A Deeper Understanding of the Diels–Alder Reaction

A thesis submitted in fulfilment of the requirements for admission to the degree of

Doctor of Philosophy

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Declaration

Except where specific acknowledgments of others are made, the work described in this thesis was carried out by the author between June 2004 and January 2010 in the Research School of Chemistry, Australian National University, Australia, under the supervision of Associate Professor Michael S. Sherburn. The material presented has not been submitted for any other degree and is less than 100,000 words in length.

William Lording

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Abbreviations

%	percentage yield
Δ	heat
°C	degree/s Celsius
Ac	acetyl
aq.	aqueous
Ar	aryl or argon
atm.	atmosphere
B3LYP	Becke, three parameter, Lee-Yang-Parr exchange-correlation functional
BHT	2,6-di-*tert*-butyl-4-methylphenol
bp	boiling point
br	broad
Bu	butyl
ca.	circa
calc.	calculated
cat.	catalytic
cm^{-1}	wave number
COSY	correlation spectroscopy
δ	chemical shift
d	day/s or doublet/s
DA	Diels-Alder
DCC	dicyclohexyl carbodiimide
DEPT	distortionless enhancement by polarisation transfer
DFT	density functional theory
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DQF	double quantum filter
d.r.	diastereomeric ratio
EDG	electron donating group
EIMS	electron impact mass spectrometry

Et	ethyl
EWG	electron withdrawing group
eV	electron Volts
e.r.	enantiomer ratio
FMO	frontier molecular orbital
GC	gas chromatography
hr	hour/s
HMBC	heteronuclear multiple bond correlation
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
IMDA	intramolecular Diels-Alder
IR	infrared
IS	internal standard
J	coupling constant
J	joule
K	Kelvin
KIE	kinetic isotope effect
lit.	literature
LUMO	lowest unoccupied molecular orbital
M	molar
M^+	molecular ion
Me	methyl
min	minute/s
MHz	megahertz
mol	mole
mol equiv	molar equivalent(s)
mp	melting point
MS	mass spectrometry
m/z	mass to charge ratio
λ_{max}	absorption maximum (IR)
n	*endo*
n-BuLi	*n*-butyl lithium

NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser and exchange spectroscopy
P	product
Pr	propyl
Ph	phenyl
PTAD	4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione
ppm	parts per million
q	quartet
R_f	retention factor
RT	room temperature
sat.	saturated
SCRF	self consistent reaction field
S.M.	starting material
SOI	secondary orbital interaction
t	time
temp.	temperature
THF	tetrahydrofuran
tlc	thin layer chromatography
t_R	retention time
TS	transition structure
w.r.t.	with respect to
x	*exo*
ZPE	zero point energy

Abstract

The Diels-Alder reaction was discovered in 1928 and has become the most efficient and practical method for the synthesis of six-membered carbocyclic and heterocyclic rings. This thesis comprises three chapters of results and discussion with the Diels-Alder reaction as a theme. Chapter 2 details an investigation of *endo:exo* selectivity in the Diels-Alder reactions of 1,3-butadiene. Chapter 3 explores aspects of the intramolecular Diels-Alder reactions of some substituted 1,3,8-nonatrienes, and Chapter 4 describes the domino Diels-Alder reactions of 1,4-diiodo-1,3-butadiene.

The Diels-Alder reaction is powerful, general, and widely used in chemical synthesis, and it is well known that many Diels-Alder reactions exhibit *endo* selectivity, in accord with Alder's empirical rule. The origins of *endo:exo* selectivity in the Diels-Alder reaction, however, are not completely understood and there is a dearth of experimental evidence concerning the Diels-Alder reactions of the archetypal 1,3-diene, 1,3-butadiene. Chapter 2 describes a study of the Diels-Alder reactions of an isotopically labelled 1,3-butadiene with a range of simple dienophiles, allowing the *endo:exo* selectivities of these important reactions to be determined for the first time. The experimental data shed light on the origins of *endo:exo* selectivity in the Diels-Alder reaction and will serve as an important reference for future computational investigations in this area.

The intramolecular Diels-Alder reaction shares many of the virtues of its intermolecular counterpart, however its use in chemical synthesis is limited because intramolecular Diels-Alder reactivity and stereoselectivity are often governed by subtle factors, and can be very difficult to predict. As part of a comprehensive experimental and computational collaboration, Chapter 3 describes an investigation of the heat and Lewis acid promoted intramolecular Diels-Alder reactions of some ether tethered 1,3,8-nonatrienes. Also presented are the results of a rate study and a kinetic isotope effect study involving the intramolecular Diels-Alder reactions of some 1,3,8-nonatrienes. The experimental data are analysed and compared with predicted stereoselectivities, activation barriers and kinetic isotope effects obtained from computational modelling.

Increased efficiency in chemical synthesis conserves resources, reduces waste, and saves time and money. Domino reactions are particularly efficient processes, which can generate complex products from simple reactants. Chapter 4 describes an investigation of the domino Diels-Alder reactions of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene with maleimide dienophiles, through which a family of bicyclo[2.2.2]oct-2-ene derivatives are produced in one high yielding and stereoselective synthetic step.

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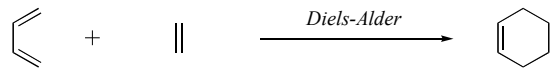
1 Introduction

1.1 The Diels-Alder Reaction

The Diels-Alder (DA) reaction, first described in 1928,[1] is one of the most powerful and important transformations at the disposal of the organic chemist (**Scheme 1.1**). Its discoverers, Otto Diels (1876-1954) and Kurt Alder (1902-1958), shared the Nobel Prize in Chemistry in 1950 for its identification and development.



(**1**) diene (**2**) dienophile (**3**) product

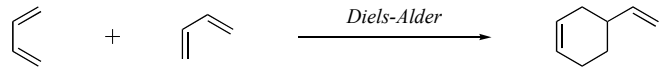
Scheme 1.1 *The Diels-Alder reaction.*

The reaction is a thermally allowed [$_{\pi}2_{s}+_{\pi}4_{s}$] cycloaddition between a 1,3-diene and a dienophile, typically an electron poor alkene, through which two new carbon-carbon σ-bonds are formed at the expense of two carbon-carbon π-bonds.[2] The reaction is suprafacial with respect to both reactants, and proceeds through a boat-like transition state to give a product containing a carbon-carbon π-bond and up to four contiguous stereogenic centres within a six-membered carbocyclic ring. Virtues of the DA reaction include its broad functional group tolerance, mild reaction conditions, and the simplicity and diversity of its reactants, which contribute to its remarkable generality.[3] The DA reaction was central to the development of 20th century theories of organic reactivity, including the conservation of orbital symmetry[4,5] and frontier molecular orbital (FMO) theory[6,7] for which Roald Hoffman (1937-) and Kenichi Fukui (1918-) shared the 1981 Nobel Prize in Chemistry.

The literature on the DA reaction is vast, and a comprehensive review of DA chemistry would fill many volumes. The following is a short summary of aspects of the literature relevant to the work described herein. The scope and mechanism,[2,8,9] aspects of reactivity and selectivity[10,11] and the many variations of the DA reaction have been reviewed. Variations include hetero DA reactions, which form unsaturated, six-membered heterocycles,[12,13] retro DA reactions, in which a cyclohexene unit fragments

to give a 1,3-diene and an alkene,[14,15] intramolecular Diels-Alder (IMDA) reactions, in which the 1,3-diene and dienophile are linked by a tether,[16-19] and transannular DA reactions, in which the 1,3-diene and dienophile are contained within a macrocyclic ring.[20] In addition, catalytic and enantioselective DA reactions,[12,13,21] applications of the DA reaction in natural product synthesis,[22] and the application of computational methods to DA reactions[23,24] have all received considerable attention.

The thermodynamic driving force in the DA reaction is the net conversion of two carbon-carbon π-bonds to two carbon-carbon σ-bonds, but this is offset by the entropic penalty encountered in forming a single cyclic product from two acyclic reactant molecules. The prototypical DA dimerisation of 1,3-butadiene (**1**), giving 4-vinylcyclohex-1-ene (**4**), (**Scheme 1.2**) is exergonic and highly exothermic; the enthalpy of reaction (ΔH_R) is around -111 kJmol^{-1} and the entropy of reaction (ΔS_R) is relatively large and negative, approximately -140 JK^{-1}mol^{-1}, giving a free energy of reaction (ΔG_R) of around -70 kJmol^{-1} at 298 K.[10,25,26] Many DA reactions become reversible at sufficiently high temperatures, as the influence of the negative entropic term gradually increases with temperature.



(**1**) (**1**) (**4**)

Scheme 1.2 *The Diels-Alder dimerisation of 1,3-butadiene (**1**).*

Rate studies have found the uncatalysed DA reaction is a simple bimolecular process which is first order in 1,3-diene and dienophile, and the 1,3-diene must adopt the *s-cis* conformation to react. The rate of reaction is largely independent of the solvent, suggesting that the DA transition state is only slightly more polar than the reactants.[2,10]

FMO theory assumes that the behaviour of bimolecular reactions proceeding under orbital control, such as the DA reaction, can be rationalised by analysing the dominant frontier molecular orbital interaction. Normal electron demand DA reactivity is generally well handled by FMO theory, as it is determined by the difference in energy between the frontier molecular orbitals of the reactants (**Figure 1.1**).[27,28]

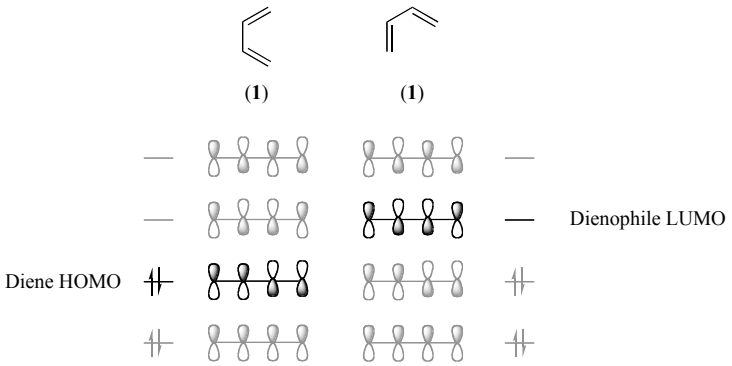


Figure 1.1 *Frontier molecular orbitals involved in a normal electron demand Diels-Alder reaction.*

The HOMO of the 1,3-diene and the LUMO of the dienophile are chosen when considering a DA reaction proceeding with normal electron demand, and the HOMO of the dienophile and the LUMO of the 1,3-diene are chosen in a DA reaction proceeding with inverse electron demand. In special cases, known as neutral-type DA reactions,[10] the properties of both HOMO-LUMO pairs must be considered because the differences in energy between them are comparable (**Figure 1.2**).

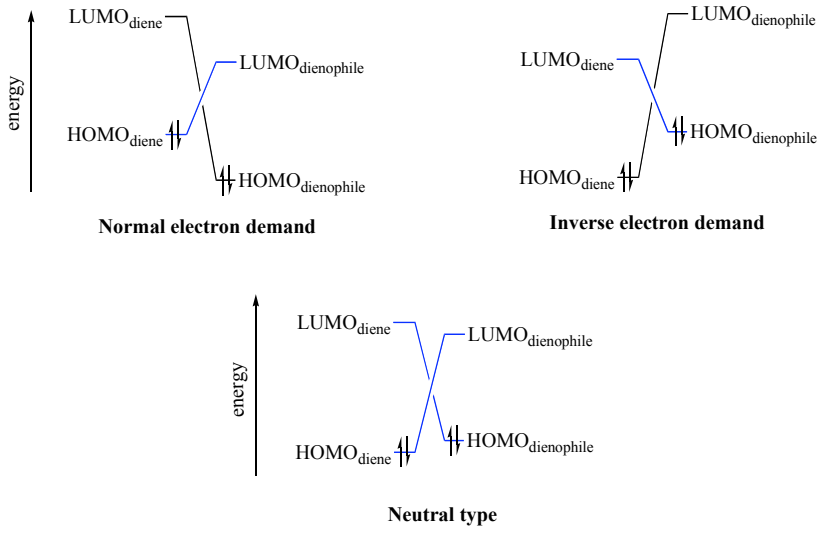
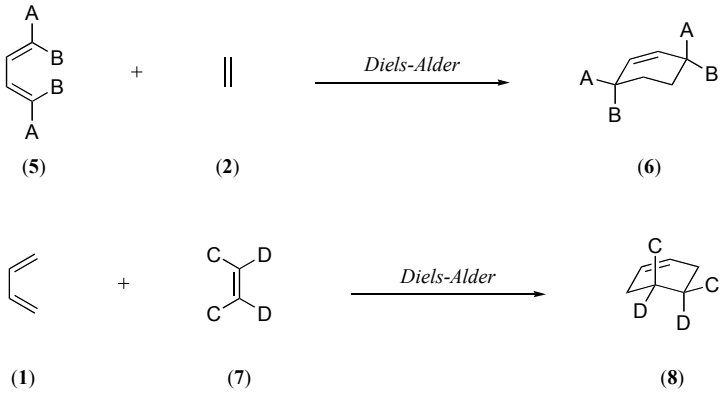


Figure 1.2 *Orbital energy depictions of normal electron demand, neutral type, and inverse electron demand Diels-Alder reactions.*

1.1.1 Selectivity in the Diels-Alder reaction

In addition to its broad scope, the DA reaction proceeds with remarkable, and largely predictable, selectivity. The reaction generally exhibits good chemoselectivity and regioselectivity and, in appropriately substituted systems, *endo:exo* selectivity and π-facial selectivity.[2,22] It can also be rendered enantioselective through the use of chiral

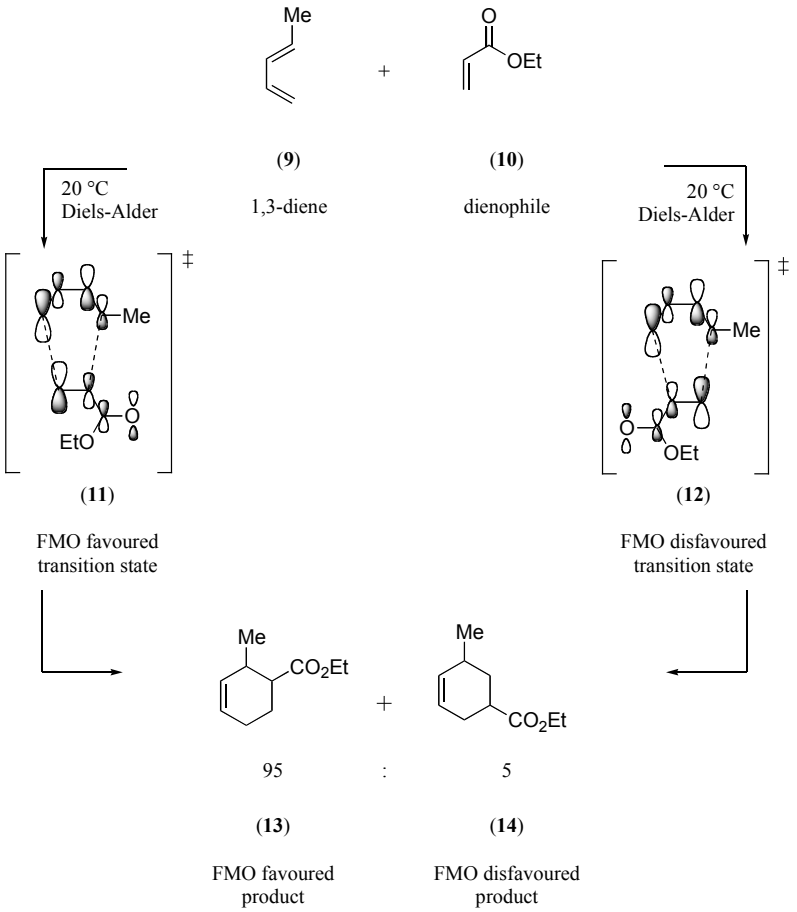
Lewis acid catalysts and organocatalysts.[21,29,30] Three types of selectivity associated with the DA reaction are of particular importance to the work described in this thesis, and the first and simplest of these is described by Alder's "*cis* principle",[31] which states that the stereochemistry of the addends is conserved in the adducts **(Scheme 1.3)**. The DA reaction is a concerted pericyclic process, and geometrical and orbital symmetry constraints ensure that it is suprafacial with respect to the both the 1,3-diene and the dienophile. Thus, both of the carbon-carbon bonds generated by the reaction form in a single, geometrically defined mechanistic step, leaving no opportunity for processes which might otherwise lead to the loss of stereochemical information in the adducts.



Scheme 1.3 *Illustration of Alder's "cis principle" selectivity in the Diels-Alder reaction.*

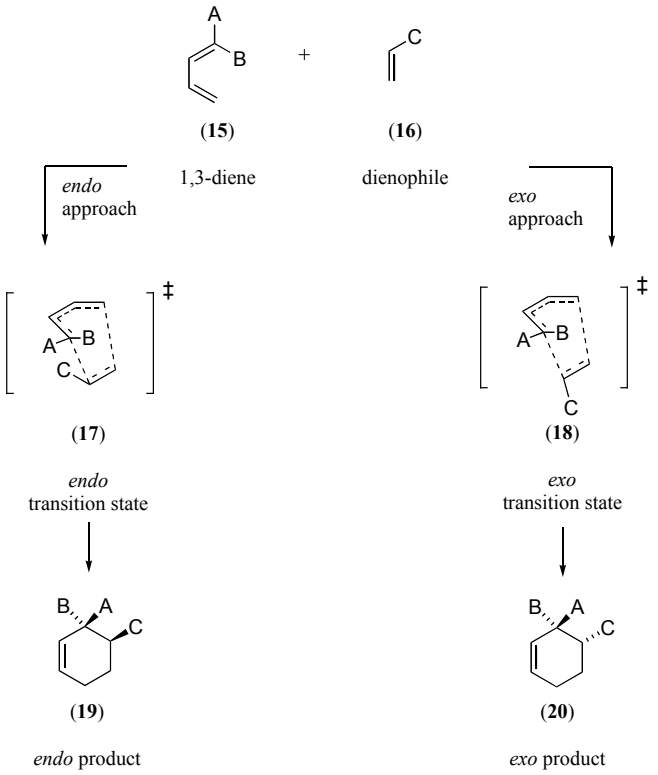
A second type of selectivity associated with the DA reaction is regioselectivity, and this is easily understood through FMO theory. There are two distinct ways in which unsymmetrical addends can unite in a DA sense, and generally one will be favoured over the other.[32]

The coefficients of the frontier molecular orbitals of the dominant frontier orbital interaction at the sites of eventual bond formation are examined and paired, large with large and small with small **(Scheme 1.4)**. The bonding interaction develops rapidly along the reaction co-ordinate at the site of the paired, large HOMO and LUMO coefficients, and this determines the relative orientation of the addends in the major product.[6,27]



Scheme 1.4 *Illustration of frontier molecular orbital interpretation of regioselectivity in the Diels-Alder reaction of piperylene (**9**) with ethyl acrylate (**10**).*

A third type of selectivity, *endo:exo* selectivity, is found in the DA reactions of combinations of appropriately substituted addends (**Scheme 1.5**). In these cases, the DA reaction can proceed through two or more diastereomeric transition states, which differ in the location of the substituent in the dienophile relative to the 1,3-diene. The *endo* pathway proceeds through the more compact transition state, in which the substituent in the dienophile occupies a position proximal to carbons 2 and 3 of the 1,3-diene, and the *exo* pathway proceeds through the less compact transition state, in which the substituent in the dienophile occupies a position distal to carbons 2 and 3 of the 1,3-diene. The DA reaction often proceeds with kinetic *endo* selectivity, as expressed by the Alder *endo* rule in terms of "maximum accumulation of unsaturation."[31] This empirical rule says nothing about the origins of kinetic *endo:exo* selectivity, and the factors controlling kinetic *endo:exo* selectivity in many DA reactions are the subject of some debate.[33-35]



Scheme 1.5 *Illustration of endo:exo selectivity in the Diels-Alder reaction.*

1.1.2 Secondary orbital interactions

In their landmark work on the conservation of orbital symmetry,[4] Woodward and Hoffman introduced the concept of secondary orbital interactions (SOI). For the purposes of this discussion, primary orbital interactions are simply those which lead to the formation or breakage of σ-bonds during a pericyclic reaction. SOIs, on the other hand, are interactions between centres which may be involved in the σ/π reorganisation, but which do not lead to the formation or breakage of σ-bonds during the reaction.[36]

Woodward and Hoffman used the DA dimerisation of 1,3-butadiene (**1**) to illustrate their ideas about the influence of SOIs on the stereochemical outcomes of DA reactions **(Figure 1.3)**.[4,37] They proposed that symmetry allowed mixing of the HOMO of the 1,3-diene with the LUMO of the dienophile, and perhaps also the HOMO of the dienophile with the LUMO of the 1,3-diene, at the specified site should stabilise the *endo* transition state relative to the *exo* transition state, in which no such interactions are possible. Further, they generalised these concepts to other types of cycloadditions, and to 3,3-sigmatropic shifts.[4,38] Regarding DA reactions, the Woodward-Hoffman (WH) SOI concept appeared to be an elegant theoretical explanation for the large and

otherwise puzzling body of evidence supporting the Alder *endo* rule.[31] It is noteworthy that SOIs only operate in the transition states of chemical reactions, if at all, making the SOI hypothesis very difficult to test experimentally. No stable compounds displaying interactions analogous to SOI are known.[33]

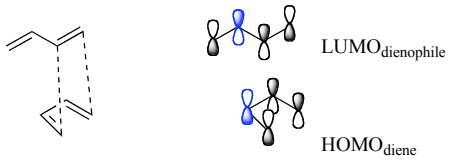


Figure 1.3 *Woodward-Hoffman secondary orbital interactions.*

The stereochemical outcome of the DA dimerisation of 1,3-butadiene (**1**) was eventually studied experimentally, and the reaction was found to give the *endo* and *exo* products in a 56:44 ratio, in favour of the *endo* product.[39,40] Theoreticians have since studied this reaction in considerable detail, and have found that the *endo*, *s-trans* transition state, nominated by Woodward and Hoffman as benefitting from SOI, is actually the highest in energy of the four diastereomeric concerted transition states.[25,26] WH SOIs have received little computational support, but since the SOI hypothesis was first put forward, theoreticians have found other types of SOIs, and have produced case-specific evidence of their influence on the stereochemical outcomes of many DA reactions.[33,41-45]

The Salem-Houk (SH) SOI, first proposed by Salem when considering the DA dimerisation of 1,3-butadiene (**1**),[41] can only operate in an *endo* transition state in which the dienophile adopts the *s-cis* conformation (**Figure 1.4**).

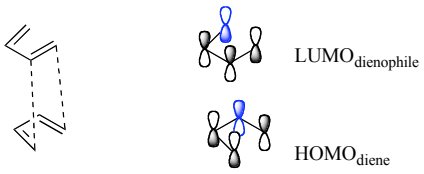


Figure 1.4 *Salem-Houk secondary orbital interactions.*

Experimental support for these interactions was provided by Houk,[46] in a study of the DA reactions of 2,5-dimethyl-3,4-diphenylcyclopentadienone (**21**) with cyclopentene (**22**) and cyclopentadiene (**23**). This type of SOI has received a great deal of support from computational investigations of the DA reaction.[34,47-49] In two recent

computational investigations of the dimerisation of 1,3-butadiene (**1**), the *endo* transition structures involving the dienophile in the *s-cis* conformation were found to exhibit SH SOIs.[25,26]

The Singleton (S[4+3]) SOI was first described by Singleton when considering the DA reaction of 1,3-butadiene (**1**) with vinyl borane (**24**) (**Figure 1.5**).[42] It was found that in the *endo* transition structure, the terminal carbon of the 1,3-diene was closer in space to the boron substituent in the dienophile than to the carbon atom to which the new σ-bond eventually formed. In addition, the carbon in question was pyramidalised towards boron in the transition structure. It is noteworthy that this type of SOI has been described as a neighbouring group effect, and while it involves a site to which a σ-bond is formed during the reaction, it is not the interaction which leads to the formation of the σ-bond. Computational investigations have since found SOIs of this type in a number of Lewis acid promoted DA reactions of α,β-unsaturated carbonyl compounds, where the boron is replaced by the carbon of a carbonyl group.[48,50]

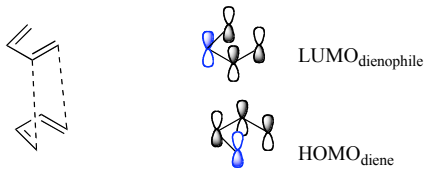
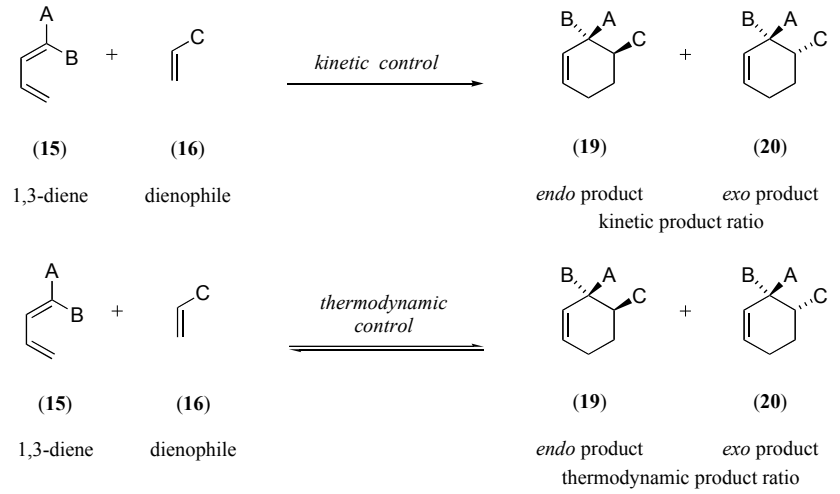


Figure 1.5 *Singleton [4+3] secondary orbital interactions.*

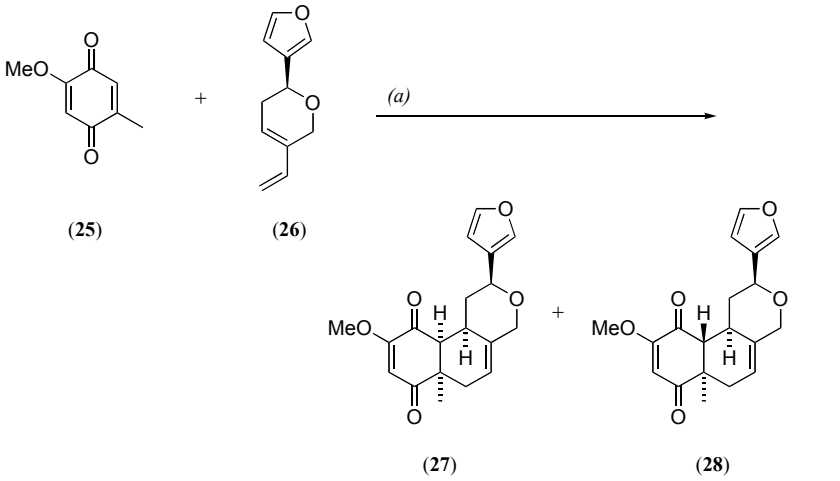
1.1.3 Exo selectivity in the Diels-Alder reaction

While the majority of DA reactions proceed with kinetic *endo* selectivity, in accord with the Alder *endo* rule,[31] many exceptions to the rule are known. A clear distinction must be made at this point between DA reactions under kinetic control, and those under thermodynamic control. Under sufficiently vigorous conditions, most DA reactions will become reversible, allowing an equilibrium between the products and the reactants to be established (**Scheme 1.6**).[14] The ratios of products obtained from reversible DA reactions reflect the relative stabilities of the products, rather than the relative energies of the transition states of the reaction channels through which they are formed. In these cases, a preponderance of the *exo* isomer is often observed, as the *exo* product is generally thermodynamically more stable than the *endo* product.[32,51] Thus, when discussing *endo:exo* selectivity in DA reactions, it is important to be clear whether the selectivity observed is kinetic or thermodynamic in origin.



Scheme 1.6 *Kinetic and thermodynamic reaction pathways in the Diels-Alder reaction.*

Simple α,β-unsaturated carbonyl compounds are commonly used as dienophiles in the DA reaction. Instances are known in which the products of the DA reactions of these dienophiles have epimerised at the stereocentre bearing the carbonyl group. In these cases, product mixtures which do not reflect the inherent *endo:exo* selectivity, or even the *cis* principle selectivity of the DA reaction can be produced (**Scheme 1.7**).[52-55]

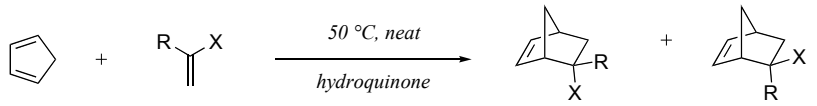


Scheme 1.7 *A Lewis acid promoted Diels-Alder reaction which appears to violate Alder's cis principle; the minor diastereomer (**28**) is produced by epimerisation of the Diels-Alder adduct (**27**). Conditions: (a) 1. (**25**), $TiCl_4$ in toluene, -78 °C, 1 hr. 2. (**26**), warm to -45 °C, 5 hr, 37%.*[55]

Certain structural elements in either the 1,3-diene, dienophile or catalyst are associated with *exo* selectivity in the DA reaction, although the experiments necessary to confirm that the observed selectivity is kinetic in origin are seldom reported. Formal DA

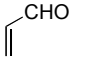
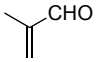
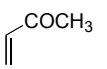
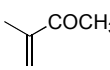
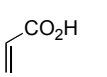
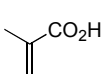
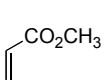
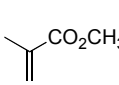
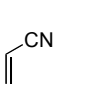
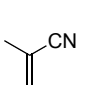
reactions involving polar intermediates such as those of hydrazino-1,3-butadienes[56] and 1-amino-3-siloxy-1,3-butadienes[57] can exhibit *exo* selectivity, but these reactions are mechanistically distinct from from concerted DA reactions.[51] In the DA reactions of α-substituted, α,β-unsaturated carbonyl dienophiles, one may consider the experimentally observed *endo:exo* ratio the outcome of a competition between the α-substituent and the carbonyl activating group for the *endo* orientation relative to the 1,3-diene.

