.156184	-0.001452
K	-0.780824	-1.965264	-0.001710
H	1.167741	2.078997	0.002213
C	-3.441756	0.893304	0.000579
H	-3.747152	1.951690	0.004029
H	-3.910796	0.436859	0.884474
H	-3.910560	0.441957	-0.886231

5.4.2 Summary of *endo* calculations

Diene anion *endo* (127)



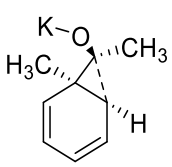
127



Free energy = –1024.545954 H

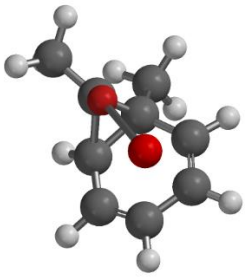
	X, Y, Z (Å)		
C	-1.590819	1.063759	-1.033052
H	-2.244394	1.209702	-1.895246
C	-2.152035	1.156862	0.277087
H	-3.171249	1.494580	0.432728
C	-1.243246	1.037245	1.352805
H	-1.614382	1.161871	2.371987
C	0.104307	0.764053	1.198022
H	0.752474	0.762277	2.072540
C	0.789831	0.702923	-0.173983
C	-0.276265	0.755539	-1.271529
H	0.090395	0.721660	-2.296482
C	1.811309	1.857707	-0.362739
H	2.536624	1.918451	0.458860
H	1.262075	2.803370	-0.390271
H	2.365489	1.758712	-1.307435
C	1.504427	-0.669269	-0.141159
C	2.869212	-0.780574	0.514063
H	3.107543	-1.830992	0.697528
H	2.911913	-0.217272	1.452182
H	3.631689	-0.352501	-0.148533
O	0.960194	-1.695602	-0.564922
K	-1.484740	-1.641817	0.048128

TS close 1 *endo* (128)



TS close 1

128

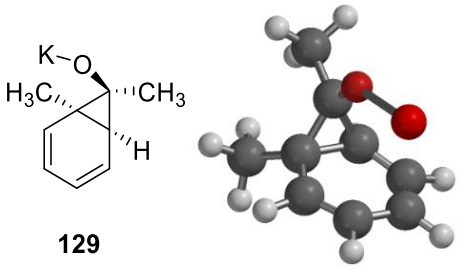


Free energy = –1024.54486 H

	X, Y, Z (Å)		
C	-1.243999	0.404366	0.438234
C	0.080569	1.100074	-1.661916
C	0.927575	1.678082	0.538422
C	1.131027	1.559452	-0.893600
C	-0.171104	1.173970	1.156650
C	-1.076820	0.496984	-1.113707
H	1.973014	2.067707	-1.359809
H	-0.370683	1.439466	2.194357
H	0.126784	1.215958	-2.744689
H	1.628357	2.285595	1.115401
C	-0.897168	-0.954775	-0.085945
O	0.278824	-1.475699	0.079651
K	2.499467	-0.873697	0.337558
C	-2.005382	-1.935727	-0.452909
H	-2.214534	-2.578365	0.414069
H	-1.650284	-2.581863	-1.262789
H	-2.944313	-1.469977	-0.764957
H	-1.976747	0.451431	-1.720493
C	-2.632221	0.688932	1.008071
H	-2.732112	0.280896	2.022815
H	-3.428460	0.255716	0.396782
H	-2.806349	1.771129	1.058711

This calculated structure has one imaginary frequency –315.35 cm^{-1}, intensity 288.75 km/mol.

1st Cyclopropane *endo* (129)