Thus, formal *exo* selectivity has been observed in the DA reactions of α-substituted, α,β-unsaturated dienophiles including α-alkyl carbonyl,[58] α-alkynyl carbonyl,[59] and α-halo carbonyl[60] dienophiles (**Scheme 1.8**). Conformationally constrained cyclic *s-cis* α,β-unsaturated carbonyl dienophiles[61-63] also exhibit *exo* selectivity with a range of dienes. In the DA reactions of some silyloxydienes and silylated dienes with acyclic α,β-unsaturated ketones and N-acyloxazolidinones, the observed *endo:exo* selectivity depends on the presence of particular substitution patterns in both the 1,3-diene and the dienophile.[49]



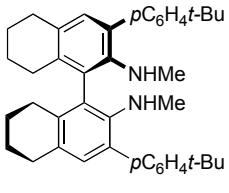
(**23**) (**29**) (**30**) (**31**)

1,3-diene dienophile *endo* product *exo* product

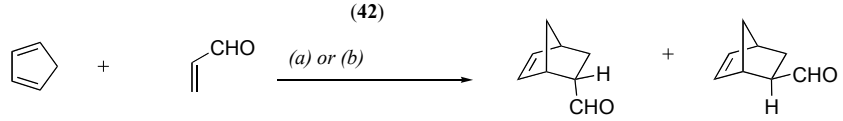
Dienophile		*Endo:exo*	Dienophile		*Endo:exo*
	(**32**)	72:28		(**37**)	19:81
	(**33**)	77:23		(**38**)	46:54
	(**34**)	79:21		(**39**)	31:69
	(**35**)	73:27		(**40**)	30:70
	(**36**)	56:44		(**41**)	13:87

Scheme 1.8 *Comparison of endo:exo selectivities of Diels-Alder reactions of cyclopentadiene (**23**) with α,β-unsaturated dienophiles (**32**) to (**36**) and α-methyl-α,β-unsaturated dienophiles (**37**) to (**41**). Endo and exo in this context refer to the disposition of the electron withdrawing substituent, X. The ratios in the right hand column are the outcome of competition of the electron withdrawing substituent, X, and the methyl group for the endo orientation. Endo:exo ratios determined by gas chromatography; yield and time data not reported.*[58]

Exo selective, asymmetric, organocatalysed DA reactions have been developed by a number of groups (**Scheme 1.9**).[29,64,65]



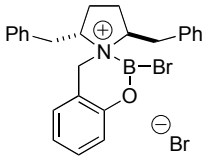
(**42**)



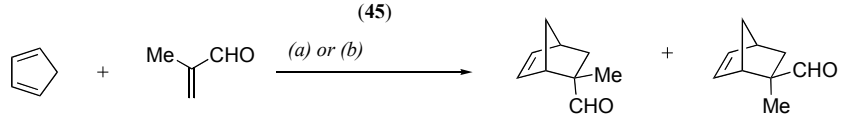
(**23**)	(**36**)	(**43**)	(**44**)
1,3-diene	dienophile	*endo* product	*exo* product
(a) neat, hydroquinone, 50 °C		*72* :	*28*
*(b) $PhCF_3$,, (**42**) 12 mol %, $TsOH•H_2O$ 10 mol. %, -20 °C, 45 hr, 93%, 93:7 er (exo adduct)*		*34* :	*66*

Scheme 1.9 *Chemical structure of Maruoka's binaphthyl modified diamine salt for asymmetric, exo selective Diels-Alder reactions. Heat promoted and organocatalysed Diels-Alder reactions of cyclopentadiene (**23**) with acrolein (**32**).*[58,64]

Exo selective, asymmetric, Lewis acid catalysed DA reactions have also been developed (**Scheme 1.10**),[66-69] and *exo* selective, asymmetric, antibody catalysed DA reactions are known. [70]



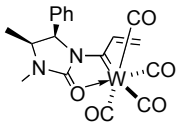
(**45**)



(**23**)	(**37**)	(**46**)	(**47**)
1,3-diene	dienophile	*endo* product	*exo* product
(a) neat, hydroquinone, 50 °C		*19* :	*81*
*(b) CH_2Cl_2, (**45**) 10 mol %, -94 °C, 96%, 98:2 er (exo adduct)*		*1* :	*99*

Scheme 1.10 *Chemical structure of Corey's oxazaborolidine catalyst for asymmetric, exo selective Diels-Alder reactions. Heat promoted and Lewis acid catalysed Diels-Alder reactions of cyclopentadiene (**23**) with methacrolein (**37**).*[58,67]

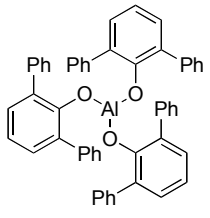
Chiral, α,β-unsaturated *N*-acylamino imidazolidinone Fischer carbene complexes function as dienophiles in *exo* selective, asymmetric DA reactions, as the apical ligands bonded to the metal centre prevent the *endo* approach of the 1,3-diene (**Figure 1.6**).



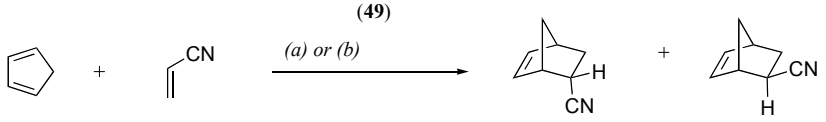
(**48**)

Figure 1.6 *Chemical structure of Wulff's Fischer carbene complex for asymmetric, exo selective Diels-Alder reactions.*[71]

While many exceptions to the Alder *endo* rule are known, and certain reactants and catalysts have been shown to favour *exo* selectivity in DA reactions, these systems appear limited in scope, and a general and robust strategy for obtaining the *exo* adduct in high yield from a given DA reaction has yet to be developed. A unique and ingenious approach to *exo* selective DA reactions has been pursued by Yamamoto and coworkers, who developed ATPH (**49**), a sterically hindered aluminium Lewis acid (**Scheme 1.11**).



(**49**)



(**23**)	(**36**)		(**50**)		(**51**)
1,3-diene	dienophile		*endo* product		*exo* product
(a) conditions and yield not reported			*78*	:	*22*
*(b) CH_2Cl_2, (**49**) 1.1 eq., -78 °C to 0 °C, 72%*			*29*	:	*71*

Scheme 1.11 *Chemical structure of ATPH (**49**) and heat and ATPH promoted Diels-Alder reactions of cyclopentadiene (**23**) with acrylonitrile (**36**).*[72]

Lewis acid catalysis of DA reactions usually results in enhanced *endo* selectivity, but ATPH (**49**) binds dienophiles in a pocket, favouring the *exo* cycloaddition pathway through steric inhibition of the *endo* pathway (**Figure 1.7**). ATPH (**49**) is unique in its ability to alter, and in some cases reverse, the *endo:exo* selectivity of a number of DA reactions.[72]

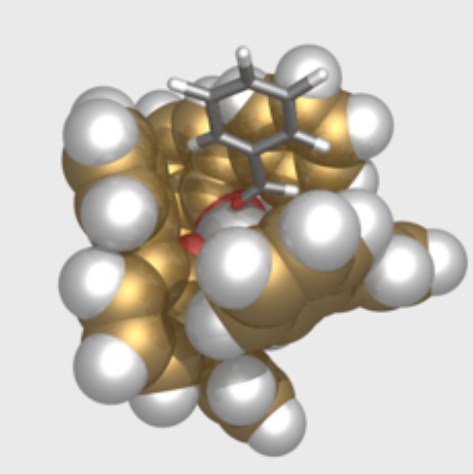


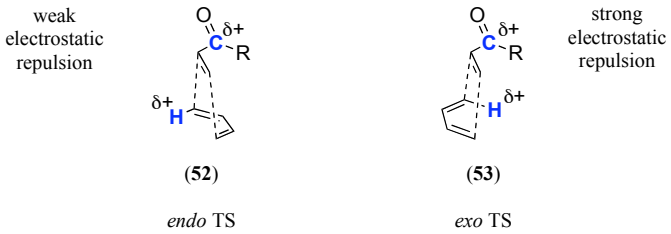
Figure 1.7 *Space filling model of ATPH-benzaldehyde complex showing binding cleft.*

The DA reaction is a powerful tool in organic synthesis, but for its full potential to be realised, the stereochemical outcomes of DA reactions must be controllable. While DA reactivity and regioselectivity are generally well handled by FMO theory, prediction of *endo:exo* selectivity is problematic at times.[21,22,52] In the absence of evidence to the contrary, it is commonly assumed that most DA reactions proceed, or will proceed, with *endo* stereoselectivity, in accord with the Alder *endo* rule.[31] Often this assumption turns out to be correct, however it has not been experimentally verified in a number of fundamental cases.

In addition, a second assumption is commonly made; that *endo* stereoselectivity is a result of SOI. *Endo* stereoselectivity has been ascribed to van der Waals attraction,[73,74] charge transfer interactions,[75] solvent effects,[76,77] steric interactions,[58] and electrostatic interactions,[33,78] but none of these alternative explanations have enjoyed the ongoing popularity of SOI.[2,25,26,34,36,43,45-47,79]

SOI were originally proposed by Woodward and Hoffman in association with their ideas on the conservation of orbital symmetry. The resounding success of the orbital symmetry considerations, in general, lent credence to the SOI hypothesis, although it is yet to receive comprehensive experimental verification. Woodward and Hoffman used five examples to illustrate their ideas about the role of SOI in cycloaddition reactions.[4] In 2000, the five examples chosen by Woodward and Hoffman were reviewed by the Salvatella group, who concluded that the SOI were not necessary in explaining the stereochemical outcomes of the reactions in question.[33] The authors proposed a simple

electrostatic interaction, which appears to account for many of the instances of *endo* selectivity observed in the DA reaction (**Figure 1.8**).



(**52**) (**53**)

endo TS *exo* TS

Figure 1.8 *The Garcia-Mayoral-Salvatella electrostatic interaction between the carbonyl carbon of the dienophile and the proximal inside hydrogen of the 1,3-diene. A strong electrostatic repulsion in the exo transition state (**53**) is thought to disfavour the exo pathway.*

This review stimulated debate and prompted contributions from a number of computational groups. The next year, the Cossio group published the results of a study of the DA reaction of maleic anhydride (**54**) with cyclopentadiene (**23**), and calculated the energy benefit associated with SOI at numerous points along the intrinsic reaction coordinate (IRC) using second order perturbation theory. They concluded that SOIs are responsible for an important part of the experimentally observed stereocontrol.[34] In 2002, Caramella reported that a *bis*-pericyclic transition structure, in which SH SOI played an important part, had been located for the dimerisation of cyclopentadiene (**23**).[44] In the same year, the Fujimoto group published the results of a study of the DA reaction of maleic anhydride (**54**) with 1,3-butadiene (**1**) using an interaction frontier orbital (IFO) method. They found that the *endo* preference for this reaction was the result of a balance of energy terms involving electrostatic attractions and closed shell repulsion, rather than SOI.[78]

In 2005, the Salvatella group published a second article, developing their ideas further, criticising the approach used by the Cossio group,[34] and attributing the *endo* preference in the DA reaction of maleic anhydride (**54**) with cyclopentadiene (**23**) to steric inhibition of the *exo* approach.[35] In 2008, Werstiuk and Sokol published the results of a study of the dimerisation of cyclopentadiene (**23**), citing the work of Caramella. They found it was not necessary to invoke SOI to explain the observed selectivity in this reaction.[80]

Perhaps the strongest evidence for the existence of SOIs has come from the Houk and von Rague Schleyer groups, who used sophisticated computational techniques to probe

the degree of electron delocalisation in transition structures located for a number of DA reactions. The reactions they studied computationally include the dimerisation of 1,3-butadiene (**1**), the dimerisation of cyclopentadiene (**23**), the dimerisation of cyclobutadiene (**55**), the reaction of 1,3-butadiene (**1**) with cyclobutadiene (**55**), and the reactions of cyclopentadiene (**23**), as the diene, with maleic anhydride (**54**), 1,3-butadiene (**1**), cyclobutadiene (**55**), cyclopropene (**56**), cyclobutene (**57**), cyclopentene (**22**), propene (**58**), and aziridine (**59**). The authors addressed a number of the assertions made by the Salvatella group,[33] and supported the case made by the Cossio group regarding the DA reaction of cyclopentadiene (**23**) with maleic anhydride (**54**).[34] In almost every case studied, magnetic susceptibility and nucleus independent chemical shift (NICS) data supporting the SOI hypothesis were provided. Despite its thorough examination of specific cases, this paper is noteworthy for its lack of examples involving familiar DA dienophiles, particularly α,β-unsaturated carbonyl compounds.[45]

1.1.4 Recent computational work

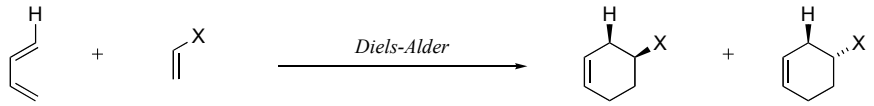
While incremental progress in experimental physical organic chemistry continues to be made, the application of computational methods to contemporary problems has progressed rapidly in recent decades, as computational power has grown and increasingly sophisticated computational techniques have been developed. Computational studies now regularly achieve chemical accuracy and complement experimental investigations, particularly in the study of transient species such as transition states and reactive intermediates.[81] The DA reaction has been the subject of a number of comprehensive theoretical investigations, which have contributed to our modern understanding of the reaction and its variations. The DA dimerisation of 1,3-butadiene (**1**) has been studied computationally[25,26] and the DA reactions of 1,3 butadiene (**1**) with maleic anhydride (**54**),[78] acrylonitrile (**36**) and maleonitrile (**60**),[76] methyl acrylate (**35**),[82] and cyclopropene (**56**)[43,45,83] have also received attention. In addition, the DA reaction of 1,3-butadiene (**1**) with acrolein (**32**) has been studied frequently, both in the presence,[47,50,84-86] and absence,[86-88] of Lewis acid catalysts.

The DA reactions of 1,3-butadiene (**1**) with a large number of simple dienophiles were the subject of a gas phase B3LYP/6-31+G(d) density functional theory (DFT) study carried out by Prof. M. N. Paddon-Row, School of Chemistry, University of New South Wales. This study formed part of an extensive computational investigation of the

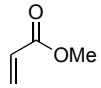
intramolecular Diels-Alder (IMDA) reactions of 1,3,8-nonatrienes conducted by Prof. M. N. Paddon-Row.[89] This was the first time that the DA reactions of 1,3-butadiene (**1**) with many simple dienophiles, including methyl vinyl ketone (**33**), acrylic acid (**34**), and acrylamide (**61**) had been studied computationally.

The computational investigation found that SOI play an important part in determining the *endo:exo* selectivities of the DA reactions of 1,3-butadiene (**1**) with simple dienophiles, and that the strength of the SOI, and hence the degree of *endo* selectivity expected, is related to the difference in energy between the HOMO of the diene and the LUMO of the dienophile, the orbitals which take part in the secondary interaction. Thus, Prof. M. N. Paddon-Row found that the difference in energy between the HOMO of 1,3-butadiene and the LUMO of a simple dienophile is important in determining both the reactivity and the *endo:exo* selectivity of their DA reaction.[89] These considerations provide a simple explanation for the well known empirical correlation of DA reactivity with *endo* selectivity.[33]

A striking feature of the computational data was the absence of a significant *endo* preference with many dienophiles, a result at odds with the Alder *endo* rule, but in accord with the relatively low HOMO energy and reactivity of 1,3-butadiene (**1**), as described above (**Scheme 1.12**).



(**1**) diene + (**16**) dienophile → (**62**) *endo* product + (**63**) *exo* product

Entry	Dienophile	Conformation	Number	*Endo:Exo*^{DFT}	$\Delta\Delta G^{\ddagger}$ ^{DFT} (kJ/mol^{-1})	*Endo:Exo*^{EXP}	$\Delta\Delta G^{\ddagger}$ ^{EXP} (kJ/mol^{-1})
1		(*s-trans*)	(**1**)	19:81	*x* 4.9	56:44	0.8
2		(*s-cis*)	(**32**)	59:41	*n* 1.0	-	-
3		(*s-cis*)	(**33**)	49:51	*x* 0.3	-	-
4		(*s-cis-syn*)	(**34**)	42:58	*x* 1.1	-	-
5		(*s-cis*)	(**35**)	42:58	*x* 1.0	-	-
6			(**36**)	28:72	*x* 3.3	-	-

Scheme 1.12 *Gas phase B3LYP/6-31+G(d) endo:exo ratios for selected Diels-Alder reactions of 1,3-butadiene (**1**) with simple dienophiles (**1**), (**32**) - (**36**), derived from Boltzman populations at 383.15 K,*[89] *and available experimental data.*[40]

Of the intermolecular DA reactions studied by Prof. M. N. Paddon-Row, only one, the dimerisation of 1,3-butadiene (**1**), has been carried out with a deuterium labelled 1,3-butadiene (**1**), allowing its *endo:exo* ratio to be determined. While DFT methods are known to generate acceptable transition structures and relative energies for pericyclic reactions,[81,90-92] the discrepancy of approximately 4 kJmol^{-1} at 383 K between theory (*endo:exo* 19:81) and experiment (*endo:exo* 56:44) for the dimerisation of 1,3-butadiene (**1**) appears significant.[39,40] This difference is due to the fact that the calculations performed by Prof. M. N. Paddon-Row only model cycloadditions involving *s-trans* 1,3-butadiene (**1**) as the dienophile. Using DFT calculations of their own, the Caramella and Houk groups have found that the *s-cis-endo* transition structure for the dimerisation of 1,3-butadiene (**1**) is approximately isoenergetic with the *s-trans-exo* transition structure, a result which brings the calculations into line with

experimental findings.[26] In addition, part of the difference between theory and experiment is likely to be the result of medium effects.[89] The calculations presented in (**Scheme 1.12**) modelled reactions occurring in the gas phase, in order to give a clearer picture of the fundamental processes taking place. This is significant, as the vast majority of DA reactions are carried out in solution. The experimental study of the dimerisation of 1,3-butadiene (**1**) was carried out in *n*-decane solution at 138 °C.[40]

In many simple DA reactions, the *endo* transition state is more polar than the *exo* transition state, and for this reason, the *endo:exo* selectivities of many DA reactions vary with the polarity of the medium, with more polar media favouring the *endo* adducts.[2,93] In a computational study of the DA reactions of 1,3-butadiene (**1**) with acrylonitrile (**36**) and maleonitrile (**60**), the Sauer group observed that the modest *exo* preferences found for reactions modelled in the gas phase reverted to *endo* preferences when the calculations included a self consistent reaction field (SCRF) dielectric continuum model of solvation with CH_2Cl_2. The *endo* transition structures located were consistently more polar than the corresponding *exo* transition structures, and were stabilised relative to the *exo* transition structures by the inclusion of solvation effects. [76]

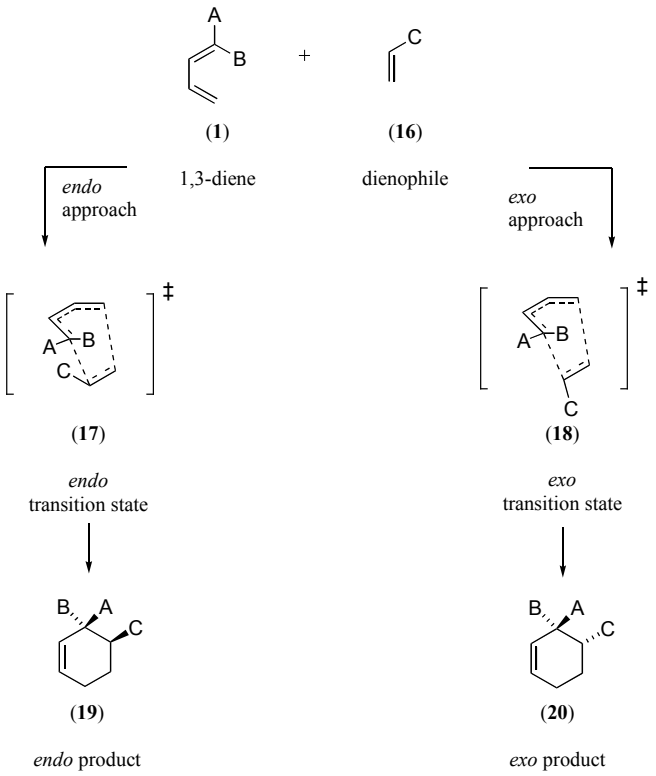
The gas phase computational data[89] are likely to be systematically skewed towards the less polar *exo* transition structures by the omission of solvation effects. Still, the ratio obtained experimentally for the dimerisation of 1,3-butadiene (**1**) is surprising in itself, and a number of questions leap to mind. How significant are the solvation effects? Is *endo* selectivity the norm in the DA reactions of 1,3-butadiene (**1**)? What is the role of SOI, and other effects or interactions in the DA reactions of 1,3-butadiene (**1**)? We stand to learn a great deal from observing the stereochemical outcomes of the DA reactions of a series of simple dienophiles with 1,3-butadiene (**1**), and the knowledge gathered is likely to be fundamental, broadly applicable, and an important experimental reference for future computational investigations.

1.2 Summary of Research Objectives

1.2.1 Diastereoselectivity in the Diels-Alder reaction

DA reactivity and regioselectivity are generally well handled by FMO theory, but the *endo:exo* selectivity of some DA reactions can be difficult to predict, as many exceptions to the Alder *endo* rule are known (**Scheme 1.13**). Further, although many

important contributions have recently been made by computational groups, the origins of *endo:exo* selectivity in intermolecular DA reactions are the subject of ongoing debate.



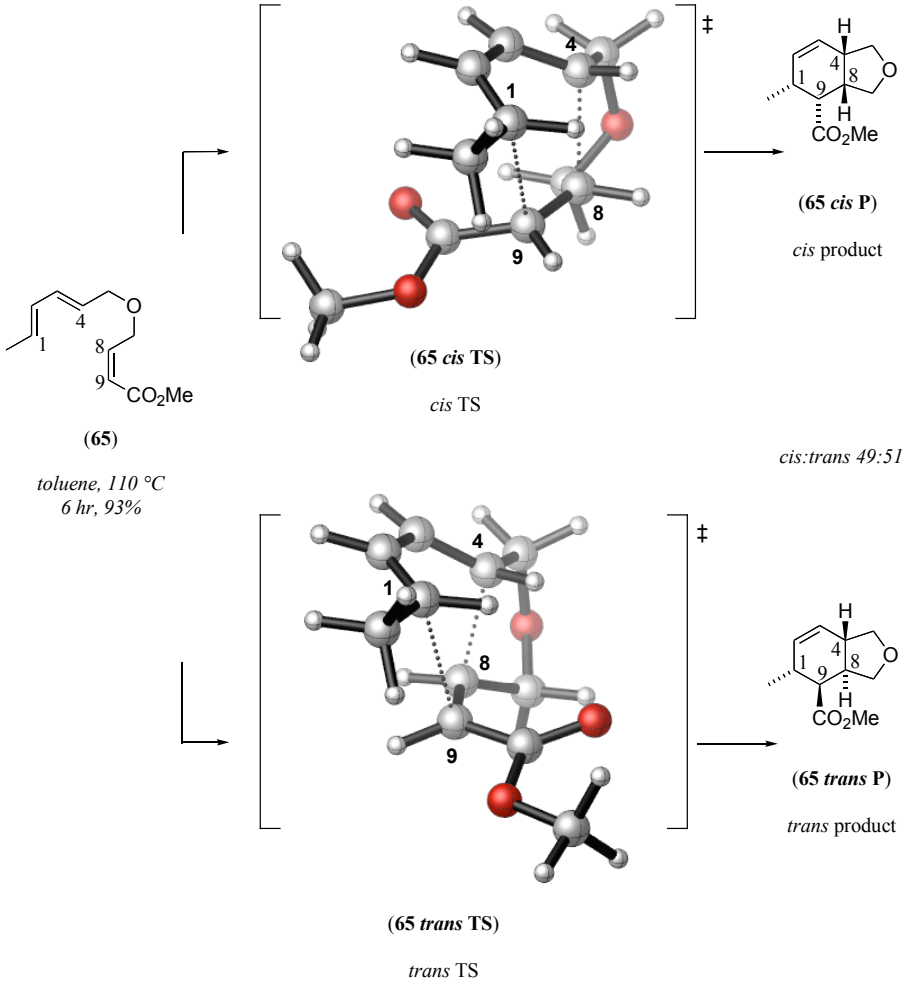
Scheme 1.13 *Endo:exo selectivity in the Diels-Alder reactions of 1,3-butadiene (**1**).*

Many fundamental DA reactions, including the DA reactions of 1,3-butadiene (**1**), have not been the subject of systematic experimental investigation, and the widespread use of Lewis acid catalysts and promoters in DA reactions only serves to obscure the inherent *endo:exo* selectivities of these processes. Chapter two of this thesis describes a detailed study of the DA reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) with simple dienophiles, in which the intrinsic and unbiased stereoselectivities of these fundamental reactions are measured for the first time. In addition, a series of carefully designed experiments are described, proving that the DA reactions of the isotopically labelled 1,3-butadiene (**64**) are kinetically controlled, and allowing the effect of Lewis acid promotion on *endo:exo* selectivity in the DA reaction to be examined for the first time.

1.2.2 The intramolecular Diels-Alder reaction

The DA reaction has been the subject of considerable study and is widely applied in chemical synthesis. The intramolecular Diels-Alder (IMDA) reaction, where both 1,3-

diene and dienophile are within the same molecule, is arguably even more powerful than the intermolecular DA reaction, as it forms two rings and up to four contiguous stereocentres in a single bond-forming event. Its use in synthesis, however, is hindered because simple methods for predicting IMDA reactivity and stereoselectivity have not yet been developed (**Scheme 1.14**).

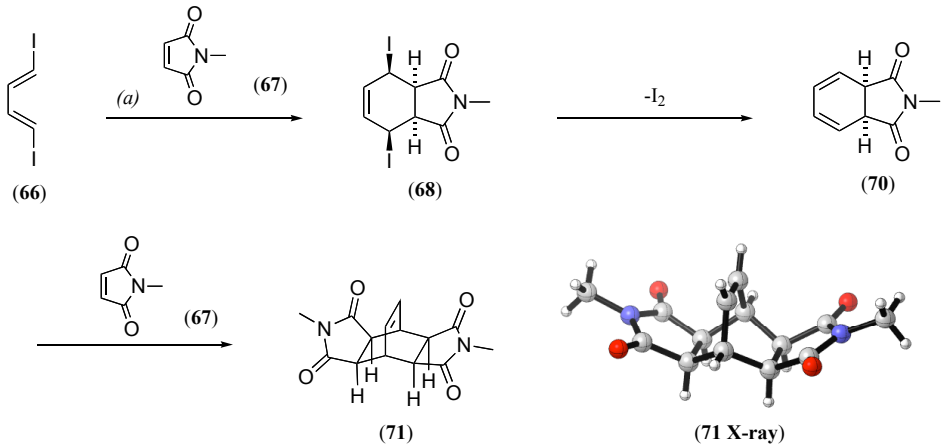


Scheme 1.14 *Intramolecular Diels-Alder reaction of ether tethered triene (**65**).*

Chapter three of this thesis explores important aspects of the IMDA reaction, including the use of Lewis acid promoters to alter or enhance the inherent IMDA selectivities of some ether tethered 1,3,8-nonatrienes. This chapter also describes a detailed study of IMDA reactivity involving three ester tethered 1,3,8-nonatrienes and two ether tethered 1,3,8-nonatrienes, and concludes with an investigation of the use of secondary deuterium kinetic isotope effects (KIEs) to probe the transition state geometries of IMDA reactions of some ester tethered 1,3,8-nonatrienes.

1.2.3 A new domino Diels-Alder reaction

Domino reaction sequences are powerful and efficient methods for constructing complex target molecules. Domino sequences involving DA reactions show particular promise, as the DA reaction is a particularly powerful and general chemical transformation. Chapter four of this thesis describes the discovery and development of a new domino DA process which generates a family of bridged, bicyclic adducts in one high yielding step from (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) (**Scheme 1.15**).

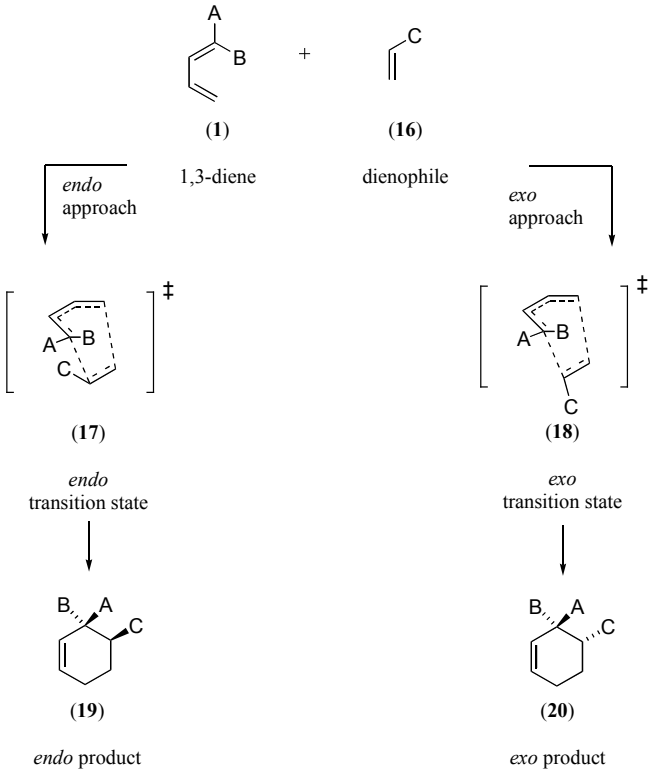


Scheme 1.15 *A new domino Diels-Alder reaction. Conditions (a) (1E,3E)-1,4-diiodo-1,3-butadiene (**66**) with N-methyl maleimide (**67**) (5.0 molar equiv.), CH_2Cl_2, 19 kbar, 85%.*

2 Diastereoselectivity in the Diels-Alder Reaction

2.1 Introduction

Since its discovery in 1928,[1] the DA reaction has been the subject of extensive theoretical[23,24] and mechanistic[2,11] investigation, but many important DA reactions have not been systematically studied, for one reason or another. By carefully investigating a set of fundamental systems, namely the DA reactions of 1,3-butadiene (**1**) with simple dienophiles, it should be possible to understand the origins of diastereoselectivity in this important reaction more completely (**Scheme 2.1**). The primary aim of this work is to measure the intrinsic and unbiased *endo:exo* selectivities of a range of archetypal Diels-Alder reactions. Such a task, however, poses a number of experimental challenges.



Scheme 2.1 *Endo:exo selectivity in the Diels-Alder reactions of 1,3-butadiene (**1**).*

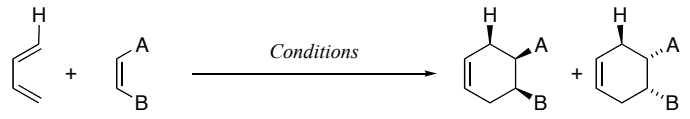
In attempting to measure the *endo:exo* selectivity of a DA reaction of 1,3-butadiene (**1**), one must distinguish between the diastereotopic positions at one or both termini of the 1,3-diene. The use of an appropriately substituted 1,3-butadiene solves this problem, but it introduces a new problem, as the observed selectivity may be influenced by the

nature of the substituent in the 1,3-diene. We reasoned that the substituent least likely to perturb the stereochemical course of the reaction was deuterium, and thus the body of work described in this chapter has been carried out with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**). In this case, the effect of the substituent is a secondary kinetic isotope effect (KIE). In an investigation of secondary KIEs in the DA reaction of isoprene (**74**) with maleic anhydride (**54**), Singleton and Thomas found that the KIEs at the positions corresponding to those bearing the deuterium labels in this study were between 0.95 and 0.97.[94] While the secondary KIEs at these positions in the *endo* and *exo* pathways may not be identical, as would be ideal, they are likely to be small.

Another challenge is to demonstrate that the observed *endo:exo* ratios are indeed kinetic in origin. Two mechanisms through which the observed diastereoselectivity may differ from the kinetic diastereoselectivity can be imagined. If the DA reaction is reversible[14] or the adducts epimerise under the reaction conditions,[53,54] the observed *endo:exo* ratio will approach the thermodynamic distribution with time. By carrying out a series of experiments described later in this chapter, the DA reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**1**) in this study were shown to be under kinetic control.

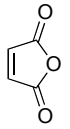
2.1.1 Previous work with labelled 1,3-butadienes

The DA reactions of 1,3-butadiene (**1**) are well known, but only a few have been carried out with a labelled 1,3-butadiene, allowing the *endo:exo* selectivity to be evaluated. Deuterium labelled 1,3-butadienes have been synthesised and used to study the DA dimerisation of 1,3-butadiene (**1**) and the DA reactions of 1,3-butadiene with maleic anhydride (**54**) and cyclopropene (**56**) (**Scheme 2.2**).



(**1**) (**75**) (**76**) (**77**)

1,3-diene dienophile *endo* adduct *exo* adduct

Entry	Dienophile		Time (hr)	*endo:exo*	$\Delta\Delta G^{\ddagger}$ (kJ/mol)
1[a]		**54**	-[b]	85:15	5.1
2[c]		**78**	66	56:44	0.8
3[d]		**56**	-[b]	>99:1	>10.4

Scheme 2.2 *Literature endo:exo selectivities of Diels-Alder reactions of 1,3-butadiene. Conditions: (a) (1Z,3Z)-1,4-dideutero-1,3-butadiene (**78**), maleic anhydride (**54**), benzene, sealed tube, 80 °C;[95] (b) Not reported; (c) Conditions: (1Z,3Z)-1,4-dideutero-1,3-butadiene (**78**), n-decane, sealed tube, 138 °C;[39,40] (d) Conditions: (E)-deutero-1,3-butadiene (**79**) or (Z)-deutero-1,3-butadiene (**80**), cyclopropene (**56**), 0 °C, sealed tube.[96]*

An experimental study of the DA reaction of (1*Z*,3*Z*)-1,4-dideutero-1,3-butadiene (**78**) with maleic anhydride (**54**) was described by Stephenson in 1982. The observed *endo:exo* ratio was 85:15, corresponding to a stabilisation of the *endo* transition state relative to the *exo* transition state of approximately 5.0 kJmol^{-1}. A computational investigation of this system found that the observed *endo* preference was due to a balance of several energy terms involving electrostatic attractions and closed shell repulsions, rather than SOI.[78]

Experimental studies on the DA dimerisation of (1*Z*,3*Z*)-1,4-dideutero-1,3-butadiene (**78**) were described by Stephenson in 1975[39] and Klarner in 1994,[40] and the reaction has since been investigated computationally.[25,26] Both experimental studies found that the reaction exhibited little *endo:exo* selectivity, a result congruent with the computational findings.

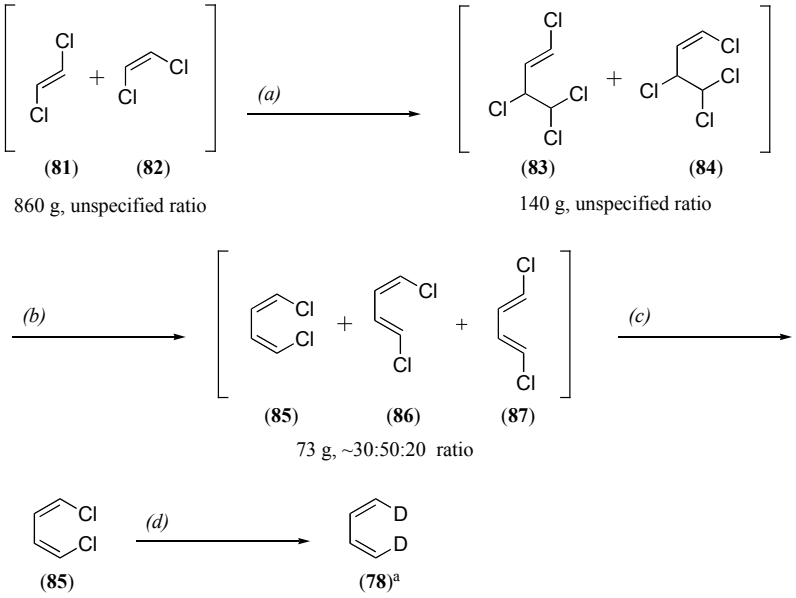
The DA reactions of cyclopropene (**56**) with (*E*)-1-deutero-1,3-butadiene (**79**) and (*Z*)-1-deutero-1,3-butadiene (**80**) were described by John Baldwin in 1989. It was found that both DA reactions gave *endo:exo* ratios >99:1, corresponding to a stabilisation of

the *endo* transition state relative to the *exo* transition state of approximately 10.4 kJmol^{-1}.[96] Computational studies of these systems have ascribed the observed *endo* preference to SOI.[43,45,83]

2.1.2 Literature syntheses of labelled 1,3-butadienes

1,3-Dienes are ubiquitous in both natural products and synthetic compounds, and a wide variety of methods for their synthesis exist. A thorough literature search of this area was carried out and particular attention was given to 1,4-dihalo-1,3-butadienes as putative synthetic precursors to 1,4-dideutero-1,3-butadienes.

(1*Z*,3*Z*)-1,4-Dideutero-1,3-butadiene (**78**) has been used to study the DA dimerisation of 1,3-butadiene (**1**) and the DA reaction of 1,3-butadiene with maleic anhydride (**54**). This 1,3-diene (**78**) was synthesised from a stereoisomeric mixture of 1,2-dichloroethylenes (**81**) and (**82**) by an inefficient route (**Scheme 2.3**).[40,97,98]

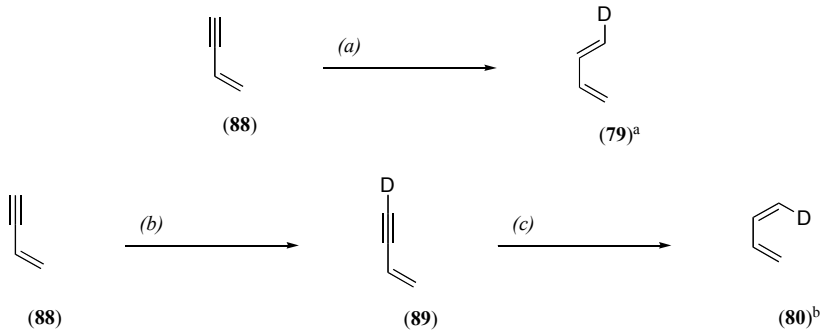


Scheme 2.3 *Literature synthesis of (1Z,3Z)-1,4-dideutero-1,3-butadiene (**78**). Conditions: (a) dibenzoyl peroxide, reflux, 14 d, two vacuum distillations, 28%; (b) MeOH, zinc dust, RT, 24 hr, aqueous workup, vacuum distillation, 82%; (c) preparative GC, yield not reported; (d) Zinc/copper couple, D_2O, 1,4-dioxane, reflux, 4 hr, nitrogen stream, -78 °C trap, 80%; [a] >98% (1Z,3Z), >99% d_2.*

Dibenzoyl peroxide-initiated radical dimerisation gave a mixture of stereoisomeric tetrachlorobutenes (**83**) and (**84**), which was purified by repeated vacuum distillations before being reduced with zinc dust to a mixture of 1,4-dichloro-1,3-butadienes (**85**), (**86**) and (**87**). (1*Z*,3*Z*)-1,4-Dichloro-1,3-butadiene (**85**) was isolated from the mixture

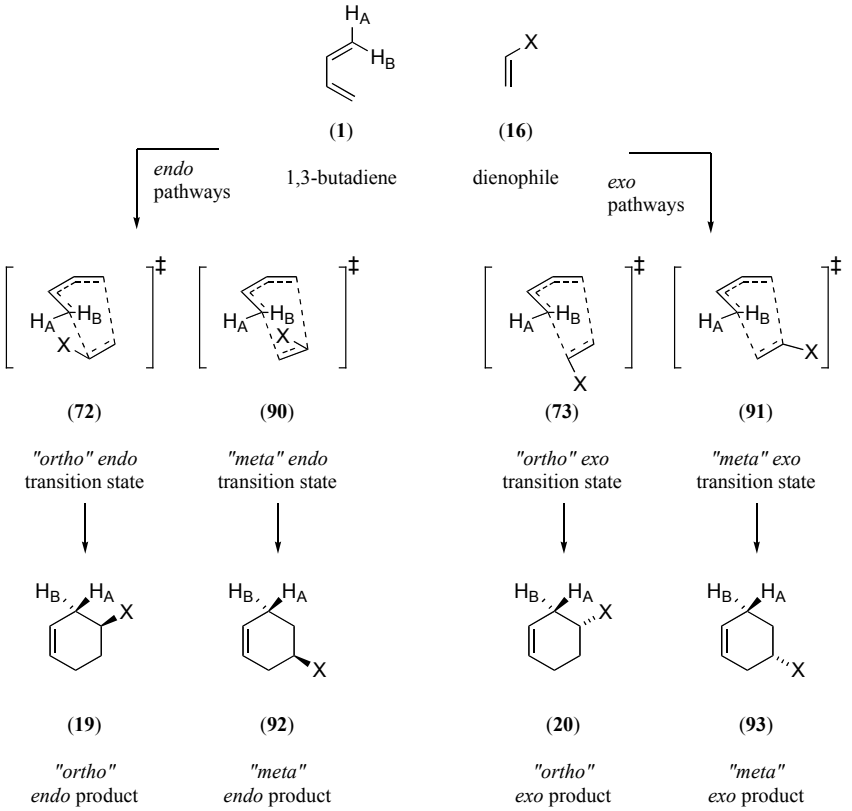
by preparative GC.[97] This compound was reductively dechlorinated to (1*Z*,3*Z*)-1,4-dideutero-1,3-butadiene (**78**) with zinc/copper couple and D_2O in 1,4-dioxane at reflux. The (1*Z*,3*Z*)-1,4-dideutero-1,3-butadiene (**78**) thus produced was entrained in a gentle stream of nitrogen flowing through the headspace of the reaction vessel and isolated in a trap cooled to -78 °C. The first step of this synthesis was carried out on 860 g of the mixture of stereoisomeric 1,2-dichloroethylenes (**81**) and (**82**), and the final step produced one gram batches of the labelled product (**78**), in an overall yield of less than 6%. Significant drawbacks of this synthetic sequence include its length, the production of unwanted 1,4-dichloro-1,3-butadienes (**86**) and (**87**), the use of preparative GC, and its low overall yield.[98]

The unsymmetrical deuterium labelled 1,3-butadienes, (**79**) and (**80**) (**Scheme 2.4**) have been synthesised and used to study the stereoselectivity of the DA reaction of 1,3-butadiene (**1**) with cyclopropene (**56**). (*E*)-1-Deutero-1,3-butadiene (**79**) was synthesised from but-3-en-1-yne (**88**) by the stereospecific *cis* addition of a sterically hindered borane reagent, followed by deutero-deboronylation with acetic acid-d_4. (*Z*)-1-Deutero-1,3-butadiene (**80**) was synthesised from 1-deutero-but-3-en-1-yne (**89**) prepared by deprotonation of unlabelled but-3-en-1-yne (**88**) with *n*-BuLi and quenching with methanol-d_1. In this case, the subsequent stereospecific *cis* addition of a sterically hindered borane reagent, followed by protio-deboronylation with acetic acid gave the (*Z*)-1-deutero-1,3-butadiene (**80**).[96]



Scheme 2.4 *Literature synthesis of (1E)-1-deutero-1,3-butadiene (**79**) and (1Z)-1-deutero-1,3-butadiene (**80**). Conditions: (a) 1. disiamylborane, THF, 0 °C, 15 min. 2. CD_3CO_2D, 0 to 60 °C, 1 hr, yield not reported; (b) 1. n-BuLi, THF, -78 °C, 15 min. 2. CH_3OD, 0 °C to RT, 30 min, yield not reported; (c) 1. disiamylborane, THF, 0 °C, 15 min. 2. CH_3CO_2H, 0 to 60 °C, 1 hr, yield not reported; [a] % d and E:Z ratio not reported; [b] 99% d_1, E:Z ratio not reported.*

The yields of the deuterium labelled 1,3-dienes (**79**) and (**80**) were not reported, but the sequences are short and appear to be suited to the production of useful quantities of these compounds. It is noteworthy that the 1,3-butadienes thus produced bear a single deuterium label, and will give mixtures of isotopomeric adducts in DA reactions with unsymmetrical dienophiles. (**Scheme 2.5**) In principle, the analysis of such mixtures can yield useful data on the stereoselectivities of the DA reactions studied, but any analysis performed would be much simpler if the 1,3-butadiene was symmetrically labelled.

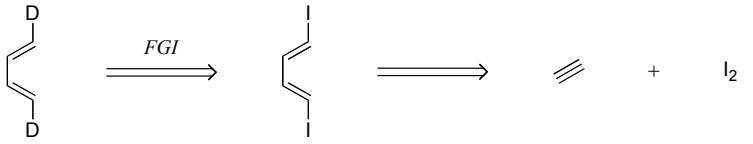


Scheme 2.5 *Illustration of a Diels-Alder reaction of an unsymmetrical labelled 1,3-butadiene with an unsymmetrical dienophile.*

2.1.3 (1E,3E)-1,4-Diiodo-1,3-butadiene

Literature syntheses of deuterium labelled 1,3-butadienes (**78**), (**79**) and (**80**) are either lengthy and inefficient or unsuitable for an in depth study of the DA reactions of 1,3-butadiene (**1**). What was needed was a short and efficient synthesis of a symmetrically-labelled 1,3-butadiene, which could be used to study the DA reactions of simple electron poor monosubstituted alkenes.

In 1997, the Beletskaya group described a stereoselective and regioselective, one step, platinum (IV) catalysed synthesis of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) from acetylene and molecular iodine.[99,100] The product is formed through a catalytic cycle involving twofold iodoplatination of acetylene followed by reductive elimination of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**), and oxidation regenerating the active species, PtI_6^{2-}. (1*E*,3*E*)-1,4-Diiodo-1,3-butadiene (**66**) is an attractive intermediate for the synthesis of a (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**), as a simple twofold reductive removal of the iodide substituents is required to produce the stereochemical probe (**Scheme 2.6**).



(**64**) (**66**) (**94**) (**69**)

Scheme 2.6 *Retrosynthetic analysis of (1E,3E)-dideutero-1,3-butadiene (**64**) using the one step preparation of (1E,3E)-1,4-diiodo-1,3-butadiene (**66**) from acetylene.*

2.1.4 Summary and research objectives

The results of a gas phase DFT investigation by Prof. M. N. Paddon-Row of the DA reactions of 1,3-butadiene (**1**) with simple dienophiles suggested that *exo* selectivity might be observed in some cases.[89] This is a significant finding, as the Alder *endo* rule is assumed by many to reflect an inherent bias for the *endo* reaction channel in the DA reaction.

Debate over the origins of *endo:exo* selectivity in the DA reaction continues and many computational studies have been published, but the *endo:exo* selectivities of only three DA reactions of 1,3-butadiene (**1**), the archetypal 1,3-diene, have been reported. The work presented in this chapter had a series of objectives, the first of which was to synthesise a symmetrical deuterium labelled 1,3-butadiene for use in determining the *endo:exo* selectivities of the reactions of 1,3-butadiene (**1**) with a library of simple dienophiles.

Literature investigations of the DA reactions of 1,3-butadiene have used either (1*Z*,3*Z*)-1,4-dideutero-1,3-butadiene (**78**), accessible through a long and inefficient synthetic route, or (*E*)-1-deutero-1,3-butadiene (**79**) and (*Z*)-1-deutero-1,3-butadiene (**80**), which

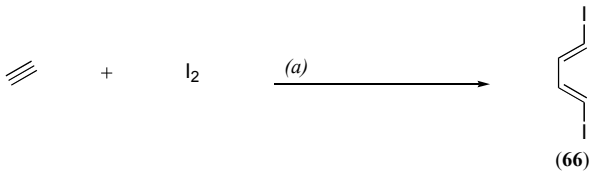
are most suitable for the study of DA reactions with symmetrical dienophiles. The one step, regioselective and stereoselective literature synthesis of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) from acetylene and molecular iodine made this compound an attractive intermediate in a two step synthetic route to (1*E,*3*E*)-1,4-dideutero-1,3-butadiene (**64**).

After making the required stereochemical probe (**64**), the next goal was to measure the *endo:exo* selectivities of the DA reactions of 1,3-butadiene with a library of simple dienophiles. It was also important to demonstrate that the DA reactions were kinetically controlled events, and a set of experiments were performed which proved that this was the case. The experiments described in this chapter were designed to assemble an important empirical data set for comparison with data from computational studies of fundamental DA reactions. They arguably constitute the best experimental test of the SOI hypothesis to date, and the application of modern computational methods to these systems will generate new insights into the origins of *endo:exo* stereoselection in DA reactions.

2.2 Results and Discussion

2.2.1 Synthesis of (1E,3E)-1,4-diiodo-1,3-butadiene

The literature syntheses of deuterium labelled 1,3-butadienes were either lengthy and inefficient, or deemed unsuitable for an in depth study of the DA chemistry of 1,3-butadiene (**1**). The one-step synthesis of (1*E,*3*E*)-1,4-diiodo-1,3-butadiene (**66**) described by the Beletskaya group[99,100] was investigated using potassium hexachloroplatinate (**95**) in place of sodium hexachloroplatinate dihydrate (**96**), the platinum salt stipulated in the original report, as the potassium salt was readily available. The literature method involved saturating a solution of sodium iodide in methanol with acetylene, and then adding the catalyst (**96**) and molecular iodine and stirring at room temperature for six hours. The authors conducted the reaction in batches, obtaining 60 mg of the product with a turn over number (TON) of approximately 4.1. The reaction was reproduced on small scale using the literature conditions and potassium hexachloroplatinate (**95**), but was relatively inefficient, and improvements were sought (**Scheme 2.7**).



(**66**)

Scheme 2.7 *Literature one step platinum catalysed stereoselective synthesis of (1E,3E)-1,4-diiodo-1,3-butadiene (**66**). Conditions: (a) I_2 (1.4 mmol.) Na_2PtCl_6 (3.4 mol. %), NaI (2.85 mol. equiv.), MeOH, RT, 6 hr, 14% (based on I_2), TON = 4.1.*[99,100]

The product (**66**) was found to be light sensitive, and measures taken to exclude light appeared to produce material of higher purity. The literature workup involved precipitation of the product with the addition of water, followed by filtration and washing of the residue with an aqueous solution of sodium iodide to the remove traces of molecular iodine. This workup appeared to be inefficient, exposed to the product to both light and air, and did not seem to remove all of the residual molecular iodine. After some experimentation, it was found that the majority of the product could be precipitated with the addition of water, and the residual molecular iodine could be destroyed by addition of a saturated aqueous solution of sodium metabisulphite. Once all of the molecular iodine had been destroyed, diethyl ether and BHT could be added and a standard aqueous workup incorporating practical measures to exclude light could be carried out. It was important to destroy all of the molecular iodine before the diethyl ether was added, otherwise the product was often contaminated with molecular iodine after purification.

The literature procedure called for a small quantity of a solution of sodium iodide in methanol to be saturated with acetylene. To increase the amount of acetylene available to the catalyst, a slow stream of acetylene was bubbled through the reaction mixture for six hours. This produced a modest increase in the quantity of product (**66**) isolated from the reaction. When the reaction was carried out under an acetylene atmosphere for 24 hours, the crude reaction mixture contained unidentified products and appeared to contain no molecular iodine. The (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) made in this way could not be isolated through the standard aqueous workup previously developed. When the reaction under an acetylene atmosphere was repeated with approximately 16 times the original quantity of molecular iodine, the amount of the product (**66**) isolated increased significantly, and the unidentified contaminants were not formed. It was found that the reaction consumed one molar equivalent of molecular iodine per mole of

the product generated, and that the reactions which ran out of molecular iodine produced only material contaminated with unidentified products.

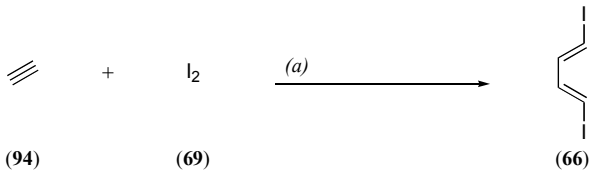
At this point, the reaction was producing useful quantities of reasonably pure (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**), and was scaled up by a factor of five to provide material for investigation of the conversion of (**66**) to (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**). A standard set of reaction conditions were developed, which used methanol (25 mL), sodium iodide (3.0 g), molecular iodine (6.0 g), acetylene (2 to 3 L) and potassium hexachloroplatinate (**95**) (25 mg), and reactions were run with vigorous stirring in darkness at room temperature. The consumption of acetylene was monitored by the reduction in volume of the balloon containing the gas, and it was found that the reaction took approximately four days to go to completion.

The role of sodium iodide was investigated, and it seemed to control the rate of the reaction. Reactions performed using the standard conditions, but omitting sodium iodide did not appear to consume acetylene. Reactions with reduced loadings of sodium iodide consumed acetylene, but they did so comparatively slowly and were not pursued.

The necessary loading of the potassium hexachloroplatinate (**95**) was thoroughly investigated due to the expense of platinum compounds. After much experimentation, it was found that the platinum(IV)-catalysed reaction competes with a background reaction in which molecular iodine adds directly to acetylene, giving small quantities of (*E*)-1,2-diiodoethylene (**98**). This impurity was not removed from the (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) by the standard aqueous workup procedure, and further purification of (**66**) was not investigated due to its instability, particularly towards light.

It was found that the background addition of molecular iodine to acetylene put a lower limit of the quantity of the platinum salt and sodium iodide that could be used. Lower platinum loadings generated batches of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) containing larger amounts of (*E*)-1,2-diiodoethylene (**98**). Eventually it was found that the standard conditions were actually a good compromise, reliably giving four gram batches of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) containing approximately 2% (*E*)-1,2-diiodoethylene (**98**), according to ^{1}H NMR spectroscopy. The yield of these reactions was increased from 14% based on molecular iodine for the literature procedure, to 76% based on molecular iodine under the standard conditions developed in this work. The catalyst loading of 0.25 mol. % under the standard conditions represents a turnover

number (TON) of around 400, which is roughly a 100-fold improvement on that reported by the Beletskaya group (**Scheme 2.8**).[99,100]

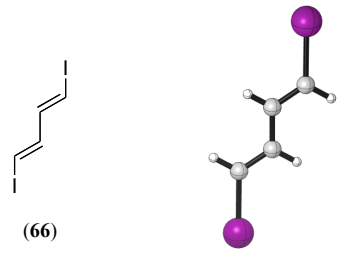


Scheme 2.8 *Optimised platinum catalysed stereoselective synthesis of (1E,3E)-1,4-diiodo-1,3-butadiene (**66**). Conditions: (a) acetylene 2-3 L, I_2 6.0 g, NaI 3.0 g, K_2PtCl_6 (**95**) (0.25 mol. %) 25 mg, MeOH 25 mL, RT, 4 d, 76% (based on I_2).*

(1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) is light sensitive and air sensitive, but samples of good purity containing a small quantity of BHT, a radical inhibitor, can be stored as the solid, in foil wrapped brown glass under nitrogen at -20 °C for two weeks with little or no decomposition. No (1*Z*,3*E*)-1,4-diiodo-1,3-butadiene (**99**) or (1*Z*,3*Z*)-1,4-diiodo-1,3-butadiene (**100**) were detected in the products of this reaction, however, solutions of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) in halogenated solvents seemed to decompose and liberate molecular iodine, which appeared to catalyse the isomerization of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene to compounds thought to be (1*Z*,3*E*)-1,4-diiodo-1,3-butadiene and (1*Z*,3*Z*)-1,4-diiodo-1,3-butadiene. Other experimental conditions investigated include the use of water as solvent and differing ratios of sodium iodide to molecular iodine.

The reaction was also explored with other alkynes, including hex-1-yne (**101**) but it was found that in all substituted cases the simple addition of molecular iodine, giving the corresponding (*E*)-1,2-diiodoalkenes, appeared to be the major reaction pathway.

In the original publication, the Mitchenko group provided an elemental analysis, and ^{1}H NMR, MS and IR spectral data for (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**). A simulated ^{1}H NMR spectrum matching the second order proton signals in the ^{1}H NMR spectrum of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) was also presented.[99] The (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) made by the method described above was characterised, and the data obtained matched those previously reported.[99] In addition, (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) was crystallised from CH_2Cl_2/heptane, and an X-ray crystal structure was obtained, proving the structure of the compound unambiguously (**Figure 2.1**).

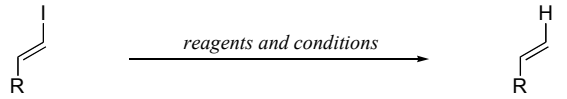


(**66**) (**66 X-ray**)

Figure 2.1 *X-ray crystal structure of 1,4-diiodo-1,3-butadiene (**66**).*

2.2.2 Reduction of (1E,3E)-1,4-diiodo-1,3-butadiene to (1E,3E)-1,4-dideutero-1,3-butadiene

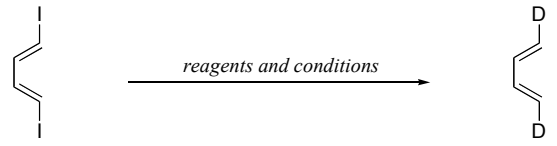
A variety of chemical methods have been developed for the reduction of alkenyl iodides to alkenes (**Scheme 2.9**), and many of these can, in principle, be adapted to allow the selective incorporation of deuterium given the availability of suitable isotopically enriched reagents.