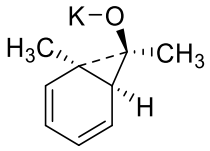


129

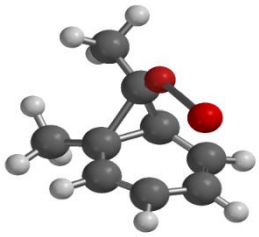
Free energy = –1024.54592 H

X, Y, Z (Å)			
H	-1.885257	-0.198420	-1.802405
C	-1.014159	-0.261307	-1.150311
C	-0.347131	-1.262781	1.115700
C	1.035755	-1.618973	-0.877220
C	0.784086	-1.759419	0.550159
C	0.117201	-1.005070	-1.674704
C	-1.320573	-0.410239	0.414006
H	1.431651	-2.417796	1.130190
H	0.198863	-1.104291	-2.756465
H	-0.610133	-1.570324	2.127981
H	1.857273	-2.180053	-1.322141
C	-0.826212	0.933659	-0.152747
O	0.387327	1.382266	0.143039
K	2.568271	0.796790	0.370188
C	-2.758917	-0.618233	0.868727
H	-2.900050	-0.260837	1.898008
H	-3.034346	-1.681064	0.843566
H	-3.472385	-0.082514	0.238086
C	-1.864631	2.044502	-0.329415
H	-1.460542	2.767422	-1.047226
H	-2.012357	2.567621	0.623749
H	-2.840994	1.710290	-0.696388

TS open 1 *endo* (130)



TS open 1
130

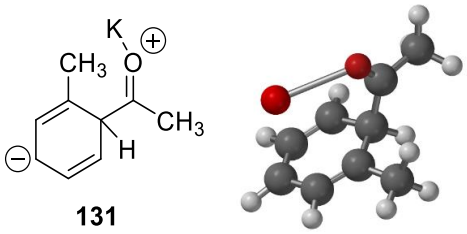


Free energy = –1024.54250 H

X, Y, Z (Å)			
H	-1.832142	-0.066792	-1.776483
C	-0.973996	-0.129834	-1.098458
C	-0.400697	-1.349294	1.044137
C	1.061381	-1.555730	-0.884644
C	0.843871	-1.702361	0.539235
C	0.190588	-0.871224	-1.673888
C	-1.370011	-0.600055	0.344323
H	1.490819	-2.363210	1.114032
H	0.252263	-0.959534	-2.756918
H	-0.678112	-1.715559	2.033452
H	1.873883	-2.118743	-1.348990
C	-0.769475	1.069916	-0.254578
O	0.391885	1.473645	0.117056
K	2.575406	0.723522	0.409047
C	-2.827488	-0.746393	0.736047
H	-2.916569	-1.373382	1.632020
H	-3.411989	-1.238580	-0.056869
H	-3.331823	0.201099	0.961977
C	-1.914204	2.063240	-0.122380
H	-1.615128	2.970725	-0.662615
H	-2.081745	2.346192	0.923535
H	-2.857063	1.712123	-0.550254

This calculated structure has one imaginary frequency –330.47 cm^{-1}, intensity 239.039 km/mol.

Methyl *ortho endo* (131)

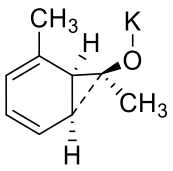


131

Free energy = –1024.56364 H

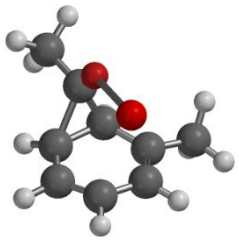
	X, Y, Z (Å)		
C	-0.069639	0.318382	1.650923
H	0.496365	0.814209	2.436875
C	0.699430	-0.618887	0.718081
H	1.304110	-1.355276	1.299332
C	-0.248397	-1.359052	-0.228360
C	-1.610542	-1.226478	-0.129474
H	-2.222207	-1.866273	-0.769920
C	-2.273775	-0.308051	0.743129
H	-3.351229	-0.336084	0.866057
C	-1.448129	0.393020	1.653781
H	-1.914987	1.027981	2.409125
C	1.726605	0.270275	-0.010146
C	3.089766	0.416077	0.629656
H	2.988381	0.711404	1.680742
H	3.697177	1.148354	0.093350
H	3.593421	-0.559989	0.628210
C	0.394998	-2.422631	-1.077227
H	-0.344756	-2.957839	-1.683927
H	0.915283	-3.168793	-0.450557
H	1.157158	-2.020638	-1.762897
O	1.444779	0.902839	-1.032299
K	-1.023097	1.503384	-1.062641

TS close 2 *endo* (132)