(**102**) (**103**)

Scheme 2.9 *Reduction of alkenyl iodides to alkenes.*

Radical chain reactions, catalytic and stoichiometric organometallic methods, dissolving metal reductions, and hydrogenolyses have all been reported. For the purposes of this work, it was important that the reduction of (1*E,*3*E*)-1,4-diiodo-1,3-butadiene (**66**) to (1*E,*3*E*)-1,4-dideutero-1,3-butadiene (**64**) occurred in a stereocontrolled manner, and that the product, a gas at room temperature (bp -4 °C at 1 atm.), could be obtained as a solution in benzene (**Scheme 2.10**). Reductions which proceed by radical chain mechanisms were considered, but the propensity of 1,3-dienes to polymerise by radical processes and the facile inversion of sp^2 carbon centred radicals, leading to E/Z equilibration, made such methods unappealing.[27]



(66) (64)

Scheme 2.10 *Reduction of (1E,3E)-1,4-diiodo-1,3-butadiene (**66**) to (1E,3E)-1,4-dideutero-1,3-butadiene (**64**).*

Dissolving metal reductions were investigated. A method using zinc/copper couple and deuterium oxide in 1,4-dioxane at reflux, developed by Stephenson and utilised in the synthesis of (1*Z*,3*Z*)-1,4-dideutero-1,3-butadiene (**78**) from (1*Z*,3*Z*)-1,4-dichloro-1,3-butadiene (**85**) was investigated for the reduction of (1*E,*3*E*)-1,4-diiodo-1,3-butadiene (**66**) to (1*E,*3*E*)-1,4-dideutero-1,3-butadiene (**64**). It was found that some of the (1*E,*3*E*)-1,4-diiodo-1,3-butadiene (**66**) subjected to the reaction conditions isomerised to compounds thought to be (1*E,*3*Z*)-1,4-diiodo-1,3-butadiene (**99**) and (1*Z,*3*Z*)-1,4-diiodo-1,3-butadiene (**100**) as the reduction proceeded, and variable mixtures of compounds thought to be isomeric 1,4-dideutero-1,3-butadienes were produced, as identified from the ^{1}H NMR spectra of the reaction mixtures. The Stephenson group observed a similar phenomenon, finding these conditions produced a mixture of isomeric 1,4-dideutero-1,3-butadienes from (1*E,*3*E*)-1,4-dichloro-1,3-butadiene (**85**).[98]

Reductions using the zinc/copper couple, deuterium oxide system developed by Stephenson were attempted at lower temperatures, as it was thought that the diiodide (**66**) would be reduced under milder conditions than the dichloride (**85**). It was found that (1*E,*3*E*)-1,4-diiodo-1,3-butadiene (**66**) appeared to isomerise above room temperature in dioxane solution, and that reduction did not take place below 50 °C. For these reasons, reduction was always accompanied by side reactions. The reduction conditions were modified, and experiments were carried out at room temperature using zinc/copper couple with acetic acid-d_4 as the deuterium source. No reaction took place. Zinc metal in acetic acid has been used to reduce alkenyl iodides to alkenes.[101] Reductions of this type, run at room temperature in acetic acid-d_4 were unsuccessful. No reduction products were observed in the ^{1}H NMR spectra of the reaction mixtures.

Aryl bromides and iodides have been reduced using lithium aluminium hydride in THF, and due to the similarities sometimes seen in the reactivity profiles of alkenyl and aryl halides, these reaction conditions were applied to the reduction of (1*E,*3*E*)-1,4-diiodo-

1,3-butadiene (**66**).[102] 1,3-Butadiene (**1**) was produced, but additional experiments with lithium aluminium hydride-d_4 gave mixtures of isomeric 1,4-dideutero-1,3-butadienes, as judged from the ^{1}H NMR spectra of the reaction mixtures, and these reactions were not investigated further.

Stereoselective palladium-catalysed reductions of deuterium labelled alkenyl iodides have been carried out with palladium tetrakis(triphenylphosphine) and tributyltin hydride.[103] These conditions were applied to the reduction of (1*E,*3*E*)-1,4-diiodo-1,3-butadiene (**66**) using tributyltin hydride, and produced 1,3-butadiene (**1**), but experiments with tributyltin deuteride gave mixtures of isomeric 1,4-dideutero-1,3-butadienes, as was evident by inspection of the ^{1}H NMR spectra of the reaction mixtures. Attention then shifted to the use of sodium formate as the stoichiometric reductant, as this reagent has also been used in palladium catalysed reductions of organic halides.[104] Reactions using sodium formate and catalytic palladium tetrakis(triphenylphosphine) in a 1:1 mixture of acetonitrile and dimethyl sulfoxide at room temperature consumed no (1*E,*3*E*)-1,4-diiodo-1,3-butadiene (**66**), as judged from ^{1}H NMR spectra of the reaction mixtures, and these reactions were not investigated further.

The formation of a Grignard reagent, followed by protonolysis, is a simple way to effect the formal reductive dehalogenation of an alkenyl halide to an alkene. The preparation of a Grignard reagent from (1*E,*3*E*)-1,4-diiodo-1,3-butadiene (**66**) with magnesium turnings in THF was attempted.[105] The reactions were stirred overnight at room temperature, but ^{1}H NMR analysis of the methanol quenched, crude mixtures indicated that the starting material was largely unchanged. The reactions did not initiate in the presence of molecular iodine or 1,2-dibromoethane, and the (1*E,*3*E*)-1,4-diiodo-1,3-butadiene (**66**) isomerised to compounds thought to be (1*E,*3*Z*)-1,4-diiodo-1,3-butadiene (**99**) when attempts were made to initiate the reactions with heat.

Metal-halogen exchange using organolithium reagents and protonolysis of the alkenyllithium intermediate also effects the conversion of alkenyl iodides to alkenes.[106] Metal-halogen exchange reactions were carried out at -78 °C with *n*-butyl lithium and *t*-butyl lithium in THF and the mixtures thus produced were quenched at -78 °C with deuterium oxide or methanol-d_1, and analysed by ^{1}H NMR spectroscopy. These reagents reacted with (1*E,*3*E*)-1,4-diiodo-1,3-butadiene (**66**), giving mixtures of

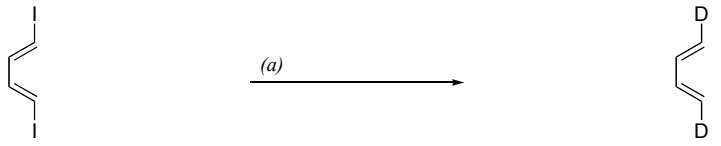
unidentified products and what appeared to be **(**1*E*,3*E*)-1-deutero-4-iodo-1,3-butadiene (**104**) containing variable amounts of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**), as dilute solutions in THF. These procedures appeared to be neither scalable nor reproducible, and interest quickly moved to milder reagents.

Metal-halogen exchange reactions of Grignard reagents with alkenyl halides are known to proceed under milder conditions than the corresponding reactions with organolithium reagents. In addition, the metal-halogen exchange reactions of some Grignard and Grignard-derived reagents have received considerable attention in the last 15 years, and significant advances in reagent reactivity and selectivity have been made.[107]

Metal-halogen exchange reactions were carried out with *i*-propyl magnesium chloride lithium chloride complex (**105**), at -78 °C in THF.[108] Upon quenching with methanol-d_1, **(**1*E*,3*E*)-1-deutero-4-iodo-1,3-butadiene (**104**) was observed by ^{1}H NMR spectroscopy. These reactions proceeded with almost complete retention of stereochemistry, and cleanly gave (1*E*,3*E*)-1-deutero-4-iodo-1,3-butadiene (**104**) at temperatures between -78 °C and 0 °C, in a chemoselective and reliable reaction. The use of stoichiometric or superstoichiometric quantities of *i*-propyl magnesium chloride lithium chloride complex (**105**) resulted in Mg/I exchange and formal reduction of only one of the two alkenyl iodide functional groups in the starting material. A one pot, two step sequence involving one Mg/I exchange, quenching with methanol-d_1, a second Mg/I exchange, and a second quench with methanol-d_1 was developed, but it was overshadowed by success with a related reagent. (*E*)-1-iodo-1,3-butadiene (**106**)[109] made from reaction of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) with 1.1 molar equivalents of *i*-propyl magnesium chloride lithium chloride complex (**105**) at -78 °C, followed by quenching with methanol at -78 °C, was isolated and characterised.

Metal-halogen exchange reactions were carried out with lithium trialkylmagnesate lithium bromide complex (**107**), formed by the addition of two molar equivalents of *n*-butyl lithium in hexanes to a solution of *i*-propyl magnesium bromide in THF at 0 °C, as reported by the Oshima group.[110] Use of as little as 1.0 molar equivalent of this reagent in THF at -78 °C, and subsequent quenching with deuterium oxide or methanol-d_1 at -78 °C, resulted in clean conversion of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) to (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**), which was observed by direct ^{1}H NMR spectroscopy of the crude reaction mixture. It was found that this reagent selectively

exchanged both alkenyl iodide functional groups in the starting material (**66**) and, after quenching of the organometallic intermediate, generated solutions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in THF. The highest deuterium incorporations were obtained when a solution of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) in THF was rapidly added to the organometallic reagent (**107**). This method is reproducible, reliable, fast and convenient, and has been carried out on 18 mmol scale without incident (**Scheme 2.11**).



(66) **(64)**

Scheme 2.11 *Reduction of (1E,3E)-1,4-diiodo-1,3-butadiene to (1E,3E)-1,4-dideutero-1,3-butadiene. Conditions: (a) 1. i-PrMgBr (1.2 molar equiv.), n-BuLi (2.4 molar equiv.), THF, 0 °C, 30 mins, (=**107**); 2. (**66**) in THF, fast addition, -78 °C, 30 mins; 3. CH_3OD (10 molar equiv.) -78 °C to rt, 30 min, 50%.*

The systematic investigation of the diastereoselectivity of the DA reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) required reproducible reaction conditions. It is well known that solvent polarity has a significant effect on the *endo:exo* selectivities of many DA reactions,[93] and benzene was considered the optimum solvent for carrying out the DA reactions. (1*E*,3*E*)-1,4-Dideutero-1,3-butadiene (**64**) could be made in THF solution, but a reproducible method of generating a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene in benzene was sought. It was important that samples of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) contained no THF.

One option was to carry out the metal-halogen exchange reaction in benzene solution, minimising or eliminating the use of THF in the synthesis of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**). To this end, attempts were made to produce a solution of *i*-propyl magnesium bromide in benzene. The Grignard reaction of 2-bromopropane with magnesium turnings in benzene could not be initiated with molecular iodine, 1,2-dibromoethane, or heat, even after extended periods of time. It was found that the reaction did initiate when one molar equivalent of THF was added, and a 1.0 M solution of *i*-propyl magnesium bromide THF complex in benzene (**108**) was prepared.[111,112] An excess of this reagent did not effect metal-halogen exchange at -78 °C to give, after quenching, (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**). Another option was to produce

(1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in a high boiling ether solvent, facilitating the separation of the product and the solvent. The Grignard reaction of 2-bromopropane with magnesium turnings in diglyme initiated spontaneously, but the reagent produced (**109**) also failed to effect metal-halogen exchange to give, after quenching, (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**). Neither *i*-propyl magnesium bromide THF complex in benzene (**108**), nor *i*-propyl magnesium bromide in diglyme (**109**) gave reagents useful for the production of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) when treated with *n*-butyl lithium in hexanes, in a manner analogous to the procedure reported by the Oshima group.[110]

It appears that the preparation of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) by metal-halogen exchange reactions with the Oshima reagent, and quenching with a suitable isotopically enriched acid, in this case methanol-d_1, is only successful in THF. After quenching, the reaction mixture contains (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**), THF, hexanes, 2-iodopropane, propene, butane, 1-iodobutane, but-1-ene, methanol-d_1, methoxide, bromide, and lithium and magnesium cations, and finding a way to purify the intended product, which is a gas at room temperature, took much experimentation. Aqueous workups were unsuccessful. After quenching with methanol-d_1, the crude reaction mixture was diluted with benzene and its water-soluble components were washed out with water. The vast majority of the (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) was lost during this procedure, presumably through evaporation. A number of different types of distillations were also unsuccessful, and most commonly resulted in the complete loss of the intended product.

(1*E*,3*E*)-1,4-Dideutero-1,3-butadiene (**64**) was eventually obtained in benzene or CH_2Cl_2 solution. The successful procedure involved passing a slow stream of nitrogen through the headspace of the flask containing the THF solution of crude (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**), made as described by metal-halogen exchange with the Oshima reagent (**107**) in THF followed by quenching with methanol-d_1. This stream then went up an air condenser, through a column packed with oven-dried silica (160 °C, 24 hours) and through a liquid nitrogen cooled trap containing a known quantity of solvent (benzene or CH_2Cl_2) before venting at a bubbler. The reaction flask was gently heated to reflux, degassing the solution within it. (1*E*,3*E*)-1,4-Dideutero-1,3-butadiene (**64**) passed through the oven dried silica and accumulated in the liquid nitrogen cooled trap, while the THF vapour was trapped by the oven dried silica (**Figure 2.2**) and

(**Figure 2.3**). When the trap was removed from the liquid nitrogen bath, a solution of (**64**) was obtained.

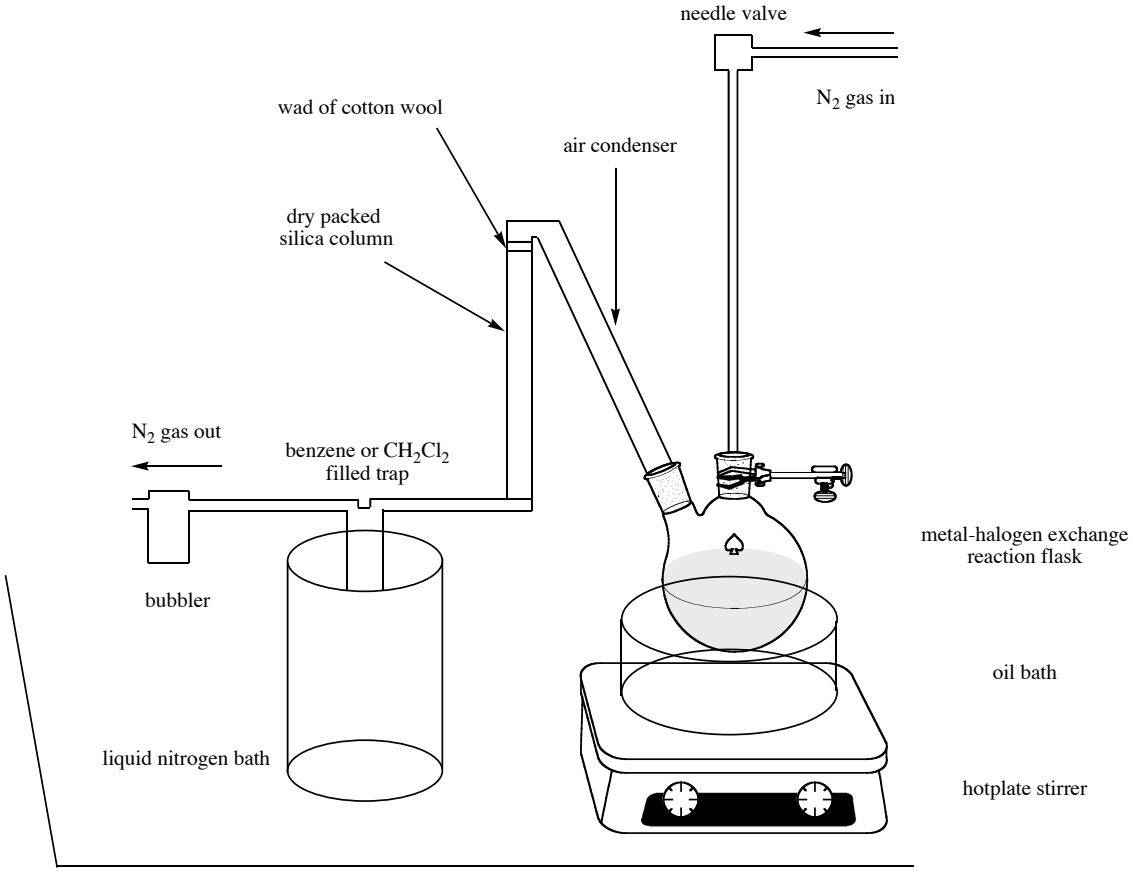


Figure 2.2 *Apparatus for production of solutions of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) in benzene or CH_2Cl_2. All joints were wrapped in parafilm and the reaction flask was protected from light.*

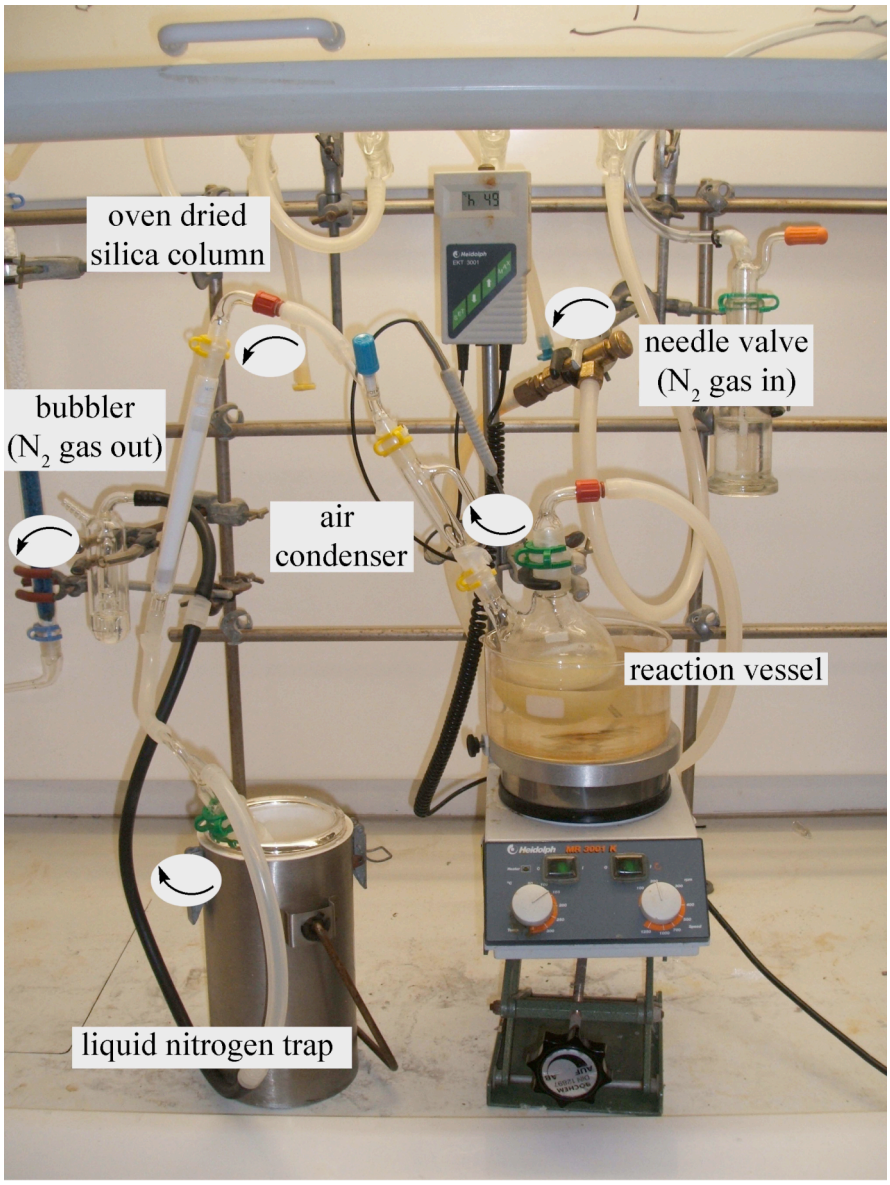


Figure 2.3 *Apparatus for production of solutions of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) in benzene or CH_2Cl_2. All joints were wrapped in parafilm and the reaction flask was protected from light.*

It took practice to carry out this procedure, as the product is a colourless gas, which could only be unequivocally detected by ^{1}H NMR spectroscopy. The solutions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in benzene produced in this way were titrated by quantitative ^{1}H NMR spectroscopy run unlocked in the solvent,[113] using the proton resonance of the solvent as an internal standard. Yields of purified (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in benzene or CH_2Cl_2 solution were as high as 80%, with 50% being typical. At 18 mmol scale, a 50% yield equates to approximately 500 mg of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**). Once the reaction was optimised, the deuterium labelled material produced was a mixture of isotopomers containing

approximately 94% (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) and 6% (*E*)-1-deutero-1,3-butadiene (**110**).

2.2.3 (1E,3E)-1,4-Dideutero-1,3-butadiene

The (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) obtained was characterised by low resolution mass spectrometry, 800 MHz ^{1}H NMR spectroscopy and ^{1}H detected 200 MHz ^{13}C NMR spectroscopy. Low resolution mass spectrometry (70 eV, EI) gave a molecular ion and base peak with a mass to charge ratio of 56.

The 800 MHz ^{1}H NMR spectrum of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in C_6D_6 contains multiplets at δ = 6.30-6.25 ppm ($\mathbf{H_a}$), δ = 5.16-5.10 ppm ($\mathbf{H_b}$) and a weak signal from residual protium at δ = 5.05-5.01 ppm ($\mathbf{H_c}$), the site of deuterium incorporation (**Figure 2.4**). The coupling between ^{1}H resonances is second order.

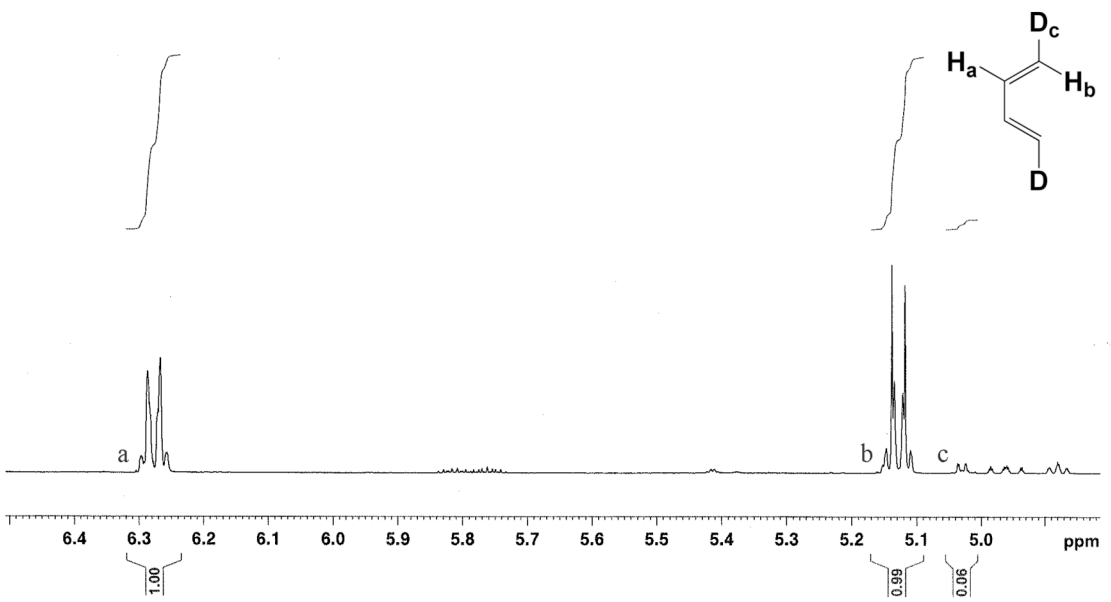


Figure 2.4 *800 MHz ^{1}H NMR spectrum of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) in benzene-d_6.*

The 800/200 MHz HSQC spectrum of (**64**) in C_6D_6 exhibits heteronuclear correlations between $\mathbf{H_a}$ and $\mathbf{C_1}$, and $\mathbf{H_b}$ and $\mathbf{C_2}$ (**Figure 2.5**). The correlation between $\mathbf{H_c}$, the site of deuterium incorporation, and $\mathbf{C_2}$ is not observed due to the small quantity of protium at $\mathbf{H_c}$. The carbon signals are 1:1:1 triplets at δ = 137.2 ppm, *J* (C-D) = 2.0 Hz, ($\mathbf{C_1}$-$\mathbf{H_a}$), and δ = 116.9 ppm, *J* (C-D) = 24.4 Hz, ($\mathbf{C_2}$-$\mathbf{H_b}$). The multiplicities of these signals and limitations on sample concentration made the acquisition of high quality carbon detected spectra unfeasible, even at 800 MHz.

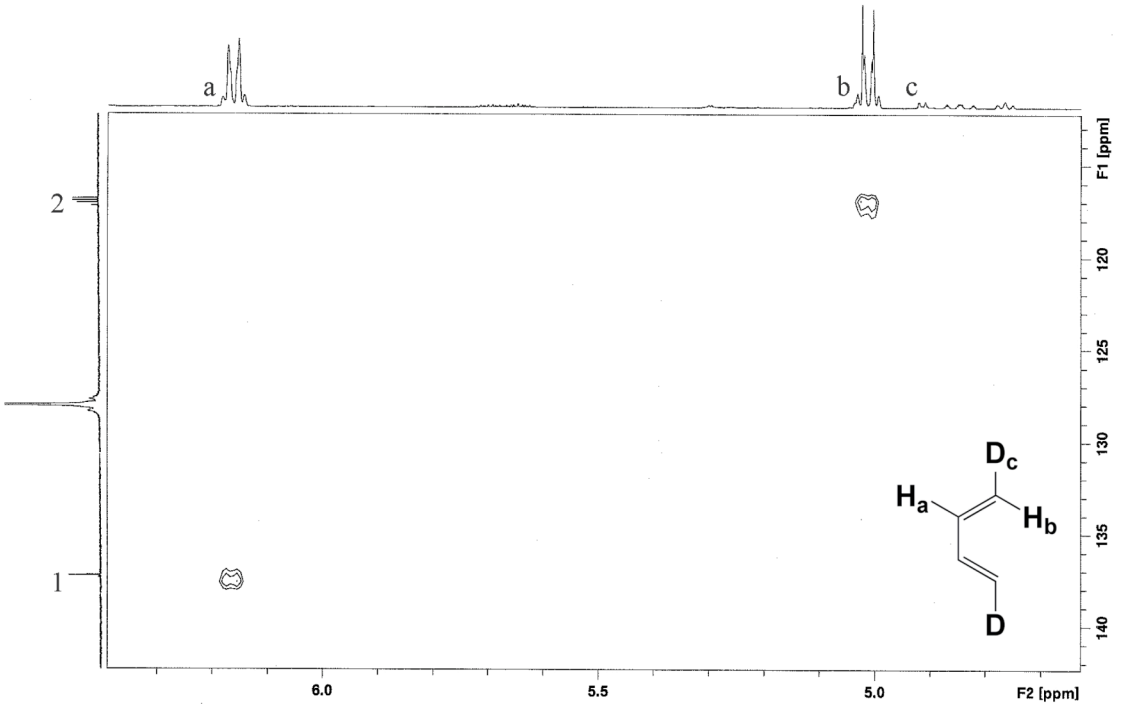
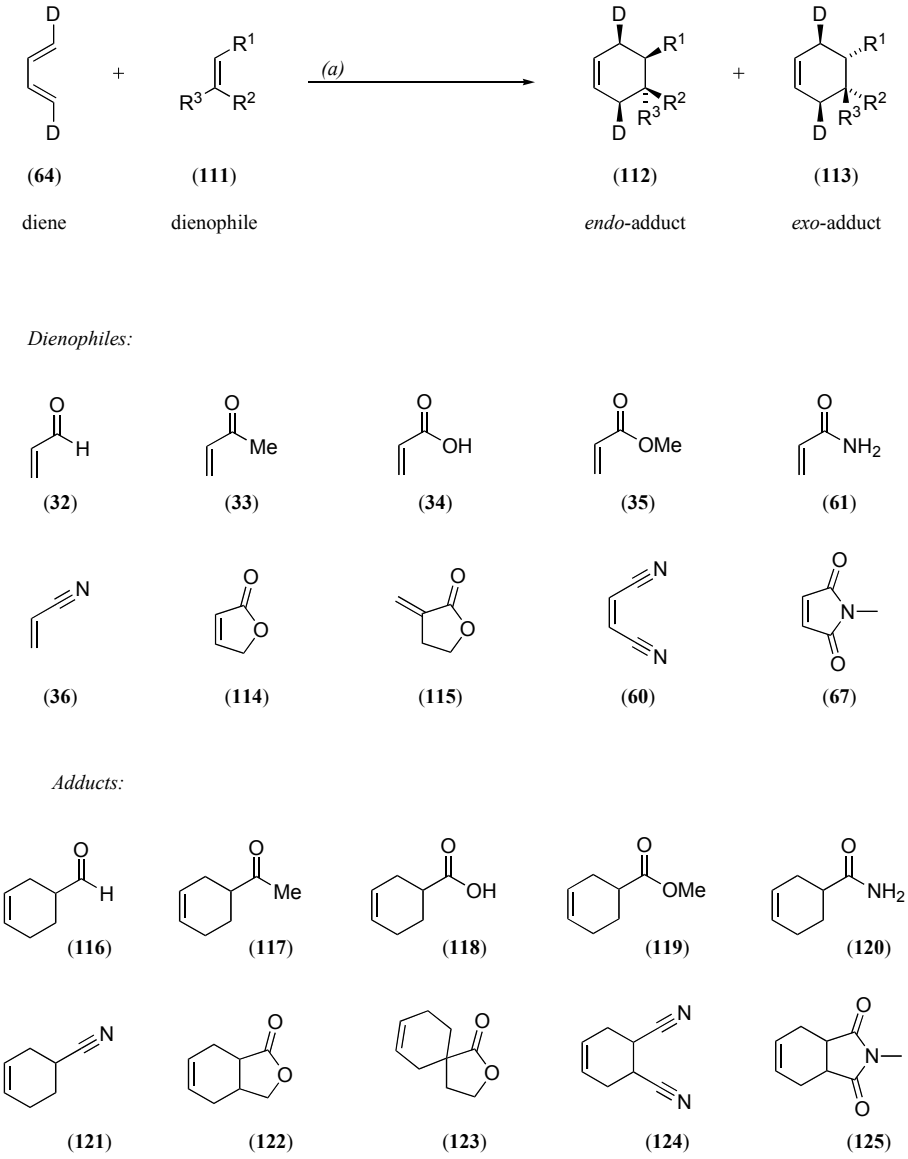


Figure 2.5 *800 MHz/200 MHz HSQC NMR spectrum of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) in benzene-d_6.*

Solutions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) and BHT in benzene or CH_2Cl_2 could be stored in sealed ampoules, or in quickfit test tubes at -20 °C, and were manipulated with cooled syringes to minimise the loss of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) through evaporation. Solutions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in CH_2Cl_2 were required for Lewis acid promoted DA reactions and were particularly difficult to handle, as the solubility of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in CH_2Cl_2 appears to be rather low.