TS close 2

132

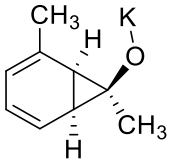


Free energy = –1024.54951 H

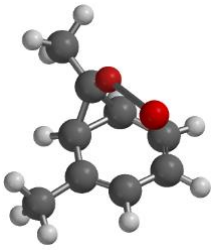
	X, Y, Z (Å)		
H	-2.220047	1.230330	0.246619
C	-1.279629	0.708668	0.033591
C	-0.018300	-0.012461	-2.062731
C	1.063571	1.415902	-0.409897
C	1.145137	0.557930	-1.581318
C	-0.068081	1.546596	0.332395
C	-1.234618	-0.003352	-1.344661
H	2.038842	0.590700	-2.202215
H	-0.013594	-0.469020	-3.052373
H	1.913406	2.065507	-0.187354
C	-1.281939	-0.753653	0.321813
O	-0.249555	-1.388135	0.768763
K	2.071797	-1.244638	0.602662
C	-2.635959	-1.434588	0.456596
H	-2.869075	-1.535051	1.526542
H	-2.602624	-2.443696	0.031097
H	-3.449487	-0.876400	-0.018857
H	-2.164960	-0.162614	-1.879358
C	-0.220010	2.595422	1.400767
H	0.688196	3.199199	1.512624
H	-0.459180	2.152652	2.378654
H	-1.050211	3.278813	1.164600

This calculated structure has one imaginary frequency –354.53 cm^{-1}, intensity 282.953 km/mol.

Second cyclopropane *endo* (133)



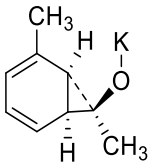
133



Free energy = –1024.55208 H

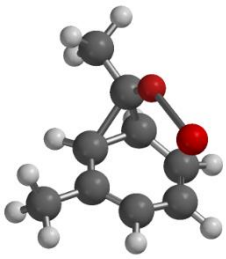
	X, Y, Z (Å)		
H	-2.108202	0.562969	-1.818285
C	-1.208319	0.337497	-1.246609
C	-0.331139	-1.565947	0.288973
C	0.994707	-0.726812	-1.608843
C	0.834098	-1.555336	-0.419758
C	-0.006196	0.087844	-2.035814
C	-1.389999	-0.585591	0.030331
H	1.592871	-2.310697	-0.210120
H	0.054442	0.538070	-3.025469
H	1.864486	-0.898298	-2.243613
C	-1.135551	0.934985	0.181553
O	0.001099	1.400016	0.685549
K	2.242979	0.973299	0.640835
C	-2.389480	1.721364	0.564161
H	-2.284197	2.759292	0.224956
H	-2.494785	1.734550	1.656064
H	-3.309044	1.307076	0.131433
H	-2.401914	-0.931192	0.244898
C	-0.609697	-2.613072	1.336433
H	0.224414	-3.315415	1.443591
H	-1.507915	-3.191618	1.077615
H	-0.806084	-2.157140	2.316101

TS open 2 *endo* (134)



TS open 2

134

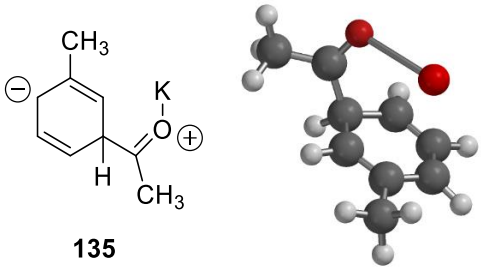


Free energy = –1024.54930 H

	X, Y, Z (Å)		
H	-2.145464	0.310482	-1.792346
C	-1.234603	0.216701	-1.191796
C	-0.162852	-1.616385	0.257131
C	1.078945	-0.614188	-1.598224
C	1.050723	-1.413850	-0.387202
C	0.012347	0.116430	-2.011246
C	-1.312706	-0.860360	-0.073968
H	1.891389	-2.071198	-0.169158
H	0.005785	0.555372	-3.006748
H	1.953073	-0.693269	-2.247907
C	-1.242603	0.970920	0.092292
O	-0.191519	1.523991	0.593458
K	2.109014	1.155778	0.670458
C	-2.592973	1.409571	0.638624
H	-2.743042	2.467784	0.380383
H	-2.610247	1.332922	1.731507
H	-3.431634	0.836171	0.230053
H	-2.287240	-1.248111	0.206482
C	-0.290903	-2.673695	1.330468
H	0.619359	-3.277729	1.417695
H	-1.126962	-3.352594	1.116439
H	-0.496380	-2.222416	2.310764

This calculated structure has one imaginary frequency –350.98 cm^{-1}, intensity 291.204 km/mol.