2.2.4 Diels-Alder reactions of 1,3-butadiene and (1E,3E)-1,4-dideutero-1,3-butadiene with library dienophiles

The DA chemistry of 1,3-butadiene (**1**) has been studied in considerable detail, but the *endo:exo* selectivities of the DA reactions of 1,3-butadiene with only three dienophiles have been determined (see **Section 2.1.1**).[39,40,95,96] A varied set of library dienophiles intended to complement the previously reported examples was chosen for study (**Scheme 2.12**).

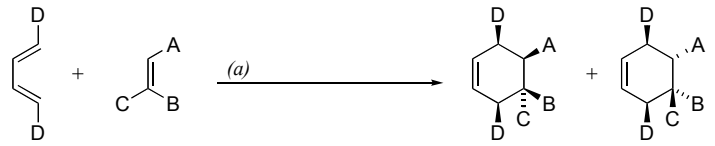


Scheme 2.12 *Conditions and dienophiles chosen for reactions with (1E,3E)-1,4-dideutero-1,3-butadiene (**64**). Conditions: (a) 1.0 M in diene (**64**) and dienophile, benzene, 145 °C, time, hydroquinone, sealed tube.*

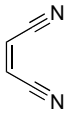
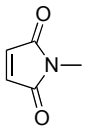
The set includes five monosubstituted dienophiles incorporating a variety of carbonyl-containing activating groups, acrolein (**32**), methyl vinyl ketone (**33**), acrylic acid (**34**), methyl acrylate (**35**), and acrylamide (**61**). It also includes two nitrile-activated dienophiles, acrylonitrile (**36**) and maleonitrile (**60**), and the doubly activated dienophile, N-methyl maleimide (**67**). Completing the set are two lactone dienophiles, dihydro-3-methylenefuran-2(3*H*)-one (**115**), and furan-2(5*H*)-one (**114**), which are locked in the *s-cis* and *s-trans* conformations, respectively.

The DA reactions of the library dienophiles were carried out with unlabelled 1,3-butadiene (**1**) and a library of DA adducts (**116**) to (**125**) were synthesised. All but one, (**123**), of the unlabelled DA adducts, (**116**) to (**125**), were known compounds, but each was characterised with modern spectroscopic methods, as analytical data for many of the compounds had not been reported in the chemical literature. Standard conditions were developed for the DA reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) with the library of dienophiles. These were carefully chosen to facilitate systematic experimental and computational investigation of the reactions, and are as follows: 1.0 M in both 1,3-diene (**64**) and dienophile, benzene solution, hydroquinone radical inhibitor, 145 °C, sealed tube. The dienophiles vary widely in their DA reactivity with 1,3-butadiene (**1**), and the concentration of the reactants was selected to be high enough to ensure the reactions would take place rapidly, but low enough that the solubility limits of the reactants would not be surpassed. The chosen temperature, 145 °C, is just sufficient for the most sluggish dienophiles to react in a reasonable period of time at the specified concentration and temperature. Benzene was chosen as the solvent because it is non polar, and its use minimises solvation effects which are difficult to model computationally. It is also an excellent solvent for a wide range of organic compounds, including 1,3-butadiene.

In an early phase of the experimental work, the reactivities of the library dienophiles were investigated using unlabelled 1,3-butadiene (**1**). 1.0 M solutions of 1,3-butadiene (**1**), durene, an internal standard (IS), and each of the dienophiles in benzene were sealed into six ampoules and placed in a heating bath at 145 °C. The ampoules were removed at regular intervals, and their contents were analysed by quantitative ^{1}H NMR spectroscopy relative to the IS, allowing the calculation of approximate half lives of reaction according to simple second order kinetics (**Scheme 2.13**).



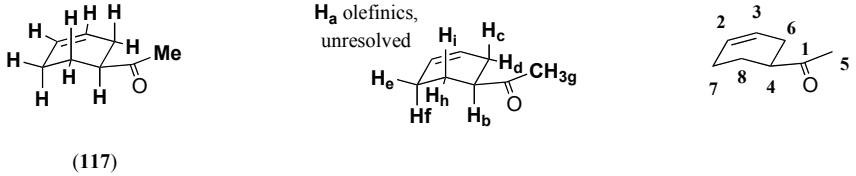
(**64**) diene (**111**) dienophile (**112**) *endo* adduct (**113**) *exo* adduct

dienophile		time (hr)	dienophile		time (hr)
	(**32**)	20		(**36**)	120
	(**33**)	24		(**115**)	20
	(**34**)	40		(**114**)	>168
	(**35**)	90		(**60**)	-[a]
	(**61**)	-[b]		(**67**)	-[c]

Scheme 2.13 *Approximate times to 75% conversion for selected dienophiles. (a) Conditions: 1.0 mmol diene (64), 1.0 mmol dienophile, 2 mol. % hydroquinone, 1.0 M in reactants in benzene solution, sealed tube, 145 °C, time.* [a] *Reaction carried out at 100 °C;* [b] *dienophile oligomerised under the reaction conditions;* [c] *reaction carried out at 25 °C.*

The calculated half lives of reaction obtained in this manner were used in the selection of optimum times for the reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) with the library dienophiles. The times chosen for the reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) with the library dienophiles corresponded, within experimental error, to two half lives of reaction, or 75% conversion of reactants to products. The adducts obtained from the DA reactions of the library dienophiles with commercial, unlabelled 1,3-butadiene (**1**) were analysed by 800 MHz ^{1}H NMR spectroscopy and 200 MHz ^{13}C NMR spectroscopy. The NMR spectra of 1-(cyclohex-3-enyl)ethanone (**117**), the product of the DA reaction of methyl vinyl ketone (**33**) with 1,3-butadiene (**1**), will be discussed in detail to demonstrate how the analytical work was carried out.

A battery of NMR spectra[114] of (**117**), including 1D ^{1}H, 1D ^{13}C, HSQC, COSY, HMBC, 1D nOe, NOESY and T1 spectra were acquired in benzene-d_6:DMSO-d_6 (24:1), a solvent system specially developed to allow all the aliphatic ^{1}H and ^{13}C resonances of the analyte to be resolved and assigned. Many deuterated solvents and solvent systems were screened. This solvent system was arrived at by dissolving the DA adduct (**117**) in 0.5 mL benzene-d_6 and adding DMSO-d_6 in five μL increments until the requisite resolution was obtained. This strategy was remarkably successful in resolving the ^{1}H signals of many DA adducts of 1,3-butadiene (**1**).[115] The ^{1}H NMR signals of (**117**) were first given letters through a simple alphabetical system based on chemical shift, beginning with $\mathbf{H_a}$ for the most downfield resonance, in this case the multiplet corresponding to the unresolved olefinic protons (**Figure 2.6**).



(**117**)

Figure 2.6 *Assignments of proton and carbon resonances of Diels-Alder adduct (**117**) in benzene-d_6-DMSO-d_6 (24:1).*

The aliphatic region of the ^{1}H NMR spectrum of (**117**), from 2.2 ppm to 1.3 ppm, is well resolved at 800 MHz (**Figure 2.7**).

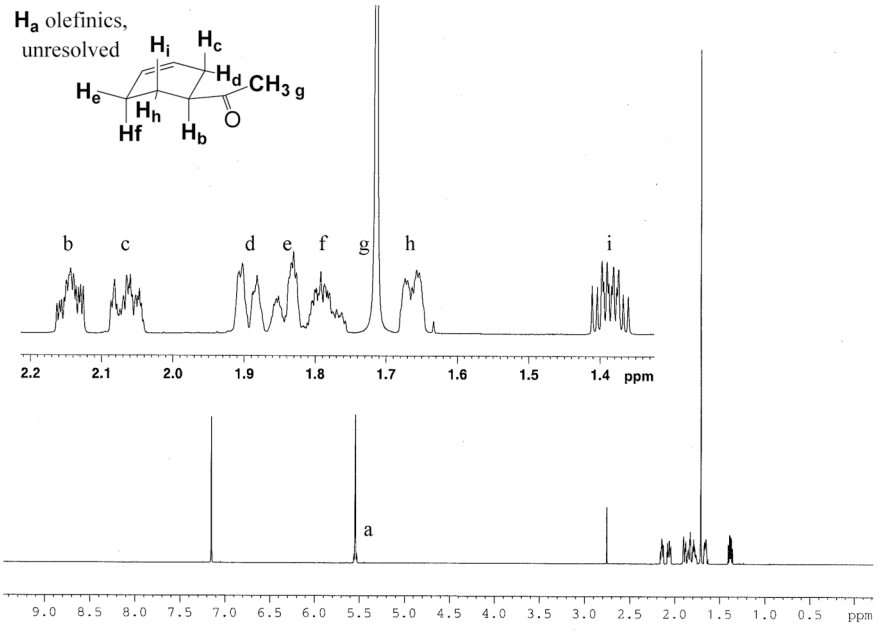


Figure 2. 7 *800 MHz ^{1}H NMR spectrum of Diels-Alder adduct (**117**) in benzene-d_6-DMSO-d_6 (24:1).*

The ^{13}C NMR signals were numbered in a similar fashion through a simple numerical system based on chemical shift, beginning with $\mathbf{C_1}$ for the most downfield resonance, in this case the signal corresponding to the carbonyl carbon. Again, the aliphatic region of the ^{13}C NMR spectrum of (**117**), from 50 ppm to 20 ppm, is well resolved at 200 MHz (**Figure 2.8**).

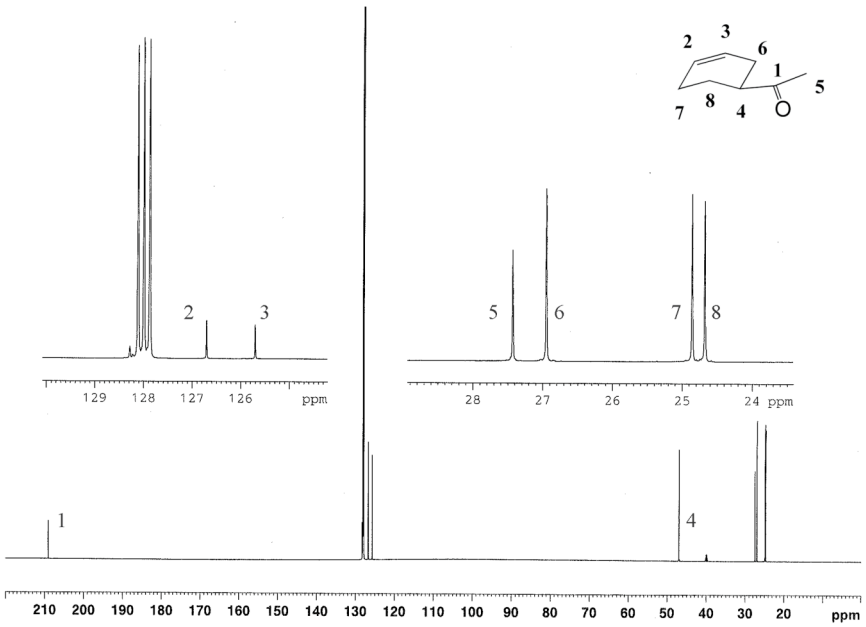


Figure 2.8 *200 MHz ^{13}C NMR spectrum of Diels-Alder adduct (**117**) in benzene-d_6-DMSO-d_6 (24:1).*

The HSQC spectrum clearly identifies the methyl, methylene, and methine signals in the aliphatic region of the ^{1}H dimension, and the methylene signals are paired by chemical shift in the ^{13}C dimension (**Figure 2.9**). Thus, $\mathbf{C_1}$ corresponds to the carbonyl carbon, $\mathbf{C_2}$ and $\mathbf{C_3}$ correspond to the olefinic carbons, $\mathbf{C_4}$ corresponds to the methine carbon, $\mathbf{C_5}$ to the methyl carbon, and carbon signals $\mathbf{C_6}$, $\mathbf{C_7}$ and $\mathbf{C_8}$ correspond to the methylene carbons. The olefinic carbon signals could not be assigned from the HSQC spectrum because the olefinic protons overlapped in the ^{1}H dimension, but these signals were assigned from three bond correlations in the HMBC spectrum. $\mathbf{C_2}$ correlates with $\mathbf{H_h}$ and $\mathbf{H_i}$, and $\mathbf{C_3}$ correlates with $\mathbf{H_b}$ (data not shown), supporting the assignments given in (**Figure 2.8**).

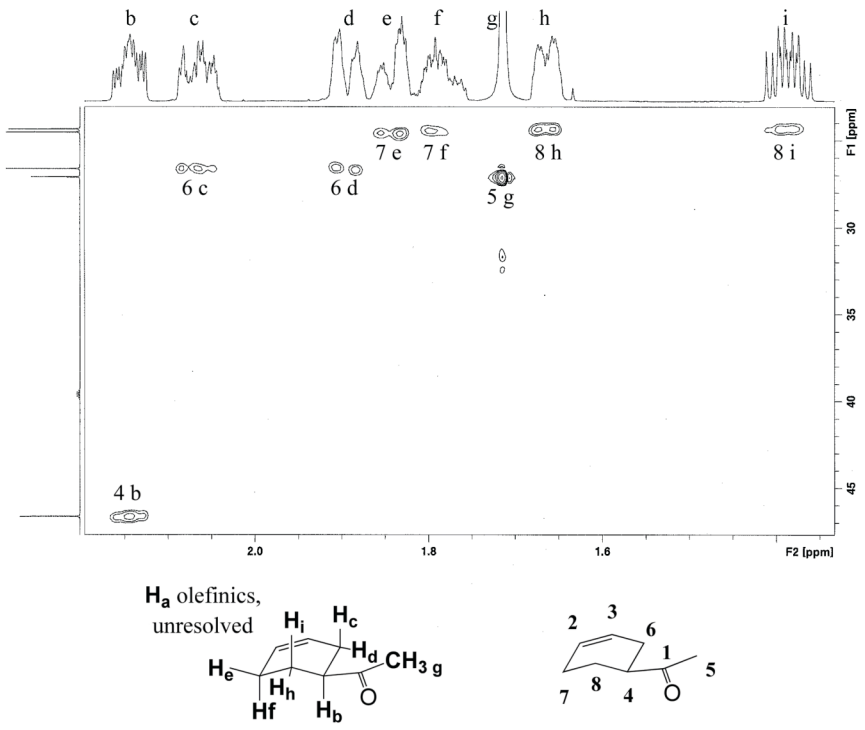


Figure 2.9 *800 MHz/200 MHz HSQC NMR spectrum of Diels-Alder adduct(**117**) in benzene-d_6-DMSO-d_6 (24:1).*

The connectivity of the compound is clear from inspection of the 800 MHz COSY NMR spectrum (**Figure 2.10**). Strong geminal coupling is observed within the methylene groups identified from the HSQC spectrum; $\mathbf{H_c}$ with $\mathbf{H_d}$, $\mathbf{H_e}$ with $\mathbf{H_f}$, and $\mathbf{H_h}$ with $\mathbf{H_i}$. The allylic methylene groups ($\mathbf{C_6}$, $\mathbf{H_c}$, $\mathbf{H_d}$,) and ($\mathbf{C_7}$, $\mathbf{H_e}$, $\mathbf{H_f}$) couple to the unresolved olefinic protons (data not shown). The remaining methylene group ($\mathbf{C_8}$ $\mathbf{H_i}$, $\mathbf{H_h}$) and the methine group ($\mathbf{C_4}$, $\mathbf{H_b}$), couple to one another and their allylic neighbours, completing the carbocycle. The methine proton, $\mathbf{H_b}$, couples particularly strongly to $\mathbf{H_c}$ and $\mathbf{H_i}$ with which it shares pseudo *trans* diaxial relationships in the dominant conformation in solution at 298 K.[115]

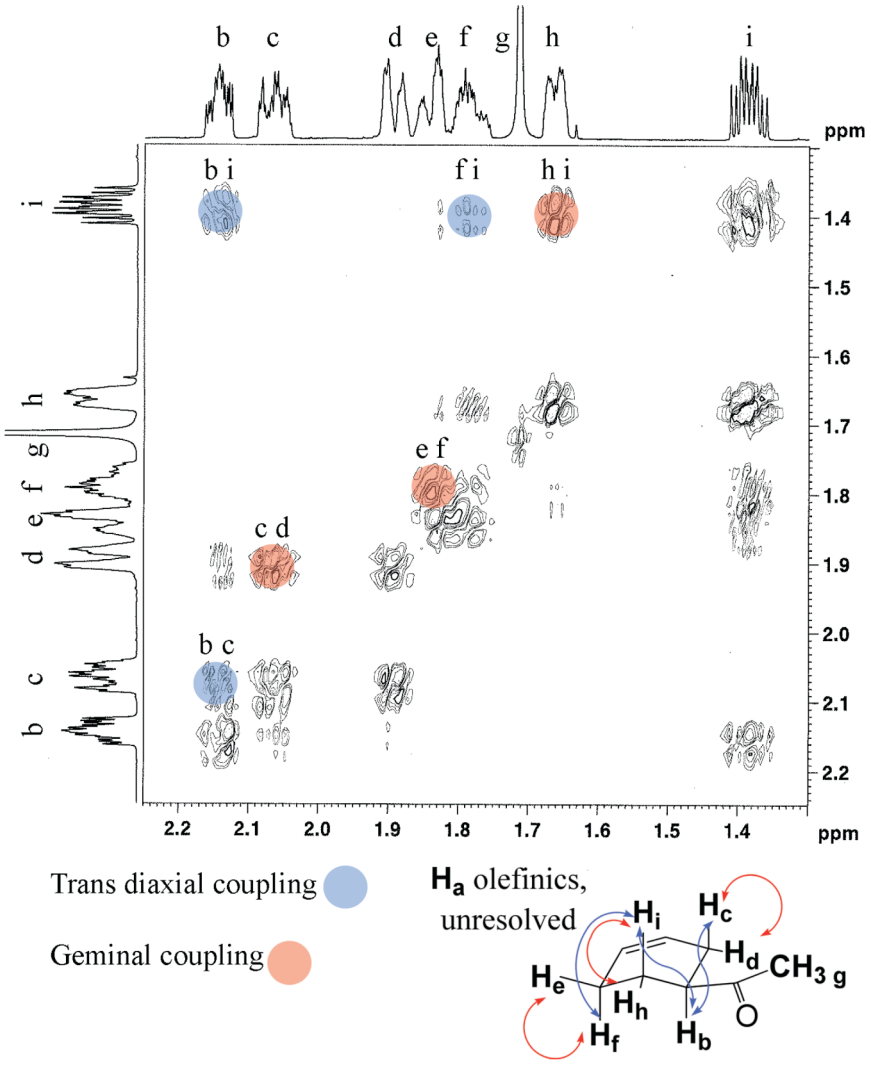


Figure 2.10 *800 MHz COSY NMR spectrum of Diels-Alder adduct (**117**) in benzene-d_6-DMSO-d_6 (24:1).*

One dimensional NOESY experiments showed $\mathbf{H_b}$, $\mathbf{H_d}$, $\mathbf{H_f}$ and $\mathbf{H_h}$ were on one side of the six-membered ring, and $\mathbf{H_c}$, $\mathbf{H_e}$, and $\mathbf{H_i}$ were on the other side, securing the three dimensional configuration of the molecule (data not shown).

The NMR spectra of each of the unlabelled DA adducts, (**116**) to (**125**), were assigned by methods analogous to the one described above.[114] With the NMR spectra of the DA adducts assigned, and a semiquantitative measure of the reactivity of the dienophiles with 1,3-butadiene (**1**) under a set of standard reaction conditions obtained, the reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) with the library of dienophiles were carried out. All reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) were conducted in duplicate.

The reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) with methyl vinyl ketone (**33**) were performed according the standard procedure. They were carried out on 1.0 mmol scale in benzene solution in sealed tubes. Each sealed tube contained 1.0 mL benzene, 1.0 mmol of the 1,3-diene (**64**), 1.0 mmol of the dienophile (**33**), and 0.02 mmol hydroquinone. The sealed tubes were heated to 145 °C for 24 hours. The crude mixtures were concentrated under vacuum and purified by column chromatography, giving the inseparable deuterium labelled *endo* and *exo* DA adducts (**117n**) and (**117x**) in 64% isolated yield. The ratio of the isotopomeric compounds in the fractions obtained through column chromatography was constant, as determined by quantitative 800 MHz ^{1}H NMR in benzene-d_6:DMSO-d_6 (24:1). The entire mixture was analysed by quantitative 800 MHz ^{1}H NMR in benzene-d_6:DMSO-d_6 (24:1), giving integral data suitable for the calculation of the *endo:exo* selectivity of the DA reaction (**Figure 2.11**).

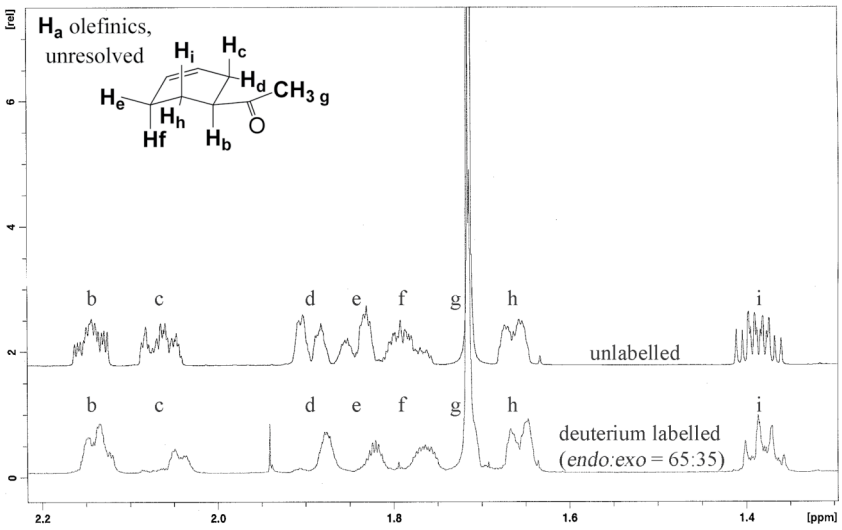
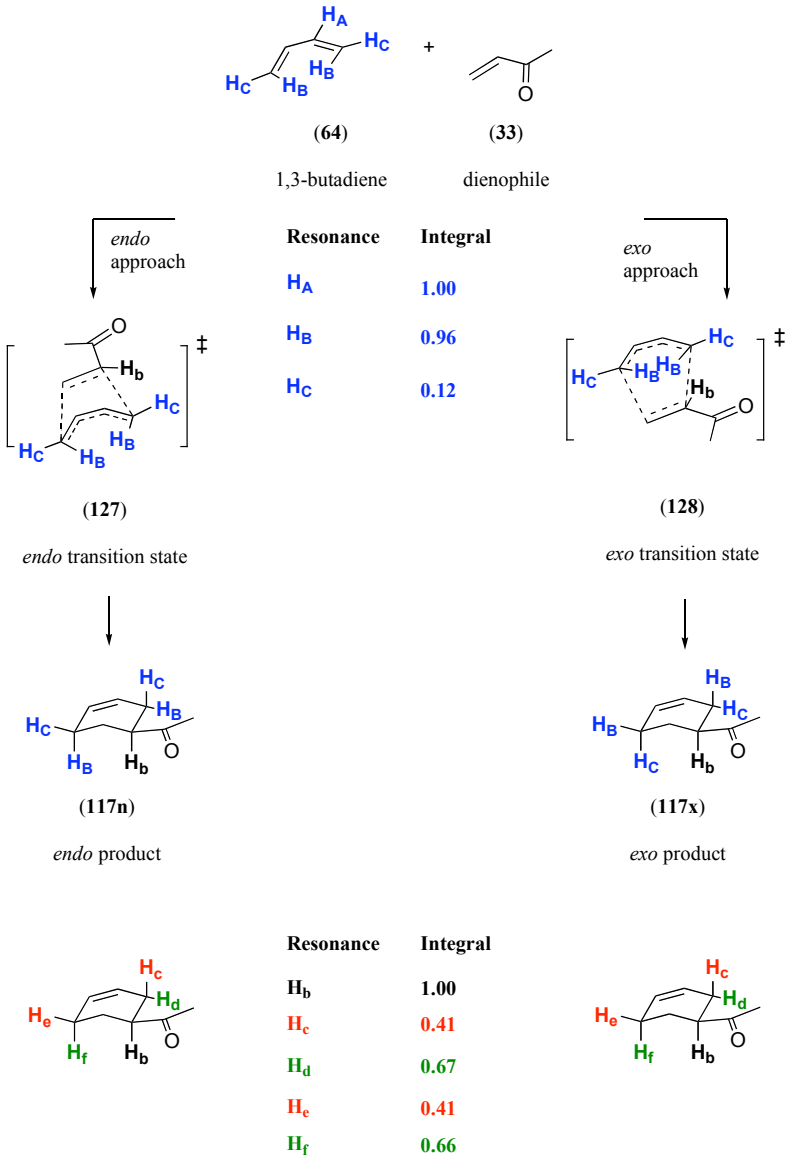


Figure 2.11 *Comparison of aliphatic regions of the NMR spectra of unlabelled and deuterium labelled samples of Diels-Alder adduct (**117**). Top: Unlabelled sample. Bottom: Deuterium labelled sample. Diels-Alder reaction between methyl vinyl ketone (**33**) and (E,E)-1,4-dideutero-1,3-butadiene (**64**) carried out in benzene at 145 °C, (endo:exo = 65:35).*

In order to measure the *endo:exo* selectivity of the DA reactions of 1,3-butadienes, one must distinguish between the diastereotopic positions at one or both termini of the diene. In this work, that objective was achieved by using a deuterium labelled 1,3-butadiene, namely (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**). Small perturbations in ^{1}H chemical shifts relative to the unlabelled DA adducts, and small ^{1}H - ^{2}H couplings were observed in the ^{1}H NMR spectra of the deuterium labelled DA adducts, but these did not hamper the acquisition and interpretation of their 800 MHz ^{1}H NMR spectra.[116] The

distribution of the deuterium in these compounds was inferred from the distribution of protium, which is more easily observed by NMR techniques. T_1 relaxation times were determined for all proton resonances of all deuterium labelled DA adducts handled in this study. To obtain quantitative integral data from NMR spectra, the use of a relaxation delay of five times the longest T_1 is recommended. All observed T_1 relaxation times were shorter than 10 s, and a relaxation delay of 60 s was used during ^{1}H NMR data acquisition. The relative uncertainties in the integrals of the 800 MHz ^{1}H NMR spectra obtained were between 0.5 and 1%. In the DA reaction of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) with methyl vinyl ketone (**33**), the stereochemical course of the reaction determines the dispositions of the deuterium labels relative to the methyl ketone substituent in the adducts (**117n**) and (**117x**). In the *endo* adduct, (**117n**) the deuterium labels occupy positions on the same side of the newly formed carbocycle as the methyl ketone substituent, positions $\mathbf{H_c}$ and $\mathbf{H_e}$. In the *exo* adduct, (**117x**) the deuterium labels occupy positions on the opposite side of the ring to the methyl ketone substituent, positions $\mathbf{H_d}$ and $\mathbf{H_f}$ (**Scheme 2.14**). In principle, the *endo:exo* selectivity of the DA reaction of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) with methyl vinyl ketone (**33**) can be calculated from the integrals of the hydrogen positions in a single deuterium enriched allylic methylene unit. In this study, every effort was made to obtain and use redundant integral data, to ensure the accuracy of the calculated *endo:exo* ratios. The experimental *endo:exo* ratio can be calculated from the observed distribution of deuterium in the adducts, and the observed distribution of deuterium in the labelled 1,3-butadiene (**64**). It is convenient to normalise the ^{1}H integrals of deuterium enriched sites by comparison with the ^{1}H integrals of sites within the same molecule containing deuterium at natural abundance (*ca.* 0.015%). This gives the ^{1}H content of ^{2}H enriched sites as a simple fraction of the natural content.



Scheme 2.14 *Normalised integral data for calculation of endo:exo selectivity of Diels-Alder reaction of methyl vinyl ketone (**33**) with (1E,3E)-1,4-dideutero-1,3-butadiene (**64**).*

It is also convenient to express the *endo:exo* ratio in a form which sums to unity, thus:

$$(n : x) = (endo : exo)$$
$$n + x = 1$$

Equations expressing the observed values of the integrals at the deuterium enriched sites of the DA adducts (**117n**) and (**117x**) in terms of the *endo:exo* ratio and the integrals of the deuterium enriched sites of the (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) were constructed:

$$H_{c,e} = xH_B + nH_C$$

and

$$H_{d,f} = xH_C + nH_B$$

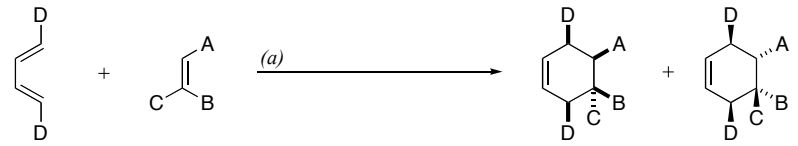
Solving the first of these for *n* gives:

$$n = (H_{d,f} - H_C)/(H_B - H_C)$$

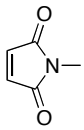
Substituting integral data gives the calculated *endo:exo* selectivity of the reaction:

$$n = (H_{d,f} - H_C)/(H_B - H_C)$$
$$n = (0.67 - 0.12)/(0.96 - 0.12)$$
$$n = 0.65$$
$$x = (1 - n) = 0.35$$

Corresponding reactions and calculations were carried out with each of the library dienophiles. The reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) with each of the library dienophiles were carried out in duplicate and additional calculations were performed using redundant integral data where available. No chromatographic separation of isotopomers was observed. The calculated *endo:exo* ratios differed by less than 2% in all cases, indicating that the chemistry and the analytical method were reasonably robust (**Scheme 2.15**).



(**64**) 1,3-diene (**111**) dienophile (**112**) *endo* adduct (**113**) *exo* adduct

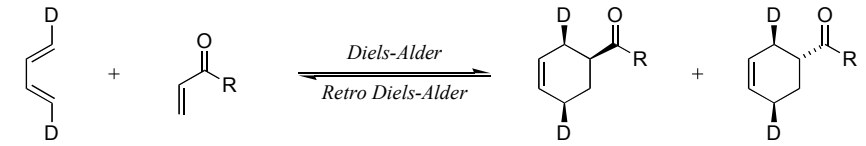
Entry	Dienophile	Adducts	Time (hr)	Yield (%)[a]	*endo:exo*[EXPb]	$\Delta\Delta G^{\ddagger}$ [EXPc]	*endo:exo*[DFTd]
1	 (**32**)	(**116n**), (**116x**)	20	37	64:36	*n* 2.00	59:41
2	 (**33**)	(**117n**), (**117x**)	24	64	65:35	*n* 2.15	49:51
3[e]	 (**34**)	(**118n**), (**118x**)	40	90	60:40	*n* 1.41	42:58
4	 (**35**)	(**119n**), (**119x**)	90	83	50:50	0.00	43:57
5[e,f]	 (**61**)	(**120n**), (**120x**)	120	9	46:54	*x* 0.56	-
6	 (**36**)	(**121n**), (**121x**)	120	76	38:62	*x* 1.70	28:72
7	 (**114**)	(**122n**), (**122x**)	120	27	73:27	*n* 3.47	-
8	 (**115**)	(**123n**), (**123x**)	20	87	39:61	*x* 1.55	-
9[g]	 (**60**)	(**124n**), (**124x**)	24	75	70:30	*n* 2.94	-
10[h]	 (**67**)	(**125n**), (**125x**)	24	92	99:1	*n* 16.0	-

Scheme 2.15 *Diels-Alder reactions of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**); (a): Typical reaction conditions 1.0 M in 1,3-diene (**64**) and dienophile, 2 mol % hydroquinone, benzene, sealed tube, 145 °C. [a]Isolated yields of purified products; [b]experimental endo:exo ratios are the average of two runs; difference between runs <2%; [c]the letters n and x designate the favoured reaction pathway, energies calculated from Boltzmann distributions at 145 °C; [d]transition structure energies derived from B3LYP 6-31+(G)d calculations;[89] ratios calculated from 2, 4, or 8-fold Boltzmann populations at 145 °C; [e]1.05 mol. equiv. 1,3-diene (**64**) used; [f]low yield due to polymerisation of dienophile; [g]Reaction conducted at 100 °C; [h]Reaction conducted at 25 °C.*

In the absence of data on the *endo:exo* selectivity of a range of the reactions of 1,3-butadiene (**1**), many chemists have assumed they proceed through *endo* transition states, in accord with the Alder *endo* rule.[22,31] As can be seen from the experimental data, however, the relative energies of the *endo* and *exo* pathways of many of the DA reactions of 1,3-butadiene (**1**) are finely balanced. The experimentally determined *endo:exo* ratio for the DA reaction of methyl vinyl ketone (**33**) with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**), 65:35, reflects an energy difference between the *endo* and *exo* pathways of only 2.2 kJmol^{-1}. Before examining the diastereoselectivity data in more detail, it is important to establish that the ratios obtained are indeed kinetic in origin.

2.2.5 Mechanistic considerations

If the DA reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) with the library dienophiles are reversible (**Scheme 2.16**), or if the adducts epimerise under the reaction conditions (**Scheme 2.17**), or both, the *endo:exo* ratios observed experimentally will approach the thermodynamic ratios over time.[53,54]

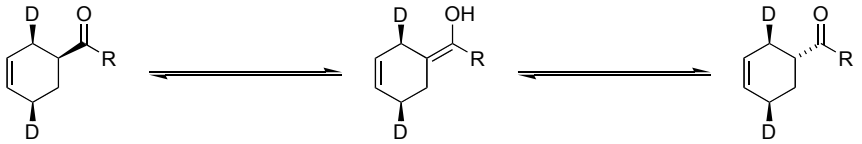


(**64**) (**129**) (**130**) (**131**)

1,3-diene dienophile *endo* adduct *exo* adduct

Scheme 2.16 *Equilibration of Diels-Alder adducts (**130**) and (**131**) through Diels-Alder/retro Diels-Alder sequence.*

A number of methods for confirming that the observed ratios are kinetically determined can be devised, and each has its benefits and limitations. In principle, separating the enantiomers of an unlabelled DA adduct by chiral HPLC, conducting an enantioselective DA reaction, and other methods, can give access to enantiomerically enriched samples of DA adducts.



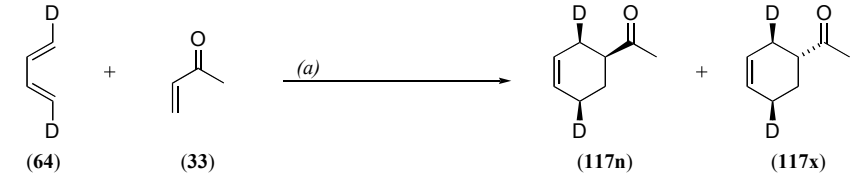
Scheme 2.17 *Epimerisation of Diels-Alder adducts (**130**) and (**131**) through keto-enol tautomerism.*

After subjecting an enantiomerically enriched sample of a representative DA adduct to the conditions used in the DA reaction of the corresponding dienophile with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**), one can recover the sample, determine its enantiomer ratio, confirm that no epimerisation has taken place, and infer that the observed *endo:exo* ratio is kinetic in origin. One of the benefits of this method is that it does not require deuterium labelled materials. Chiral HPLC separations of the enantiomers of the unlabelled DA adducts, (**116**), (**117**), (**119**) and (**121**); asymmetric, organocatalysed DA reactions of acrolein (**32**) with unlabelled 1,3-butadiene (**1**);[117] and pig liver esterase mediated enantioselective hydrolyses of unlabelled methyl cyclohex-3-enecarboxylate (**119**)[118] were all carried out. Due to success with an alternative method, these approaches were pursued no further.

Another method for establishing that the DA reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) are under kinetic control involves carrying out a Lewis acid promoted DA reaction with a representative dienophile, in this case methyl vinyl ketone (**33**), giving the DA adducts (**117n**) and (**117x**) in a ratio different to that obtained through a heat promoted DA reaction. This method has the drawback of requiring the use of deuterium labelled material, but it has advantages in that the outcomes of the experiments involved are determined by simple ^{1}H NMR analysis. It also permits the examination of the inherent diastereoselectivity of a Lewis acid promoted DA reaction of methyl vinyl ketone (**33**) with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**).

In practice, a simple way to obtain mixtures of the DA adducts, (**117n**) and (**117x**), with different *endo:exo* ratios is to carry out heat promoted (*endo:exo* = 65:35) and Lewis acid promoted (*endo:exo* > 95:5) DA reactions. Once samples of the DA adducts with differing *endo:exo* ratios have been prepared, additional experiments which involve exposing both samples to each of the two different sets of reaction conditions can be carried out. When the samples from both the Lewis acid promoted and heat promoted

DA reactions, (*endo:exo* = 65:35) and (*endo:exo* > 95:5), respectively, are recovered unchanged after exposure to both sets of reaction conditions, we can infer that the ratios of cycloadducts obtained from both sets of reaction conditions are kinetic in origin. This method was pursued in parallel with the alternatives described above and quickly bore fruit. The methyl aluminium dichloride (**133**) promoted DA reaction of methyl vinyl ketone (**33**) with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) was carried out in a mixture of CH_2Cl_2 and hexanes (**Scheme 2.18**).



Scheme 2.18 *$MeAlCl_2$ (**133**) promoted Diels-Alder reaction of methyl vinyl ketone (**33**) with (1E,3E)-1,4-dideutero-1,3-butadiene (**64**). Conditions: (a) (**33**) 1.0 molar equiv., CH_2Cl_2, (**133**) in hexanes, 0.9 molar equiv., CH_2Cl_2, -78 °C, 30 min, then (**64**) 1.0 molar equiv., CH_2Cl_2, -78 °C to RT, 20 hr, 83%, endo:exo > 95:5.*

The dienophile (**33**) was treated with 0.9 molar equivalents of the Lewis acid (**133**) in hexanes at -78 °C, and a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in CH_2Cl_2 was added to the dienophile-Lewis acid complex at this temperature. This gave a 0.25 M solution of the 1,3-diene (**64**), with 1.0 molar equivalent of methyl vinyl ketone (**33**), and 0.9 molar equiv. $MeAlCl_2$ (**133**) in 3:1 CH_2Cl_2:hexanes. The reaction mixture was then allowed to warm to room temperature and was stirred at this temperature for 20 hours. After an aqueous workup and purification by column chromatography, the DA adducts (**117n**) and (**117x**) were obtained in 83% isolated yield, with an *endo:exo* ratio > 95:5 (**Figure 2.12**).

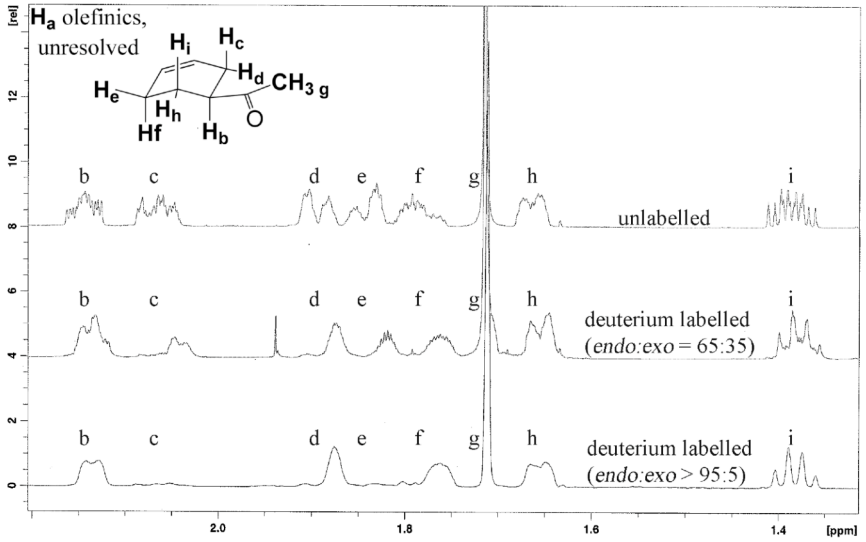


Figure 2.12 *Comparison of aliphatic regions of the NMR spectra of unlabelled and deuterium labelled samples of (**117**). Top: Unlabelled sample. Middle: Deuterium labelled sample; Diels-Alder reaction between methyl vinyl ketone (**33**) and (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) carried out in benzene at 145 °C, (endo:exo = 65:35). Bottom: Deuterium labelled sample; $MeAlCl_2$ (**133**) promoted Diels-Alder reaction between methyl vinyl ketone (**33**) and (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) carried out in CH_2Cl_2 and hexanes (3:1), from -78 °C to RT, endo:exo > 95:5.*

This material (*endo:exo* > 95:5) was then subjected to the standard thermal DA reaction conditions for 30 hours; 1.0 M in DA adduct (**117**) in benzene solution, 145 °C, with 2 mol. % hydroquinone as a radical inhibitor, in a sealed tube. The mixture of adducts (**117n**) and (**117x**) was recovered unchanged. In addition, a sample of the DA adducts (**117n**) and (**117x**) produced in the thermal DA reaction of methyl vinyl ketone (**33**) with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) under the standard conditions (*endo:exo* = 65:35) was subjected to the Lewis acid promoted reaction conditions for 30 hours; 0.25 M in DA adduct, 0.9 molar equivalents methyl aluminium dichloride (**133**), in 3:1 CH_2Cl_2:hexanes, -78 °C to room temperature over 20 hours, and was also recovered unchanged. Both samples of the DA adducts (**117n**) and (**117x**) were also resubjected to the conditions of the reactions in which they were formed, and were recovered unchanged. These experiments demonstrate unequivocally that the *endo* and *exo* DA adducts, (**117n**) and (**117x**), are stable under both the Lewis acid promoted and standard thermal DA reaction conditions, and that the *endo:exo* product ratios generated in reactions carried out under these conditions are kinetic in nature.

Both the thermal and Lewis acid promoted DA reactions of methyl vinyl ketone (**33**) with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) were found to be kinetically controlled

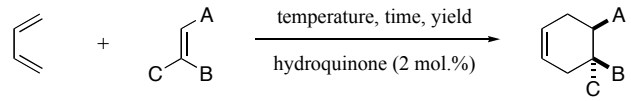
processes. It has been assumed that this DA reaction is representative of the DA reactions of all the library dienophiles with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) under the standard reaction conditions. This assumption appears reasonable.

2.2.6 Summary of Diels-Alder reactions of 1,3-butadiene and (1E,3E)-1,4-dideutero-1,3-butadiene with library dienophiles

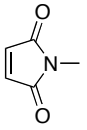
All but one of the DA reactions of unlabelled 1,3-butadiene (**1**) with the library dienophiles have been reported in the literature. The DA reaction of acrolein (**32**) with 1,3-butadiene (**1**) was described in Diels and Alder's seminal paper of 1928. The reaction conditions reported involve mixing the 1,3-diene and dienophile neat and heating at 100 °C for one hour, giving cyclohex-3-enecarbaldehyde (**116**). No yield was reported in the original publication.[1] The DA reaction of methyl vinyl ketone (**33**) with 1,3-butadiene (**1**) was first reported by Petrov in 1941. It was carried out under solvent free conditions in a sealed tube heated to 140 °C for 8-10 hours, giving 75-80% of the product 1-(cyclohex-3-enyl)ethenone (**117**).[119] The DA reaction of acrylic acid (**34**) with 1,3-butadiene (**1**) was first described by Petrov and Sopov in 1947. The reactants were heated in toluene for 12 hours at 125 °C, giving cyclohex-3-enecarboxylic acid (**118**). No yield was reported in the original publication.[120] The DA reaction of methyl acrylate (**35**) with 1,3-butadiene (**1**) was first described in 1954. The reactants were heated neat for five hours at 160 °C, giving methyl cyclohex-3-enecarboxylate (**119**) in 95% yield.[121] The DA reaction of acrylamide (**61**) with 1,3-butadiene (**1**) was first described in 1960. The neat reactants were heated for 15 hours at 140 °C, giving cyclohex-3-enecarboxamide (**120**) in 35% yield.[122] The DA reaction of acrylonitrile (**36**) with 1,3-butadiene (**1**) was first described by Petrov and Sopov in 1947. The reactants were heated with hydroquinone in toluene for 12 hours at 130 °C, giving cyclohex-3-enecarbonitrile (**121**) in 80% yield.[120] The DA reaction of furan-2(5*H*)-one (**114**) with 1,3-butadiene (**1**) was first described in 1986. The reactants were heated with hydroquinone to 210 °C for 20 hours, giving 3a,4,7,7a-tetrahydroisobenzofuran-1(3*H*)-one (**122**) in 62% yield.[123] The DA reaction of dihydro-3-methylenefuran-2(3*H*)-one (**115**) with 1,3-butadiene (**1**) has not been reported in the chemical literature, but the reaction of dihydro-3-methylenefuran-2(3*H*)-one (**115**) with cyclopentadiene (**23**) has been described.[124] The DA reaction of maleonitrile (**60**) with 1,3-butadiene (**1**) was first described in 1970. The reactants were heated together, giving cyclohex-4-ene-1,2-dicarbonitrile (**124**). No yield or reaction conditions were

reported.[125] The DA reaction of N-methyl maleimide (**67**) with 1,3-butadiene (**1**) was first described in 1954. The reactants were heated with hydroquinone in toluene for two hours at 80 °C, giving 3a,4,7,7a-tetrahydro-2-methyl-2*H*-isoindole-1,3-dione (**125**) in 95% yield.[126]

The DA reactions of the library dienophiles with excess commercial, unlabelled 1,3-butadiene (**1**) were carried out using a set of standard conditions (**Scheme 2.19**). The reactions were conducted in benzene solution in sealed tubes, at 130 °C for 24 hours in the presence of 2 mol. % hydroquinone. After purification by column chromatography the unlabelled DA adducts (**116**) to (**125**) were isolated in yields ranging from 11%, for the reaction with acrylamide (**61**), to 92% for the reaction with N-methyl maleimide (**67**).



(**1**) 1,3-diene (**111**) dienophile (**134**) adduct

Entry	Dienophile	Adduct	Temperature (° C)	Time (hr)	Yield (%)[a]
1	 (**32**)	(**116**)	130	24	84
2	 (**33**)	(**117**)	130	24	83
3	 (**34**)	(**118**)	130	24	67
4	 (**35**)	(**119**)	130	24	91
5[b]	 (**61**)	(**120**)	130	24	11
6	 (**36**)	(**121**)	130	24	54
7[c]	 (**114**)	(**122**)	130	24	19
8	 (**115**)	(**123**)	130	24	81
9	 (**60**)	(**124**)	100	24	72
10	 (**67**)	(**125**)	25	24	92

Scheme 2.19 *Diels-Alder reactions of 1,3-butadiene (**1**) with library dienophiles; typical reaction conditions: excess 1,3-diene (**1**), 2 mol % hydroquinone, benzene, sealed tube, 130 °C. [a]Isolated yields of purified products; [b]low yield due to polymerisation of dienophile; [c]low yield due to low reactivity of dienophile.*

A set of standard reaction conditions was developed for the DA reactions of the library dienophiles with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**). All reactions were carried out in the presence of 2 mol.% hydroquinone, at 1.0 M in 1,3-diene (**1**) and dienophile in benzene solution in sealed tubes. Eight of the ten reactions were conducted at 145

°C. In these reactions, differences in dienophile reactivity were accounted for by varying the length time the reactants were heated together in benzene solution. Reaction times ranged from 20 hours for the more reactive dienophiles, acrolein (**32**) and dihydro-3-methylenefuran-2(3*H*)-one (**115**), to 120 hours for the least reactive dienophiles, acrylamide (**61**), acrylonitrile (**36**) and furan-2(5*H*)-one (**114**). The DA reactions of the doubly activated dienophiles, maleonitrile (**60**) and N-methyl maleimide (**67**), with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) were carried out at 100 °C and 25 °C, respectively, for 24 hours, as they were considerably more reactive than the monosubstituted and lactone dienophiles. The crude mixtures were concentrated under vacuum and the isotopomeric DA adducts were purified by column chromatography. Analysis of the purified isotopomeric mixtures in the appropriate solvents or solvent mixtures by 800 MHz ^{1}H NMR spectroscopy gave redundant integral data from which the *endo:exo* ratios of the DA reactions were calculated. The ^{1}H NMR spectra were acquired with relaxation delays of one minute, ensuring quantitative integral data were obtained. The yields of purified deuterium labelled DA adducts ranged from 9% for the reaction with acrylamide (**61**) to 92% for the reaction with N-methyl maleimide (**67**). The observed diastereoselectivities ranged from was 38:62 (*endo:exo*) for the reaction with acrylonitrile (**36**) to 99:1 (*endo:exo*) for the reaction with N-methyl maleimide (**67**).

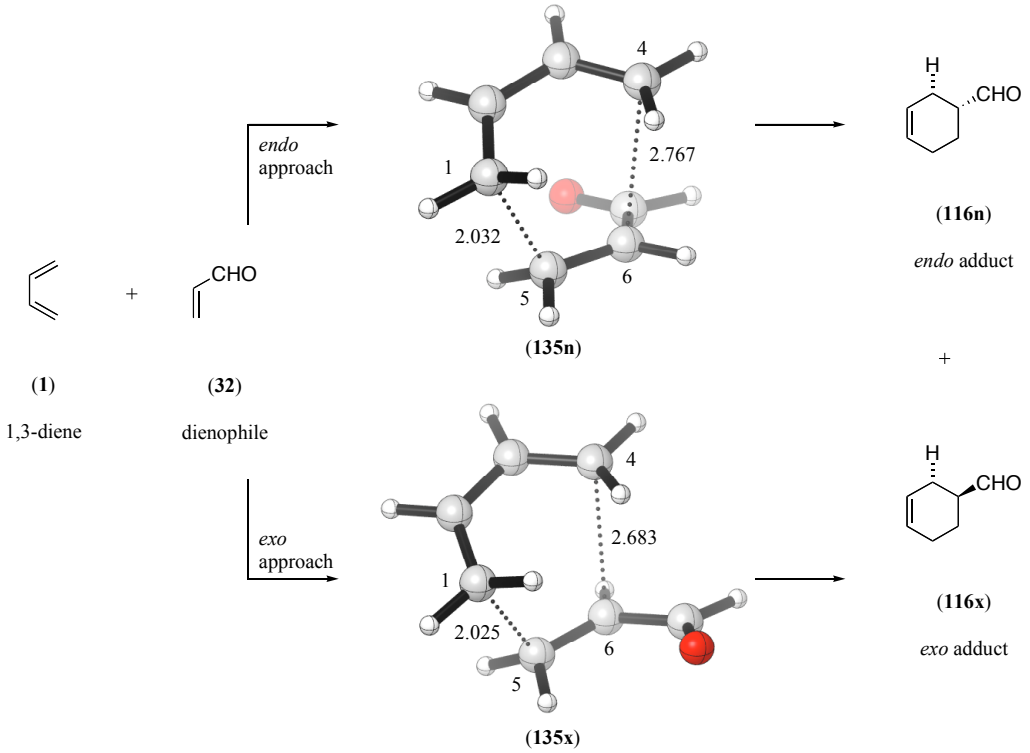
2.2.7 Analysis of Diels-Alder reactions of (1E,3E)-1,4-dideutero-1,3-butadiene with library dienophiles

It was found that (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) undergoes DA reactions with acrolein (**32**), methyl vinyl ketone (**33**), acrylic acid (**34**), methyl acrylate (**35**), acrylamide (**61**) and acrylonitrile (**36**) with little or no kinetic *endo:exo* selectivity. The nitrile activated dienophiles, acrylonitrile (**36**) and maleonitrile (**60**) have opposite stereoselectivities, the reaction with acrylonitrile (**36**) is weakly *exo* selective, and the reaction with maleonitrile (**60**) is weakly *endo* selective. Dihydro-3-methylenefuran-2(3*H*)-one (**115**), a lactone dienophile locked in the *s-cis* conformation, participates in a mildly *exo* selective DA reaction. Furan-2(5*H*)-one (**114**), a lactone dienophile locked in the *s-trans* conformation, is particularly unreactive in a DA sense and participates in a mildly *endo* selective DA reaction. Strong *endo* selectivity is observed with N-methyl maleimide (**67**).

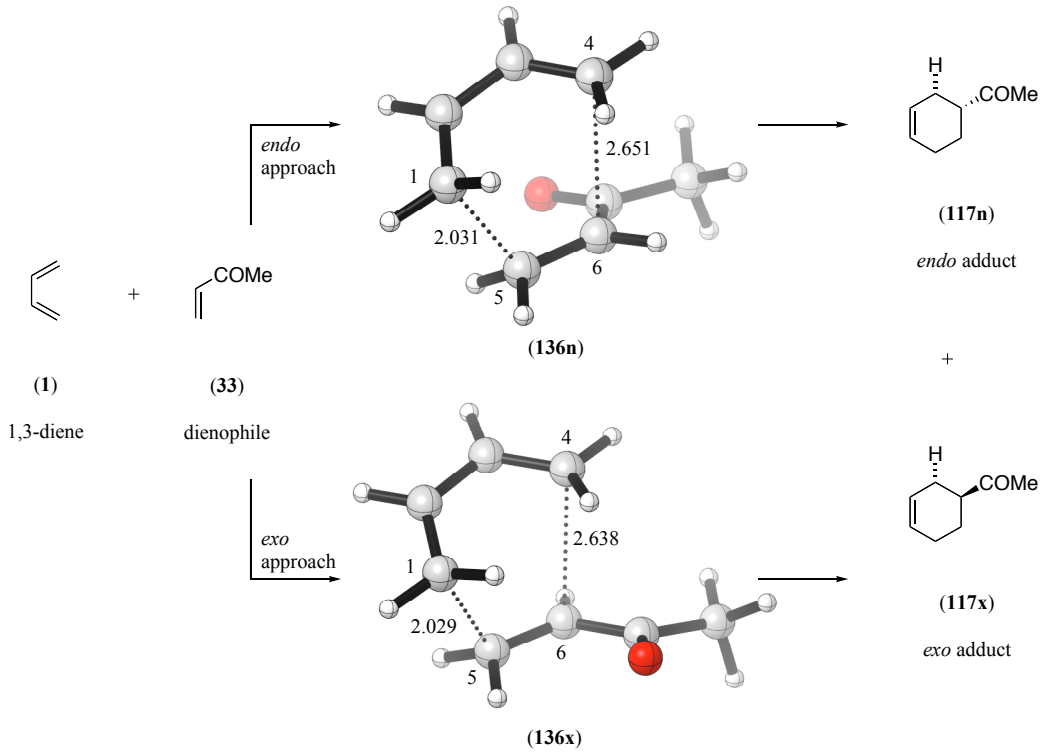
There is a good correlation between the experimentally observed *endo* selectivity of the DA reactions of the carbonyl activated dienophiles acrolein (**32**) (*endo:exo* = 64:36), methyl vinyl ketone (**33**) (*endo:exo* = 65:35), acrylic acid (**34**) (*endo:exo* = 60:40), methyl acrylate (**35**) (*endo:exo* = 50:50) and acrylamide (**61**) (*endo:exo* = 46:54), and the electron withdrawing capacity of the carbonyl substituent, with the stronger electron withdrawing groups giving greater *endo* selectivity.[32] There is also a rough correlation between *endo* selectivity and DA reactivity in the DA reactions of these dienophiles.

The addition of a second electron withdrawing group to a monosubstituted dienophile also results in significantly enhanced *endo* selectivity and reactivity. Comparing the stereoselectivities of the DA reactions of acrylonitrile (**36**) (*endo:exo* = 38:62) and maleonitrile (**60**) (*endo:exo* = 70:30), and acrylamide (**61**) (*endo:exo* = 46:54) and *N*-methyl maleimide (**67**) (*endo:exo* = 99:1) is instructive. It appears that *endo* selectivity and DA reactivity are closely related.

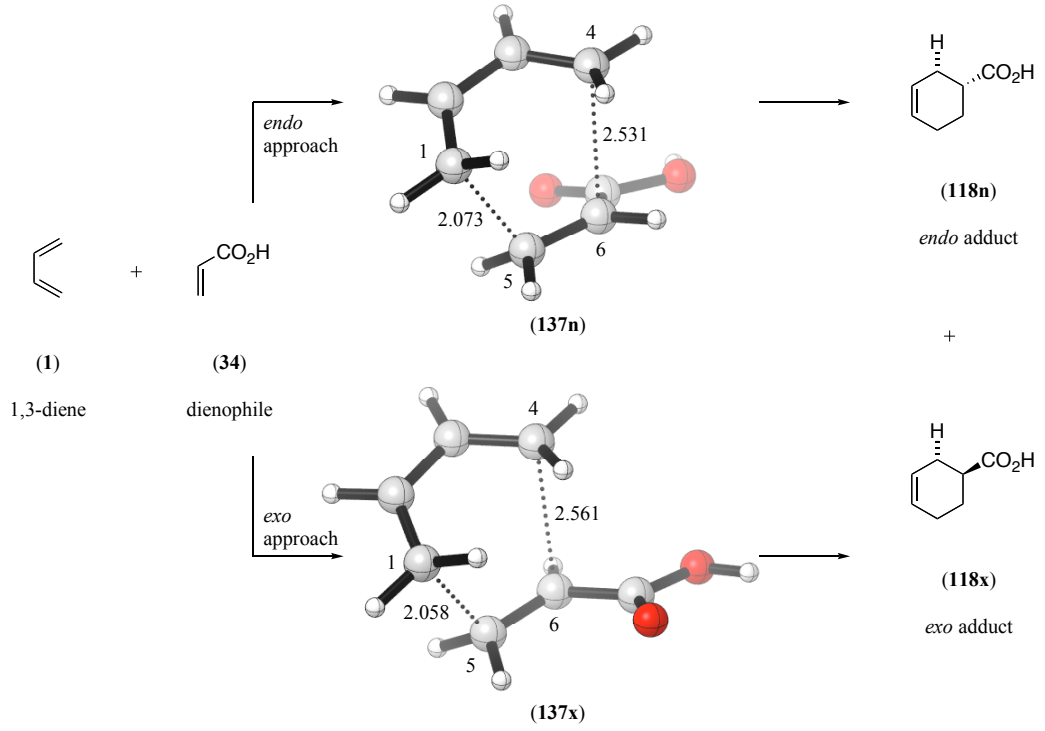
The DA reactions of 1,3-butadiene (**1**) with a number of library dienophiles have been studied by Prof. M. N. Paddon-Row as part of a gas-phase B3LYP/6-31+G(d) investigation of the intramolecular Diels-Alder (IMDA) reactions of substituted 1,3,8-nonatrienes.[89] In this study, transition structures were located for the DA reactions of 1,3-butadiene (**1**) with many dienophiles, including acrolein (**32**), methyl vinyl ketone (**33**), acrylic acid (**34**), methyl acrylate (**35**) and acrylonitrile (**36**). The two lowest energy transition structures for the DA reactions of each dienophile are shown in the following schemes. These are the *s-cis endo* and *s-cis exo* transition structures for the DA reactions of the carbonyl activated dienophiles (**32**) (**Scheme 2.20**), (**33**) (**Scheme 2.21**), (**34**) (**Scheme 2.22**) and (**35**) (**Scheme 2.23**) with 1,3-butadiene (**1**), and the *endo* and *exo* transition structures for the DA reaction of acrylonitrile (**36**) with 1,3-butadiene (**1**) (**Scheme 2.24**).