Methyl *meta endo* (135)

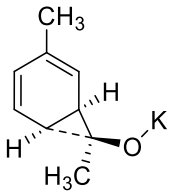


135

Free energy = –1024.56314 H

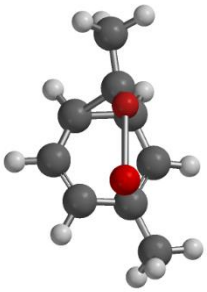
X, Y, Z (Å)			
C	-1.147304	-0.640903	-1.684000
H	-1.528004	-1.348539	-2.423339
C	-2.058511	-0.104299	-0.728927
H	-3.128036	-0.261752	-0.832221
C	-1.557036	0.909438	0.137449
C	-0.224418	1.269173	0.154141
H	0.087818	2.099540	0.786289
C	0.816076	0.725529	-0.831939
C	0.193444	-0.351923	-1.711070
H	0.820087	-0.771860	-2.495357
C	1.996679	0.217624	0.017494
C	3.128080	1.187826	0.279122
H	3.854540	0.763846	0.975742
H	2.734346	2.131461	0.676163
H	3.621658	1.432293	-0.670896
O	2.012443	-0.908302	0.519093
K	-0.376493	-1.732511	0.912546
H	1.234429	1.554343	-1.446827
C	-2.525678	1.637221	1.050185
H	-2.010730	2.326454	1.728060
H	-3.117269	0.938884	1.657659
H	-3.243004	2.221356	0.458878

TS close 3 *endo* (136)



TS close 3

136

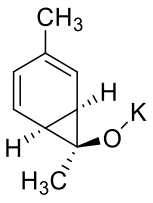


Free energy = –1024.54805 H

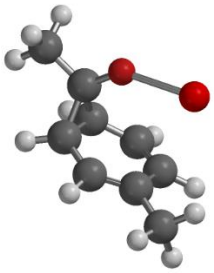
X, Y, Z (Å)			
H	-1.704583	1.858028	1.193588
C	-1.061770	1.145386	0.667532
C	-0.097629	0.927965	-1.679723
C	1.405706	0.952421	0.255642
C	1.164877	0.704270	-1.163459
C	0.368108	1.204690	1.095080
C	-1.245010	1.120896	-0.879021
H	2.021039	0.639853	-1.834631
H	0.572550	1.555661	2.105715
H	-0.218921	0.980178	-2.762007
C	-1.701652	-0.154583	0.316075
O	-1.068772	-1.281754	0.329100
K	1.075310	-2.074852	-0.094891
C	-3.222540	-0.209360	0.349488
H	-3.533225	-0.639000	1.312524
H	-3.598573	-0.867018	-0.442012
H	-3.693768	0.774052	0.245487
H	-2.114308	1.602760	-1.313966
C	2.840145	1.059690	0.727026
H	3.409012	0.129507	0.559649
H	2.898293	1.291004	1.795738
H	3.380364	1.842950	0.178198

This calculated structure has one imaginary frequency –345.50 cm^{-1}, intensity 290.612 km/mol.

3rd cyclopropane *endo* (137)



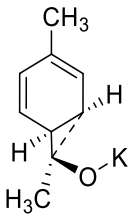
137



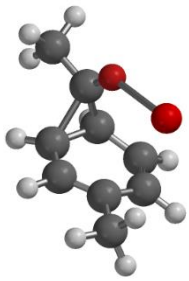
Free energy = –1024.54963 H

	X, Y, Z (Å)		
H	2.181065	1.476541	-1.324778
C	1.332832	0.961379	-0.875915
C	-0.336562	1.309502	1.062196
C	-1.117483	0.775248	-1.182945
C	-1.376702	1.008160	0.238699
C	0.138250	0.866741	-1.700663
C	1.068706	1.208653	0.671942
H	0.263761	0.915269	-2.781698
H	-0.550046	1.688916	2.061473
H	-1.974732	0.728488	-1.856595
C	1.667389	-0.125145	0.189194
O	0.973983	-1.254009	0.257344
K	-1.096194	-2.117218	-0.034815
C	3.166044	-0.259257	0.452064
H	3.605029	-0.951373	-0.276987
H	3.321724	-0.681352	1.452575
H	3.702018	0.696263	0.391005
H	1.747088	1.894204	1.180152
C	-2.815568	1.105105	0.697100
H	-3.357887	0.148239	0.604346
H	-3.383191	1.829915	0.097054
H	-2.880454	1.411788	1.746162

TS open 3 (138)



TS open 3
138

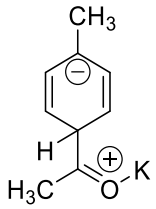


Free energy = –1024.54586 H

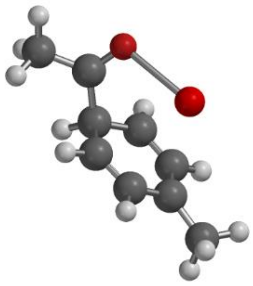
	X, Y, Z (Å)		
H	2.196026	1.248576	-1.430119
C	1.358627	0.787662	-0.897014
C	-0.270948	1.459663	0.948812
C	-1.120390	0.716888	-1.187139
C	-1.356074	1.002899	0.218441
C	0.124002	0.658436	-1.732239
C	1.063655	1.403480	0.499524
H	0.236691	0.650068	-2.814843
H	-0.454894	1.907148	1.926905
H	-1.988995	0.667269	-1.849865
C	1.739679	-0.269163	0.081505
O	1.019186	-1.311377	0.314496
K	-1.200065	-1.974849	0.026715
C	3.181026	-0.285334	0.564433
H	3.729744	-1.053150	-0.000517
H	3.228020	-0.560297	1.623808
H	3.694145	0.671921	0.424654
H	1.807773	2.045955	0.958722
C	-2.770653	1.059952	0.745806
H	-3.260872	0.069420	0.836993
H	-3.434345	1.655482	0.100252
H	-2.799100	1.503859	1.747686

This calculated structure has one imaginary frequency –338.52 cm^{-1}, intensity 294.733 km/mol.

Methyl *para endo* (139)



139

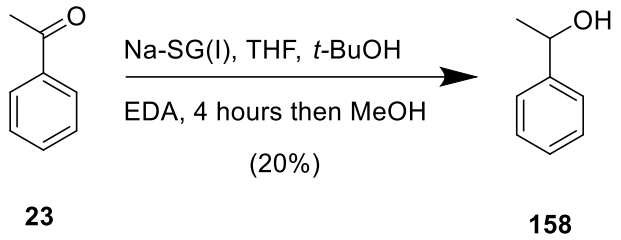


Free energy = –1024.55915 H

	X, Y, Z (Å)		
C	-2.031809	0.472196	0.019280
C	-1.369277	0.416891	-1.243515
H	-1.968125	0.195537	-2.130842
C	-0.016919	0.585624	-1.421966
H	0.396208	0.547020	-2.428237
C	0.916763	1.054205	-0.311122
H	1.333072	2.066360	-0.524258
C	-1.197176	0.822610	1.110163
C	0.165419	1.037735	1.024956
H	0.709025	1.362642	1.910145
H	-1.652821	0.926058	2.098284
C	2.143067	0.139931	-0.129137
C	3.436403	0.799305	0.295147
H	3.774815	1.476864	-0.500290
H	4.207777	0.054087	0.500838
H	3.269874	1.422787	1.182030
O	2.078717	-1.084193	-0.262600
K	-0.308829	-1.869448	0.245142
C	-3.540111	0.465071	0.130456
H	-3.999369	1.447249	-0.075746
H	-3.868627	0.176011	1.138177
H	-4.001975	-0.242971	-0.572574