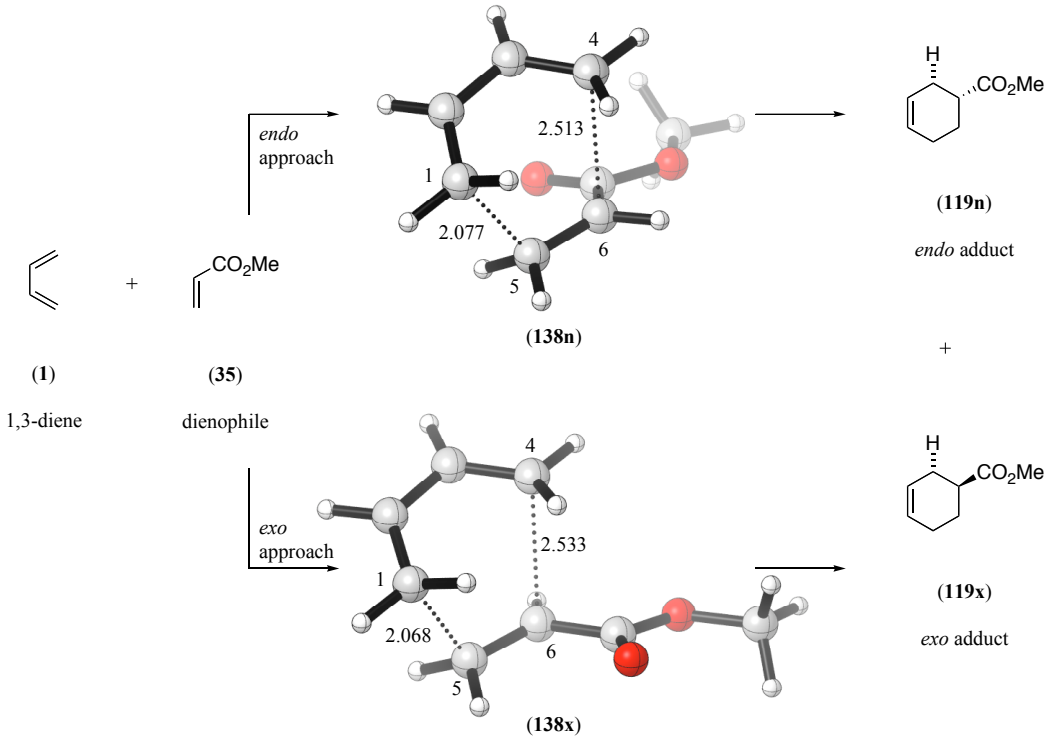
Scheme 2.20 *B3LYP/6-31+G(d) lowest energy endo and exo transition structures of Diels-Alder reaction of 1,3-butadiene (**1**) with acrolein (**32**) located by Prof. M. N. Paddon-Row.*[89]



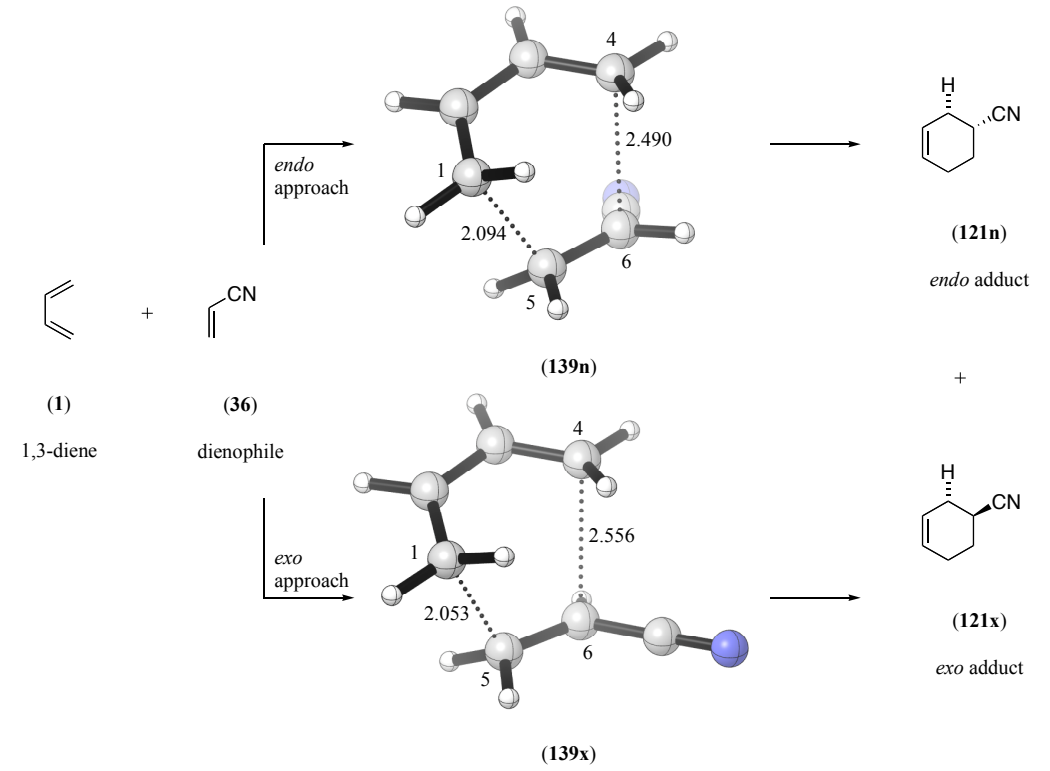
Scheme 2.21 *B3LYP/6-31+G(d) lowest energy endo and exo transition structures of Diels-Alder reaction of 1,3-butadiene (**1**) with methyl vinyl ketone (**33**) located by Prof. M. N. Paddon-Row.*[89]



Scheme 2.22 *B3LYP/6-31+G(d) lowest energy endo and exo transition structures of Diels-Alder reaction of 1,3-butadiene (**1**) with acrylic acid (**34**) located by Prof. M. N. Paddon-Row.*[89]



Scheme 2.23 *B3LYP/6-31+G(d) lowest energy endo and exo transition structures of Diels-Alder reaction of 1,3-butadiene (**1**) with methyl acrylate (**35**) located by Prof. M. N. Paddon-Row.*[89]



Scheme 2.24 *B3LYP/6-31+G(d) endo and exo transition structures of Diels-Alder reaction of 1,3-butadiene (**1**) with acrylonitrile (**36**) located by Prof. M. N. Paddon-Row.*[89]

Small geometrical variations can be seen in the transition structures located for the DA reactions of acrolein (**32**), methyl vinyl ketone (**33**), acrylic acid (**34**), methyl acrylate (**35**) and acrylonitrile (**36**) with 1,3-butadiene (**1**). The transition structures vary in their asynchronicity, with the reaction with acrolein (**32**) having the most asynchronous transition structures and the reaction with acrylonitrile (**36**) having the most synchronous transition structures. The asynchronicities of the reactions with the other dienophiles (**33**), (**34**) and (**35**) fall in the order given above. With the exception of the transition structures involving methyl vinyl ketone (**33**), the *exo* transition structures are more asynchronous than the *endo* transition structures.

In the *endo* transition structures, weak inverse correlations exist between the experimentally observed *endo* selectivities and the distances between the sites involved in the Salem-Houk and Woodward-Hoffman SOIs. Greater *endo* selectivity is associated with shorter Salem-Houk and Woodward-Hoffman distances (**Figures 2.13** and **2.14**). There is also a weak inverse correlation between the Garcia-Mayoral-Salvatella distance in the *endo* and *exo* transition structures, and the degree of *endo* selectivity. Greater *endo* selectivity is associated with shorter Garcia-Mayoral-Salvatella distances in both the *endo* and the *exo* transition structures (**Figures 2.15** and **2.16**). The significance of these relationships is unclear at present, but they are worthy of further computational study and will be explored in depth by Prof. M. N. Paddon-Row in a forthcoming publication.

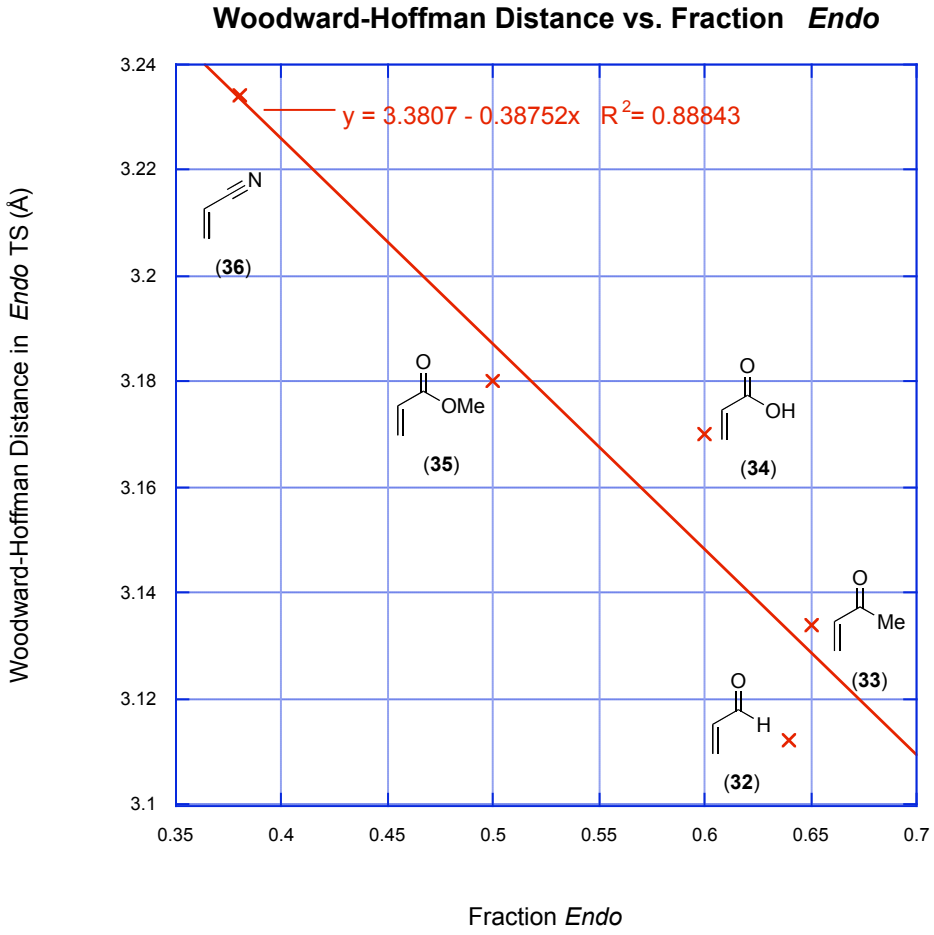


Figure 2.13 *Woodward-Hoffman distance versus experimentally determined endo selectivity in the Diels-Alder reactions of (1E,3E)-1,4-dideutero-1,3-butadiene* ***(64)*** *with selected dienophiles* ***(32)****,* ***(33)****,* ***(34)****,* ***(35)*** *and* ***(36)****.*

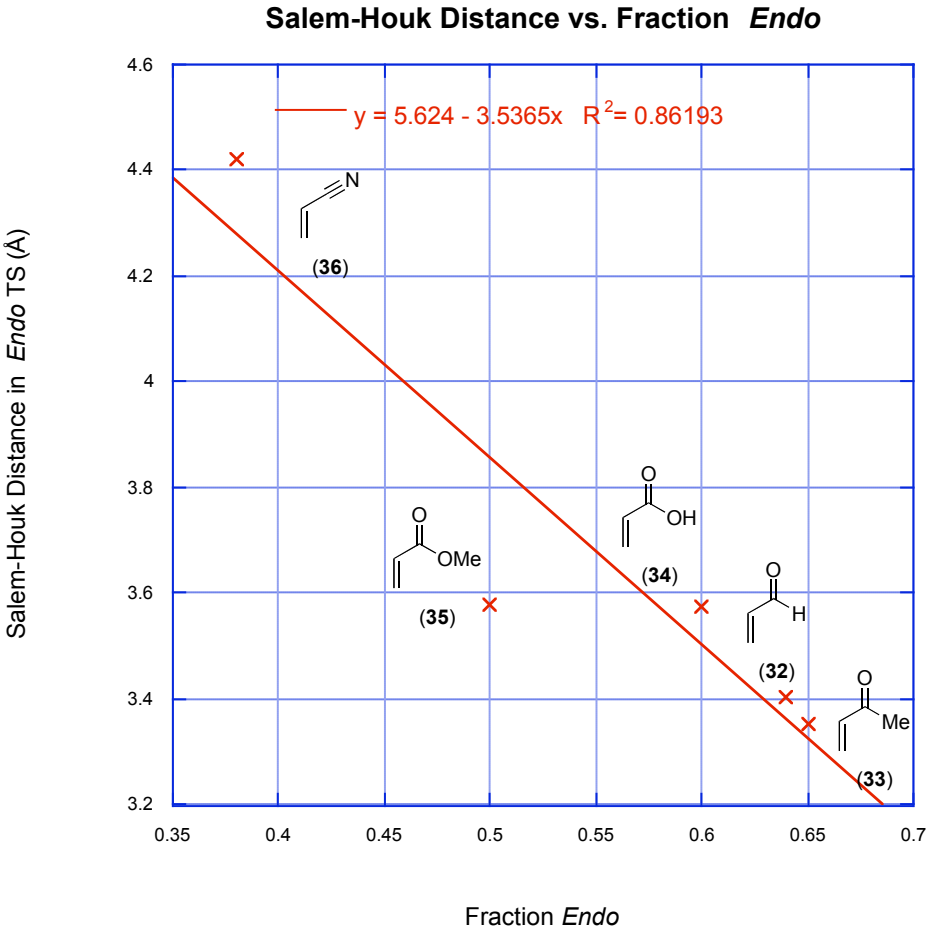


Figure 2.14 *Salem-Houk distance versus experimentally determined endo selectivity in the Diels-Alder reactions of (1E,3E)-1,4-dideutero-1,3-butadiene* ***(64)*** *with selected dienophiles* ***(32)****,* ***(33)****,* ***(34)****,* ***(35)*** *and* ***(36)****.*

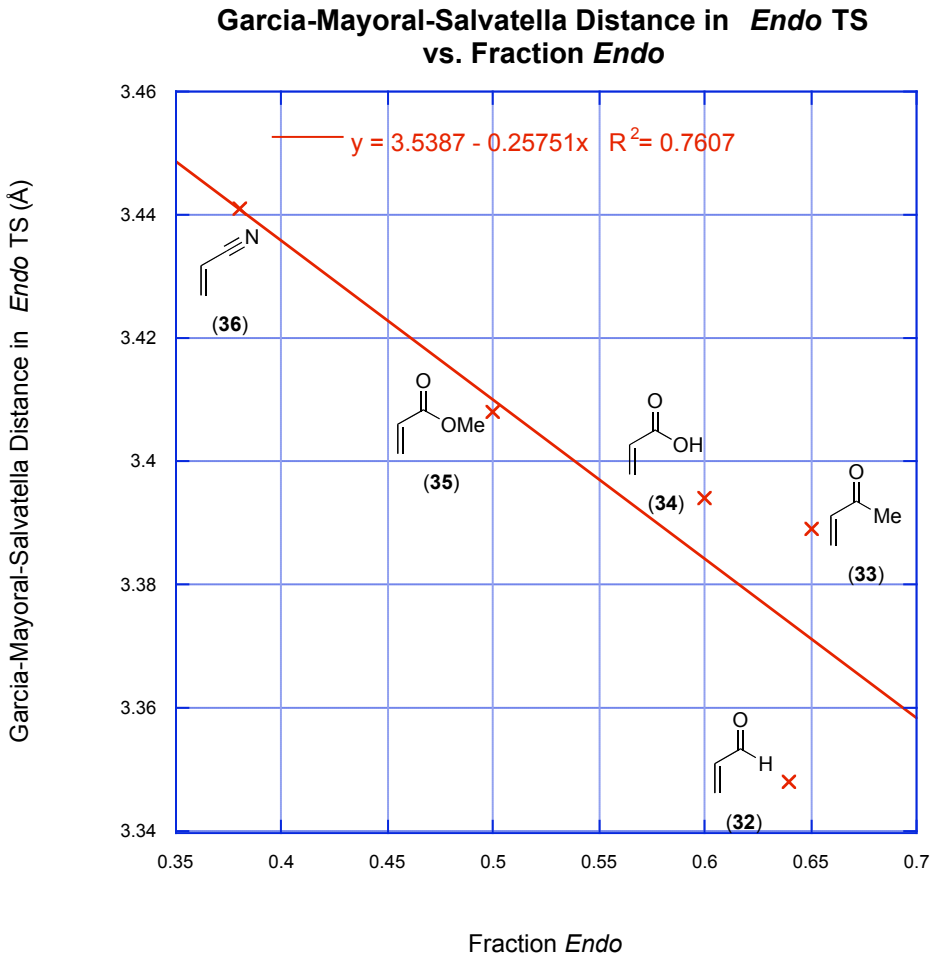


Figure 2.15 *Garcia-Mayoral-Salvatella distance in the endo TS versus experimentally determined endo selectivity in the Diels-Alder reactions of (1E,3E)-1,4-dideutero-1,3-butadiene* ***(64)*** *with selected dienophiles* ***(32)****,* ***(33)****,* ***(34)****,* ***(35)*** *and* ***(36)****.*

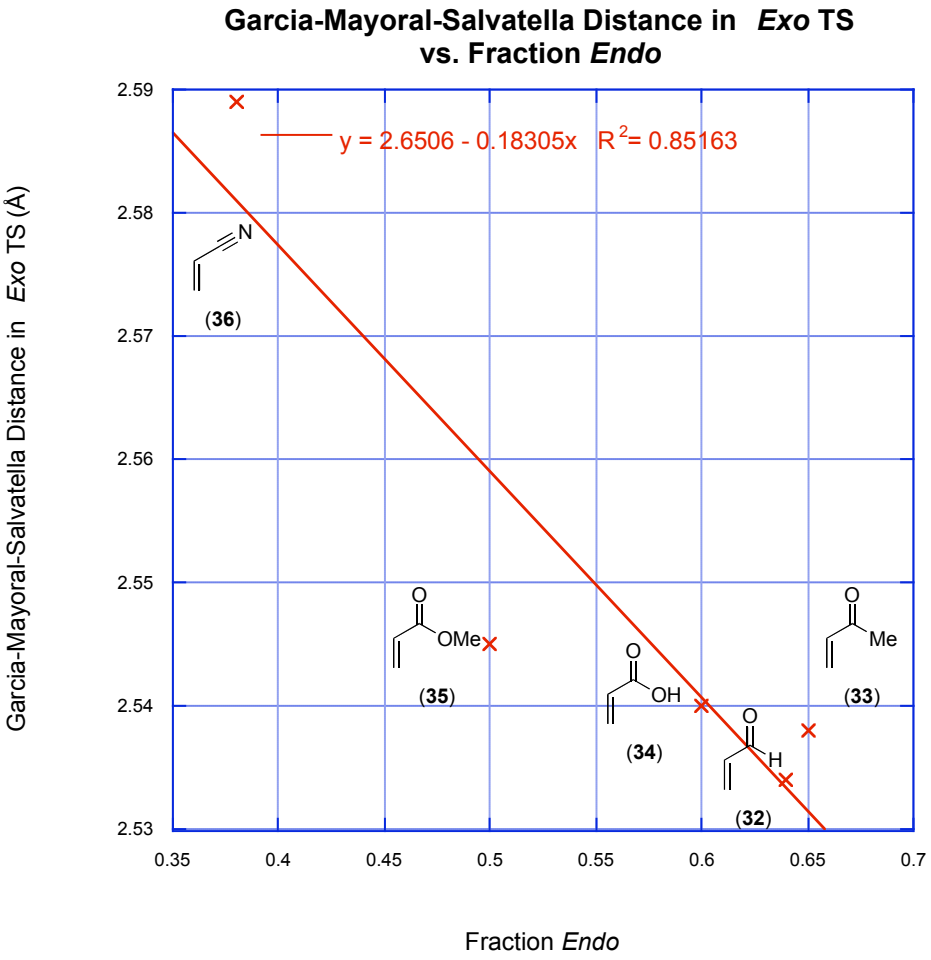


Figure 2.16 *Garcia-Mayoral-Salvatella distance in the exo TS versus experimentally determined endo selectivity in the Diels-Alder reactions of (1E,3E)-1,4-dideutero-1,3-butadiene* ***(64)*** *with selected dienophiles* ***(32)****,* ***(33)****,* ***(34)****,* ***(35)*** *and* ***(36)****.*

In order to further understand the origins of *endo:exo* selectivity in the DA reaction, another member of the Sherburn group has determined the *endo:exo* selectivities of the DA reactions of cyclopentadiene (**23**) with the library of dienophiles, (**32**), (**33**), (**34**), (**35**), (**36**), (**60**), (**61**), (**117**), (**118**), (**119**), used in the study involving (1*E*,3*E*)-dideutero-1,3-butadiene (**64**).[127] The stereoselectivities of the DA reactions of (1*E*,3*E*)-dideutero-1,3-butadiene (**64**) are a useful reference when considering those of the DA reactions of cyclopentadiene (**23**). The following figure depicts the *endo* selectivities of the DA reactions of (1*E*,3*E*)-dideutero-1,3-butadiene (**64**) plotted against those of the DA reactions of cyclopentadiene (**23**) (**Figure 2.17**).

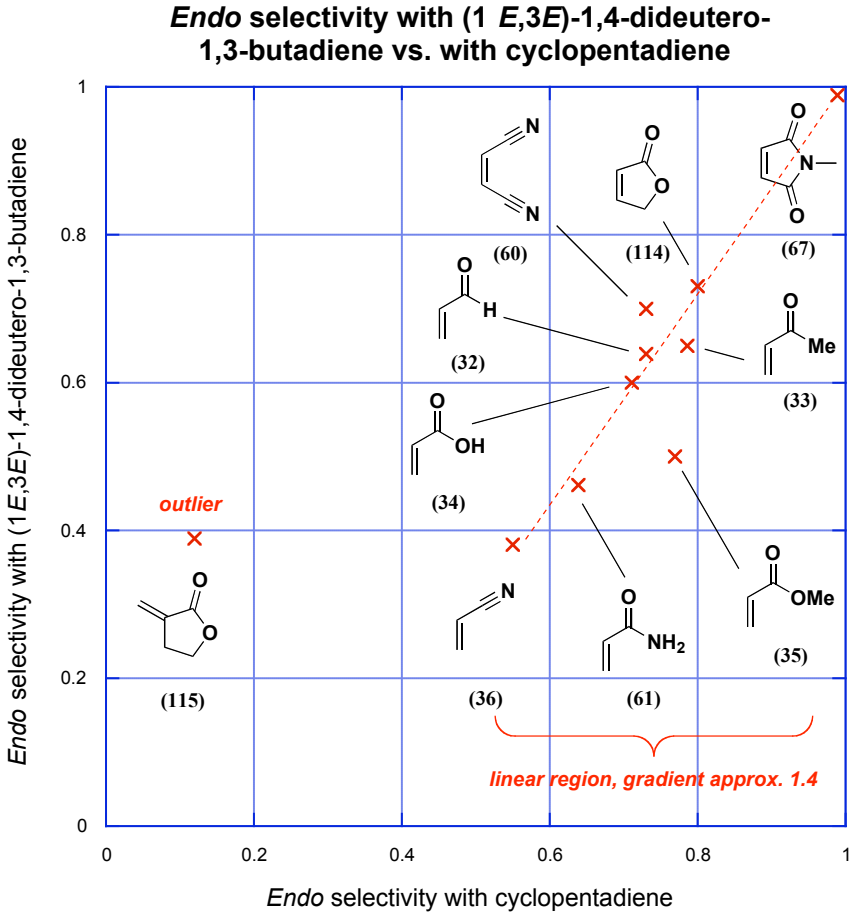


Figure 2.17 *Endo selectivity of Diels-Alder reactions of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with library dienophiles versus endo selectivity of Diels-Alder reactions of cyclopentadiene (**23**) with library dienophiles.*[127]

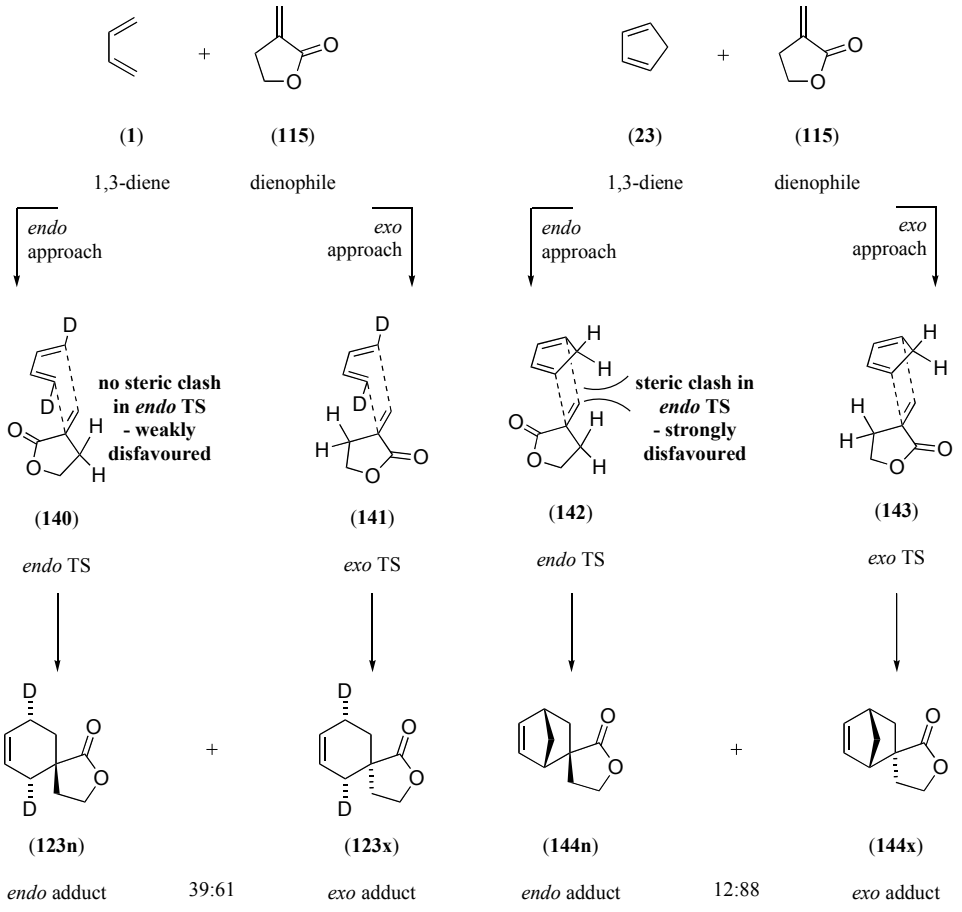
The *endo:exo* selectivities of the DA reactions of the two 1,3-dienes correlate reasonably well with one notable exception, the DA reactions of dihydro-3-methylenefuran-2(3*H*)-one (**115**). A trend line with a gradient of approximately 1.4 has been placed through the right hand side of the graph, roughly fitting nine of the ten data points. The equation relating the *endo* selectivities of the DA reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**), *endo*(butadiene), to the *endo* selectivities of the DA reactions of cyclopentadiene (**23**), *endo*(cyclopentadiene), for the nine dienophiles in the "linear" region of the graph is given here:

$$endo(butadiene) \approx 1.4 \times endo(cyclopentadiene) - 0.4$$

In contrast, in the case of dihydro-3-methylenefuran-2(3*H*)-one (**115**):

$$endo(butadiene)/endo(cyclopentadiene) \approx 3$$

The straight line fit appears to reflect the influence of the methylene bridge in the cyclic 1,3-diene (**23**), the result being slightly enhanced *endo* selectivity relative to the reactions of the acyclic 1,3-diene (**1**). The outlier (**115**) is the only α-branched dienophile in the set. The enhanced *exo* selectivity in the DA reaction of this dienophile with cyclopentadiene could result from a steric clash between the methylene group of cyclopentadiene and the methylene group adjacent to the α-carbon of the dienophile (**115**) in the *endo* transition state (**Scheme 2.25**).



Scheme 2.25 *Diels-Alder reactions of dienophile (**115**) with 1,3-butadiene (**1**) and cyclopentadiene (**23**). A steric clash in the endo transition state involving cyclopentadiene is a likely cause of the strong exo selectivity observed with that 1,3-diene.*[127].

The Alder *endo* rule[31] can now be examined in the light of the experimental findings.[89] The stereoselectivities of the DA reactions of 1,3-butadiene (**1**) with 13 dienophiles have been determined, including three literature examples; the DA dimerisation of 1,3-butadiene (**1**) (*endo:exo* = 56:44),[39,40] and the reactions of 1,3-butadiene with maleic anhydride (**54**) (*endo:exo* = 85:15),[95] and cyclopropene (**56**) (*endo:exo* = >99:1).[96] The *endo* pathway is favoured by over 5 kJmol^{-1}, giving *endo:exo* ratios of 85:15 and above at 80 °C, in only a three cases, the DA reactions of 1,3-butadiene with maleic anhydride (**54**), cyclopropene (**56**), and *N*-methyl maleimide (**67**). Thus, the Alder *endo* rule DA appears to be applicable only to the reactions of 1,3-butadiene (**1**) with highly reactive dienophiles. As the DA reactions of 1,3-butadiene (**1**) with simple dienophiles are the fundamental DA processes, and reflect the intrinsic stereoselectivity of the DA reaction, it appears that the Alder *endo* rule is much more limited in application than was once thought. This is an important finding, as the Alder *endo* rule is very widely accepted at present.