5.5 Na-SG reduction results

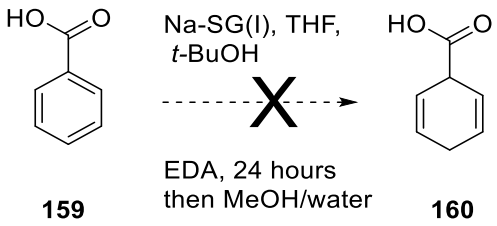
5.5.1 Reduction of acetophenone using Na-SG(I)



23 **158**

Sodium silica gel (Na-SG Stage 1) (0.28 g, 7 mmol) was dissolved in THF (5mL) and *t*-BuOH (0.25 mL, 2.6 mmol) was added. Ethylene diamine (1mL) was added to the mixture and the solution was stirred at 20 °C for 5 minutes. Acetophenone (0.12 g, 1.03 mmol) was added and the reaction was stirred at 20 °C under nitrogen for 4 hours. The reaction was quenched with methanol:water (9:1) (20 mL) and stirred for five minutes as hydrogen gas was evolved. The mixture was filtered to remove Na-SG, and the filtrate was extracted into ethyl acetate (3 x 20 mL). The ethyl acetate fractions were collected and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a clear oil (0.117 g, 98%). The ^{1}H NMR of the crude reaction mixture showed a mixture of acetophenone and 1-phenylethanol in a ratio of 4:1 respectively. 1-Phenylethanol δ_H (400 MHz, $CDCl_3$) 7.35–7.20 (5H, m, aromatic CH), 4.75 (1H, q, *J* 6.5 Hz, CH) and 1.32 (3H, d, *J* 6.5 Hz, CH_3).

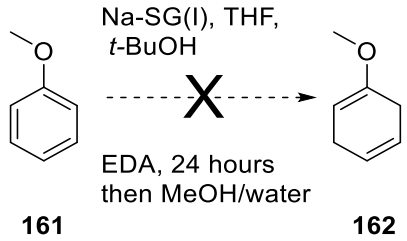
5.5.2 Attempted reduction of benzoic acid using Na-SG(I)



159 **160**

Na-SG (I) (0.47 g, 7.15 mmol) was stirred in THF (5 mL) at 0 °C under an atmosphere of nitrogen. Anhydrous ethylenediamine (2 mL, 30 mmol) was added and the reaction was stirred at 0 °C for 15 minutes. Benzoic acid was added (0.12 g, 1 mmol). *t*-BuOH (0.67 mL, 7 mmol) was added dropwise and the reaction stirred at 0 °C for 24 hours. The reaction was quenched with MeOH/water (9:1) (20 mL) and stirred for five minutes as hydrogen was evolved. The mixture was filtered; the filtrate was extracted into ethyl acetate (3 x 20 mL). The ethyl acetate fractions were collected and dried over $MgSO_4$ to yield a white solid (0.117 g). No reduction product was visible in the ^1H NMR spectrum of the crude reaction mixture, only a mixture of aromatic compounds.

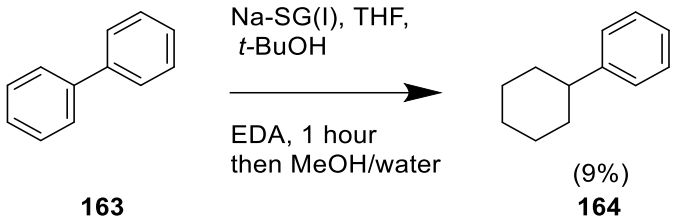
5.5.3 Attempted reduction of anisole using Na-SG(I)



161 **162**

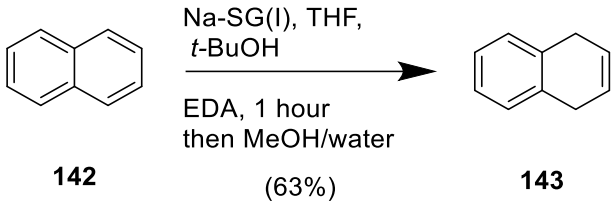
Sodium silica gel Na-SG(I) (0.47 g, 7.15 mmol) was stirred in THF (5 mL) at 0 °C under nitrogen. Anhydrous ethylenediamine (2 mL, 30 mmol) was added and the reaction was stirred at 0 °C for 15 minutes. Anisole (0.11 mL, 1 mmol) and *t*-BuOH (0.67 mL, 7 mmol) were added dropwise and the reaction stirred at 0 °C for 24 hours. The reaction was quenched with methanol:water (9:1) (20 mL) and the mixture was stirred for five minutes as hydrogen gas was evolved. The mixture was filtered to remove Na-SG, the filtrate was extracted into ethyl acetate (3 x 20 mL). The ethyl acetate fractions were collected and dried over $MgSO_4$. The product yielded unreacted anisole (**162**) (1.02g, 94%) as a colourless oil, δ_H (400 MHz, $CDCl_3$) 7.25 (2H, app. ddt, *J* 8.7, 7.4, 1.1 Hz, CH), 6.95 (1H, tt, *J* 7.4, 1.1 Hz, CH), 6.85 (2H, app. broad dd, *J* 8.7, 1.1 Hz, CH) and 3.75 (3H, s, CH_3).

5.5.4 Reduction of biphenyl using Na-SG(I)[32]



Sodium silica gel (Na-SG Stage 1) (0.47 g, 7.15 mmol) was added to a round bottom flask and purged with nitrogen. Anhydrous THF (3 mL) was added and suspension cooled to 0 °C. Ethylenediamine (0.47 mL, 7 mmol) was added and the reaction mixture was stirred at 0 °C for 15 minutes. *t*-Butanol (0.67 mL, 7 mmol) was added dropwise at 0 °C and the reaction was stirred for 5 minutes. A solution of biphenyl (0.15 g, 1 mmol) dissolved in anhydrous THF (2 mL) was added to the Na-SG reaction mixture and solution was stirred at 0 °C for 1 hour. The reaction was quenched with methanol: water (9:1) and stirred for 10 minutes as hydrogen gas was evolved. The reaction was filtered for remove Na-SG, the filtrate was diluted with water (20 mL) and extracted into ethyl acetate (3 x 20 mL). The organic extracts were combined and washed with saturated aqueous NaCl solution (50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a yellow solid (0.10 g, 63%). The product was purified by column chromatography using hexane to give compound **165** (0.014 g, 9%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 7.36–7.19 (5H, m, aromatic CH), 2.48–2.39 (1H, m, CH), 1.85–1.75 (4H, m, CH_2), 1.71–1.64 (1H, m, CH), 1.40–1.30 (4H, m, CH_2) and 1.35–1.25 (1H, m, CH). Data in agreement with reference [32].

5.5.5 1,4-Dihydronaphthalene[20]



Sodium silica gel (Na-SG Stage 1) (0.55 g, 8.4 mmol) was added to a round bottom flask, and purged with nitrogen. Anhydrous THF (3 mL) was added and the suspension was cooled to 0 °C. Ethylenediamine (0.47 mL, 7 mmol) was added and the reaction mixture was stirred at 0 °C for 15 minutes. *t*-Butanol (0.67 mL, 7 mmol) was added dropwise to the solution at 0 °C and the reaction was stirred for a further 5 minutes. A solution of naphthalene (0.128 g, 1 mmol) dissolved in anhydrous THF (2 mL) was added to the Na-SG solution and the reaction mixture was stirred at 0 °C for 1 hour. The reaction was quenched with methanol:water (9:1) and stirred for 10 minutes as hydrogen gas was evolved. The reaction was filtered to remove the Na-SG and the filtrate was diluted with water (20 mL) and extracted into ethyl acetate (3 x 20 mL). The organic extracts were combined and washed with saturated sodium chloride solution and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield 1,4-dihydronaphthalene as a yellow oil (0.10 g, 77%); δ_H (400 MHz, $CDCl_3$) 7.05–6.86 (4H, m, aromatic CH), 5.75 (2H, t, *J* 1.3 Hz, ring CH) and 3.23 (4H, d, *J* 1.3 Hz, ring CH_2). Data in agreement with reference [20].

Chapter 6

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6.0 References

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