A unified, experimentally verified picture of reactivity and *endo:exo* selectivity in normal electron demand DA reactions now emerges; the factors that enhance DA reactivity also enhance *endo* stereoselectivity.[89] In 1,3-dienes, the HOMO is involved in primary orbital interactions, and a higher HOMO energy leads to enhanced DA reactivity through more efficient orbital overlap at the sites of eventual bond formation. In dienophiles, the LUMO is involved primary orbital interactions, and a lower LUMO energy leads to enhanced DA reactivity through more efficient orbital overlap at the sites of eventual bond formation. *Endo:exo* selectivity can now be understood using a simple SOI model. Just as the energies of the HOMO of the 1,3-diene and the LUMO of the dienophile determine the strengths of the primary orbital interactions, they also determine the strengths of the secondary orbital interactions, which play an important part in determining the *endo:exo* selectivity of the DA reaction.[89] These concepts account for the well known empirical correlation between DA reactivity and *endo* selectivity, and for the effects of Lewis acid catalysis or promotion of DA reactions. Co-ordination of a dienophile to a Lewis acid reduces its LUMO energy, increasing its DA reactivity through enhanced primary orbital interactions, and the *endo* selectivity its DA reactions through enhanced secondary orbital interactions.[33]

2.2.8 Reactions of acrylonitrile with cyclic dienes

To further understand the *exo*-selectivity observed in the DA reaction of acrylonitrile (**36**) with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**), the DA reactions of acrylonitrile (**36**) with cyclopentadiene (**23**) and 1,3-cyclohexadiene (**145**) were investigated. These reactions have been described in the literature, and were originally reported by Alder.[128] According to the original publication, gentle heating of acrylonitrile (**36**) with cyclopentadiene (**23**) for one hour gave a 3:2 mixture of the *endo* and *exo* adducts, (**50**) and (**51**), respectively, in 95% yield, and heating acrylonitrile (**36**) with 1,3-cyclohexadiene (**145**) to 120 °C for 12 hours gave a 1:1 mixture of the *endo* and *exo* adducts (**146**) and (**147**), respectively, in 90% yield.

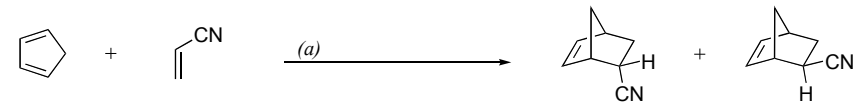
Later publications give varying *endo:exo* ratios for reactions of cyclopentadiene (**23**) with acrylonitrile (**36**) carried out under slightly different experimental conditions, including 55:45 *endo:exo,*[129] 56:44 *endo:exo,*[58] and 63:37 *endo:exo.*[130] It is noteworthy that the last two of these three ratios were determined by gas chromatography. The reaction of 1,3-cyclohexadiene (**145**) with acrylonitrile (**36**) has been reported to give the two adducts (**146**) and (**147**) in ratios of 55:45[131] and 64:36 *endo:exo*.[130] The latter ratio was also determined by gas chromatography.

In light of the variation in the literature *endo:exo* ratios reported for the DA reactions of acrylonitrile (**36**) with cyclopentadiene (**23**) and cyclohexadiene (**145**), these reactions were investigated using the standard conditions developed for the DA reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**). These conditions are 1.0 M in 1,3-diene and dienophile in benzene solution at 145 °C in a sealed tube, in the presence of 2 mol. % hydroquinone as a radical inhibitor. In addition, all adducts were characterised by modern spectroscopic methods, as previously they had been characterised as mixtures of the *endo* and *exo* isomers.[130]

The reactivity of cyclopentadiene (**23**) towards dienophiles is $>10^3$ times that of 1,3-cyclohexadiene (**145**), and the reactivity of 1,3-cyclohexadiene towards dienophiles is approximately ten times that of 1,3-butadiene (**1**).[2,9] The cyclic 1,3-dienes (**23**) and (**145**) are locked in the reactive *s-cis* configuration, whereas 1,3-butadiene exists as an equilibrium mixture of *s-cis* or gauche, and *s-trans* conformers, in which the unreactive *s-trans* conformer is energetically favoured by approximately 10.5 $kJmol^{-1}$.[132-134] At 145 °C, more than 95% of a sample of 1,3-butadiene (**1**) is in the *s-trans* conformation

and unable to participate in the DA reaction. There is also a significant difference in reactivity between the cyclic dienes (**23**) and (**145**), which is largely due to differences in the geometries of the two compounds. Cyclopentadiene (**23**) is much more reactive than 1,3-cyclohexadiene (**145**) because the distance between the termini of the 1,3-diene in cyclopentadiene is significantly shorter than the corresponding distance in 1,3-cyclohexadiene. This allows for more effective orbital overlap with dienophiles, lowering the activation barrier and increasing the rate of reaction.[135,136] The standard conditions developed for the DA reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) with the library dienophiles were used for the DA reactions of the cyclic 1,3-dienes (**23**) and (**145**) with acrylonitrile (**36**), although considerably milder conditions would have sufficed. The standard conditions were used to facilitate comparison of the experimental and computational data obtained from the reactions of the cyclic 1,3-dienes (**23**) and (**145**) with those derived from other experiments and computational investigations.

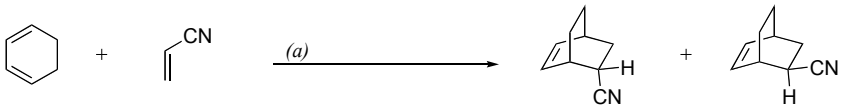
The DA reaction of acrylonitrile (**36**) with cyclopentadiene (**23**) (**Scheme 2.26**) was carried out in duplicate and proceeded smoothly in a sealed tube under the standard reaction conditions. The reaction was probably complete within one hour, but the sealed tube was kept at 145 °C for 20 hours. The reaction mixture was concentrated under vacuum and the isomeric DA adducts were purified by column chromatography eluting with 40-60 petrol:ethyl acetate (40:1). The yield for these reactions was 80% and the ratio of adducts obtained from ^{1}H NMR spectroscopy of the crude mixture and the isolated masses of the purified DA adducts was 53:47, *endo:exo*.



Scheme 2.26 *Diels-Alder reaction of acrylonitrile (**36**) with cyclopentadiene (**23**). Conditions: (a) 1.0 M, benzene, 2 mol. % hydroquinone, 145 °C, sealed tube, 20 hr, 80%, endo:exo = 53:47.*

The DA reaction of acrylonitrile (**36**) with 1,3-cyclohexadiene (**145**) (**Scheme 2.27**) was carried out in duplicate and proceeded smoothly under the standard reaction conditions in 24 hours. The reaction mixture was concentrated under vacuum and the isomeric DA adducts were purified by column chromatography eluting with 40-60 petrol:ethyl

acetate (40:1). The yield for these reactions was 78% and the ratio of adducts obtained from ^{1}H NMR spectroscopy of the crude mixture and the isolated masses of the purified DA adducts was 52:48, *endo:exo*.

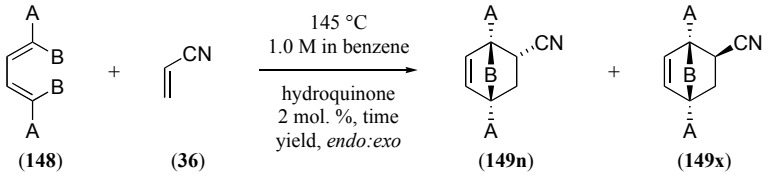


(**145**) (**36**) (**146**) (**147**)

diene dienophile *endo* adduct *exo* adduct

Scheme 2.27 *Diels-Alder reaction of acrylonitrile (**36**) with 1,3-cyclohexadiene (**157**). Conditions: (a) 1.0 M, benzene, 2 mol. % hydroquinone, 145 °C, sealed tube, 24 hr, 78%, endo:exo = 52:48.*

The reactions of acrylonitrile (**36**) with the cyclic 1,3-dienes (**23**) and (**145**) have been studied by the Alder[128] and Hall[130] groups. Different *endo:exo* ratios for reactions conducted under different, and sometimes ill defined, conditions have been reported. In carrying out these reactions under well defined conditions identical to those used for the reaction of acrylonitrile (**23**) with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**), a self consistent data set has been assembled. This approach is advantageous because it enables the direct comparison of the DA reaction of the acyclic 1,3-diene with those of the cyclic 1,3-dienes and facilitates future computational investigations (**Scheme 2.28**).



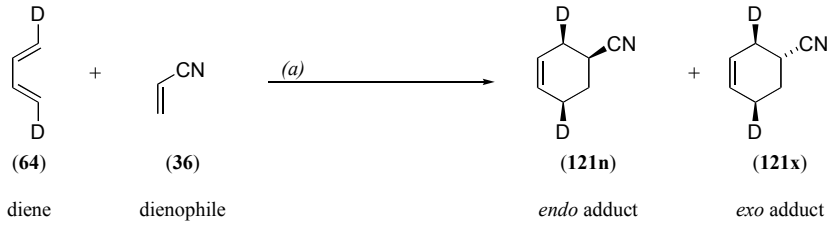
1,3-Diene	Time (hr)	Yield %[a]	*Endo:exo*[b]	$\Delta\Delta G^{\ddagger}$ (kJ/mol)[c]
D (**64**) D A = D, B = H	120	76	38:62	*x* 1.11
(**23**) A = H, B = CH_2	20	80	53:47	*n* 0.42
(**145**) A = H, B = CH_2CH_2	24	78	52:48	*n* 0.27

Scheme 2.28 *Stereoselectivities of Diels-Alder reactions of acrylonitrile (36) with (1E,3E)-1,4-dideutero-1,3-butadiene (**64**), cyclopentadiene (**23**) and 1,3-cyclohexadiene (**145**). Conditions: (a) 1.0 M, in reactants, benzene, 2 mol. % hydroquinone, 145 °C, sealed tube. [a]Isolated yields of purified products; [b]experimental endo:exo ratios are the average of two runs; difference between runs <2%; [c]the letters n and x designate the favoured reaction pathway.*

It is clear that the energetics of the competing *endo* and *exo* pathways of the DA reactions of acrylonitrile are finely balanced. In the case of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**), the *exo* pathway is favoured by just over one kilojoule per mole, and in the DA reactions of the cyclic 1,3-dienes (**23**) and (**157**), the *endo* and *exo* transition states are almost isoenergetic. Identifying the origins of *endo:exo* selectivity in these systems will be a significant challenge due to the subtlety of the factors involved.

2.2.9 Gas phase reaction

To further understand the anomalous *exo* selectivity exhibited by the DA reaction of acrylonitrile (**36**) with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) and to facilitate comparison of experimental data with DFT calculations carried out in the gas phase, the DA reaction of acrylonitrile (**36**) with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) was carried out in the gas phase (**Scheme 2.29**).



Scheme 2.29 *Gas phase Diels-Alder reaction of acrylonitrile (**36**) with (1E,3E)-1,4-dideutero-1,3-butadiene (**64**). Conditions: (a).gas phase, 350 °C, sealed tube, 40 hr, 32%, endo:exo = 50:50.*

DA reactions are first order in both 1,3-diene and dienophile, and follow second order kinetics. The rate of reaction is equal to the product of the second order rate constant and the concentrations of each of the reactants. Whereas solution phase reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) were carried out in benzene at 1.0 M in both 1,3-diene and dienophile, the gas phase reaction had to be carried out at relatively low reactant concentrations, to be sure the reaction took place safely and entirely in the gas phase. Attempts to manipulate neat (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) on the small scale on which it could be made were unsuccessful, and it was found that the deuterium labelled 1,3-diene could only be reliably handled in solution.

In the absence of specialised equipment, a simple sealed tube with a capacity of 1.0 L was made. This volume was chosen to allow for expansion of the contents of the tube as the reaction mixture heated up and evaporated, and calculations were carried out to ensure that the tube would not explode. 1.0 mmol acrylonitrile (**36**) and 1.0 mL of a 1.0 M solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in benzene were placed in the tube, the bottom of the tube was cooled with liquid nitrogen, and the tube was evacuated to 20 mbar and sealed. The tube contained approximately 12 mmol benzene, 2.0 mmol of the combined reactants, and 1.0 mmol of nitrogen molecules. At reactant concentrations of 1.0 M, it was known that the solution phase DA reaction took roughly 120 hours at 145 °C to reach 75% conversion. At reactant concentrations of 1.0 mM in the gas phase, it was calculated that the DA reaction of acrylonitrile (**36**) with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) would be around 10^6 times slower than the corresponding solution phase reaction. For this reason, it was calculated that the reaction temperature would need to be about 350 °C to produce useful quantities of the DA adduct in a reasonable period of time.

The sealed tube was placed in an oven equilibrated to 350 ± 2 °C for 40 hours, and it was visually confirmed that the contents of the flask had completely evaporated while the flask was in the oven at the stated temperature. The tube was removed from the oven, the reaction mixture was concentrated under vacuum, and the isotopomeric DA adducts were purified by column chromatography eluting with 40-60 petrol:ethyl acetate (40:1). The yield for the reaction was 32%. Analysis of the purified isotopomeric mixture in $CDCl_3$ by 800 MHz ^1H NMR gave redundant integral data from which a 50:50 (*endo:exo*) product ratio was calculated.

It is not known for certain whether the 50:50 (*endo:exo*) ratio is kinetic or thermodynamic in origin, as the experiments necessary to distinguish between those alternatives were not carried out. It is very unlikely that the gas phase kinetic ratio would be exactly 50:50 (*endo:exo*), and the gas phase reaction was expected to exhibit greater *exo* selectivity than the corresponding solution phase reaction, which gave a 38:62 (*endo:exo*) ratio. It can be concluded that the gas phase reaction was almost certainly under thermodynamic control. The observed ratio could arise from a DA-retro DA mechanism, through the direct epimerisation at the carbon bearing the nitrile functional group, or by a combination of the two mechanisms. In order to carry out gas phase DA reactions at lower temperatures, and have a greater likelihood of obtaining a kinetically controlled *endo:exo* ratio, it would be ideal for the volume of the sealed tube to be minimised, as the rate of reaction is proportional to the product of the concentrations of the reactants. A significant problem with experiments of this type is the need to use solutions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in solvent, as the evaporation and expansion of the solvent must be accommodated by the reaction vessel. The ideal solvent for the sample of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) might be the dienophile.

2.3 Concluding Remarks

This chapter described an investigation of the stereoselectivities of a series of fundamental DA reactions. For the first time, the *endo:exo* selectivities of a range of DA reactions of 1,3-butadiene with library dienophiles have been measured using (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**), a deuterium labelled stereochemical probe. (1*E*,3*E*)-1,4-Dideutero-1,3-butadiene was synthesised through a two step sequence using modified literature procedures, and its DA reactions with a variety of dienophiles

were studied under a set of carefully designed conditions. In addition, a representative DA reaction, that of methyl vinyl ketone with (1*E*,3*E*)-1,4-dideutero-1,3-butadiene was carried out with Lewis acid promotion, demonstrating for the first time that Lewis acid promoted *endo* selectivity is an intrinsic aspect of this important reaction.

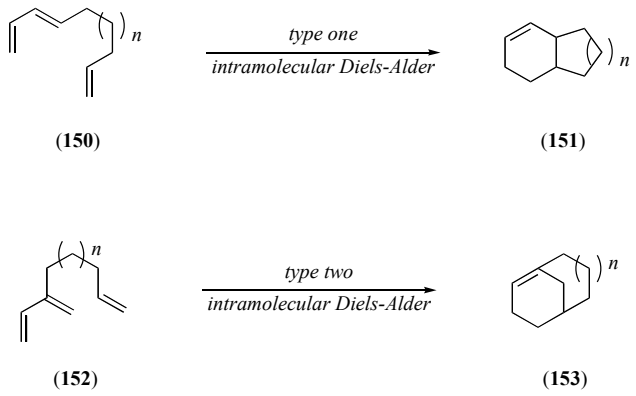
The heat promoted DA reactions of methyl vinyl ketone (**33**) and, by analogy, the rest of the dienophiles studied, were shown to be kinetically controlled events. With notable exceptions, the *endo* and *exo* pathways of the DA reactions studied are close to isoenergetic, and the Alder *endo* rule is of little use in predicting the stereochemical outcomes of these processes.

It is hoped that this work will stimulate others, particularly computational groups, to study these fascinating reactions. The body of work described in this chapter will provide an important empirical reference for computational investigations, and may encourage experimentalists to investigate other important examples of the DA reaction.

3 The Intramolecular Diels-Alder Reaction

3.1 Introduction

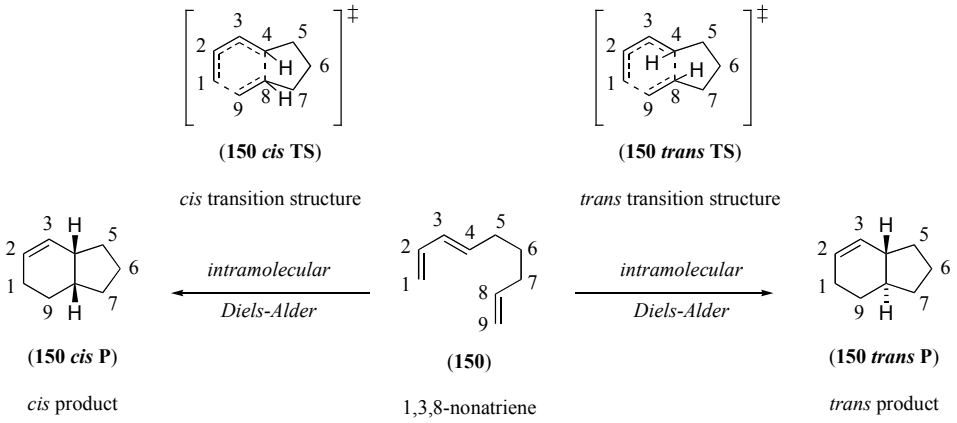
The DA reaction is an unusually powerful chemical transformation, but the intramolecular DA (IMDA) reaction is arguably even more powerful, because while both reactions form two new carbon-carbon σ-bonds and up to four contiguous stereogenic centres in a concerted event, the IMDA reaction produces not one ring, but a fused or bridged system containing two new rings. Two general types of IMDA reactions are known, and they are distinguished by the position of attachment of the tether to the 1,3-diene unit of the triene. The tether is attached at carbon one of the 1,3-diene in type one trienes, and at carbon two of the 1,3-diene in type two trienes. Type one IMDA reactions form fused ring systems containing cyclic alkenes, whereas type two IMDA reactions form bridged ring systems containing bridgehead alkenes (**Scheme 3.1**).[16,18,19,137]



Scheme 3.1 *Type one and type two intramolecular Diels-Alder reactions.*

Its unique power makes the IMDA reaction a strategy level chemical reaction with great potential, but its deployment in chemical synthesis is hindered by the fact that the activation barriers and stereochemical outcomes of many IMDA reactions are very difficult to predict. The IMDA reactions of substituted 1,3,8-nonatrienes have the potential to provide rapid and efficient access to synthetically useful 2,3,3a,6,7,7a-hexahydro-1*H*-indene derivatives, and will be the focus of this chapter. For clarity, a simple numbering system for 1,3,8-nonatrienes, the corresponding IMDA transition

structures and IMDA adducts will be used consistently through this chapter (**Scheme 3.2**).



Scheme 3.2 *Numbering system for 1,3,8-nonatrienes, intramolecular Diels-Alder transition structures, and 2,3,3a,6,7,7a-hexahydro-1H-indene intramolecular Diels-Alder adducts.*

3.1.1 Stereoselectivity in the intramolecular Diels-Alder reactions of 1,3,8-nonatrienes

The Sherburn group became interested in the IMDA reactions of trienes (**155**) and (**65**) as part of an experimental and computational investigation into the IMDA reactions of ester tethered trienes (**156**), (**157**) and (**158**) (**Figure 3.1**).

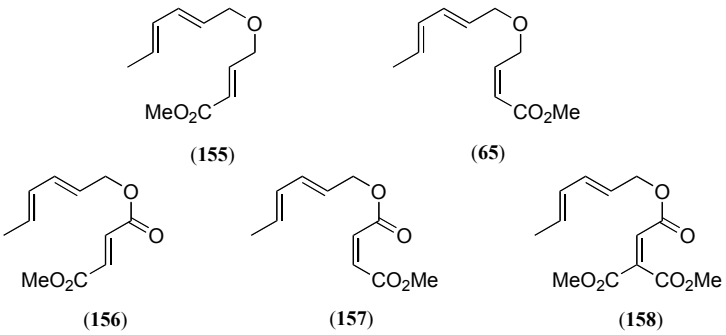
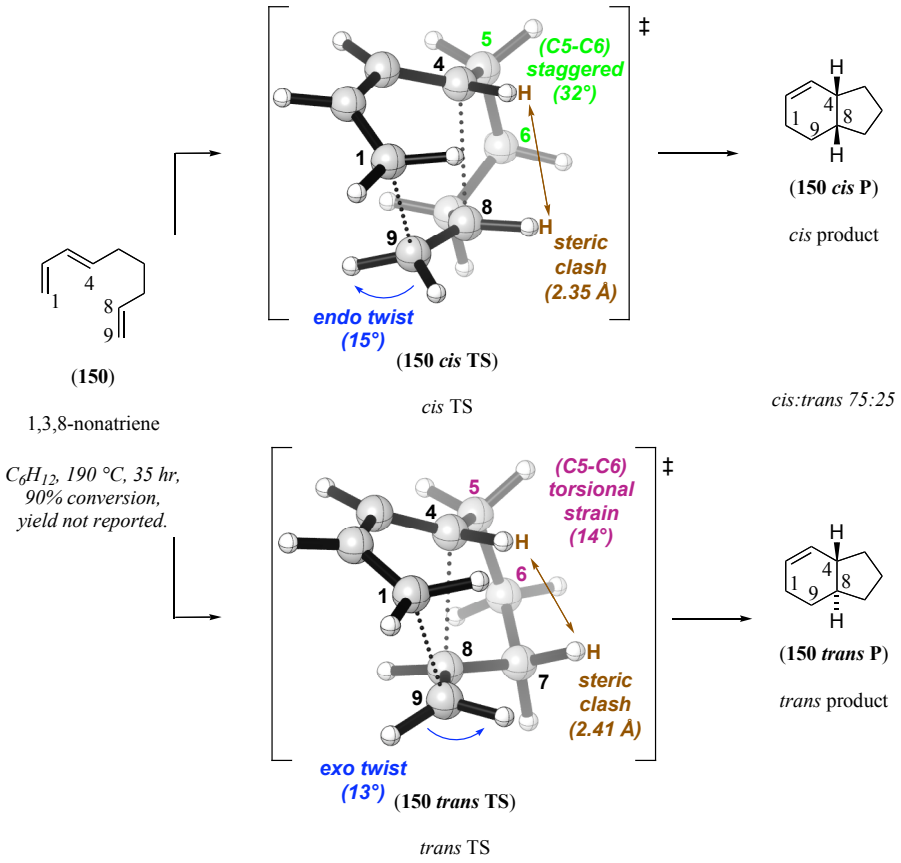


Figure 3.1 *Ether and ester linked 1,3,8-nonatrienes studied within the Sherburn group.*

Seminal investigations in this area were carried out by House and Cronin[138] in the 1960s and by Roush in the 1970s and 1980s.[139] The early work focussed on substituted 1,3,8-nonatrienes, probably because the IMDA reactivity of the parent system was expected to be low. A combined experimental and computational study of the IMDA reactions of the parent 1,3,8-nonatriene (**150**) was eventually published in 1985, and this compound was found to cyclise under rather drastic conditions, giving a 75:25 mixture of the

anticipated *cis* and *trans* fused 2,3,3a,6,7,7a-hexahydro-1*H*-indenes (**150 *cis* P**) and (**150 *trans* P**), respectively (**Scheme 3.3**).[140]

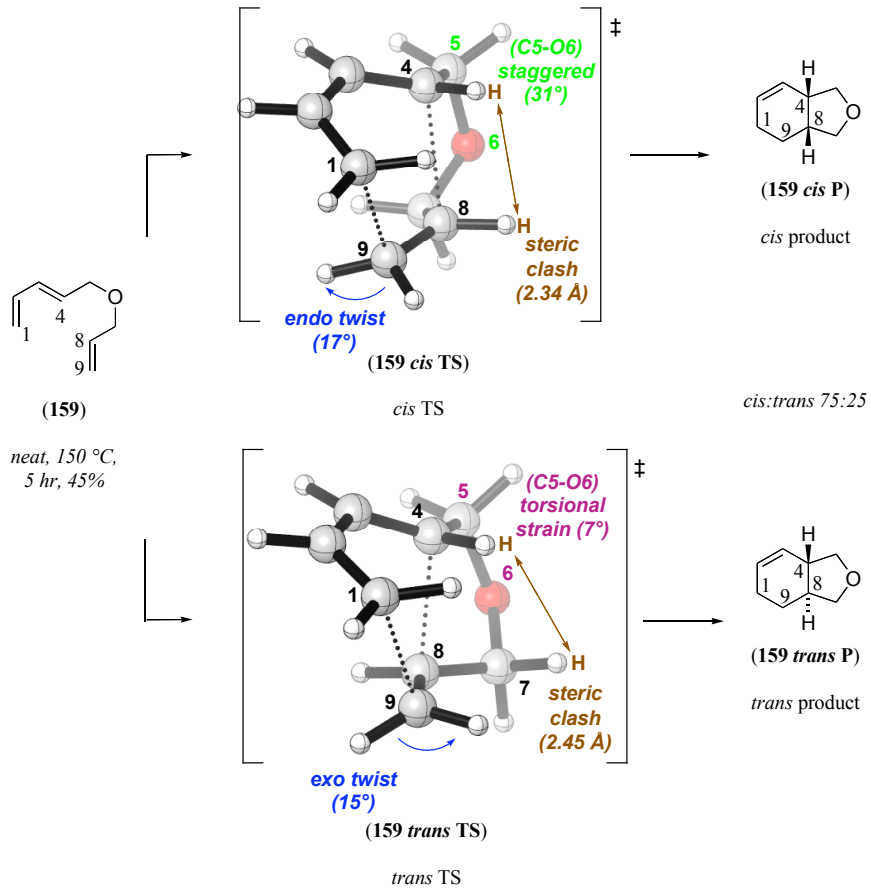


Scheme 3.3 *Intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**150**), gas phase cis and trans transition structures, and cis fused and trans fused cycloadducts. The gas phase B3LYP/6-31+G(d) transition structures were located by Prof. M. N. Paddon-Row.*[92]

The computational investigation found that the IMDA transition structures associated with this triene, (**150 *cis* TS**) and (**150 *trans* TS**), were distorted in ways which minimised strain in the forming, tether containing ring. This distortion was labelled twist mode asynchonicity, and has since been identified by Paddon-Row as a general feature of the IMDA transition structures of 1,3,8-nonatrienes.[89] Twist mode asynchronicity manifests as a twisting of the dienophile relative to the 1,3-diene around the C4-C8 internuclear axis - the internal developing bond - and is distinct from stretch mode asynchronicity, which describes a difference in the lengths of the developing bonds in a transition structure. The degree of twisting varies between trienes, but the direction of twisting, in the *endo* direction in the *cis* transition structure, and in the *exo* direction in the *trans* transition structure, is the same for every triene discussed in this

chapter. In the parent system, the Houk group found the dienophile twisted 15° in the *endo* direction in the *cis* transition structure (**150 *cis* TS**), and 13° in the *exo* direction in the *trans* transition structure (**150 *trans* TS**).[141] The IMDA reaction of this triene (**150**) has since been studied computationally by Prof. M. N. Paddon-Row, who found that while both the *cis* and *trans* transition structures, (**150 *cis* TS**) and (**150 *trans* TS**), respectively, exhibit twist mode asynchonicity, the *trans* transition structure is destabilised by residual torsional strain between C5 and C6.[89] The dihedral angle around the C5-C6 bond is 32° in the *cis* transition structure (**150 *cis* TS**), and 14° in the *trans* transition structure (**150 *trans* TS**). In addition, there are steric clashes in both transition structures; between the hydrogens at positions 4 and 8 in the *cis* transition structure (2.35 Å), and between the hydrogens at positions 4 and 7 in the *trans* transition structure (2.41 Å). The IMDA reaction of this triene (**150**) is *cis* selective because the energetic cost of the steric clash and residual torsional strain in the *trans* transition structure (**150 *trans* TS**) outweighs that of the steric clash in the *cis* transition structure (**150 *cis* TS**) by approximately 3.5 $kJmol^{-1}$. [92,142]

The transition structures located by Prof. Paddon-Row for the IMDA reaction of the ether linked triene (**159**), (**Scheme 3.4**), are very similar to those located for the IMDA reaction of the parent system (**150**).

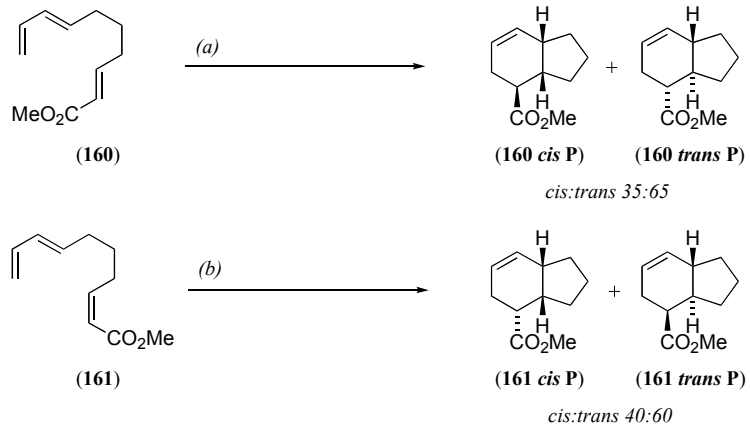


Scheme 3.4 *Intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**159**), gas phase cis and trans transition structures, and cis fused and trans fused cycloadducts. The gas phase B3LYP/6-31+G(d) transition structures were located by Prof. M. N. Paddon-Row.*[92]

The C6 methylene group of (**150**) is replaced by an ether oxygen in (**159**) and in the corresponding IMDA transition structures (**159 *cis* TS**) and (**159 *trans* TS**), but the effect of this change is small. Once again, both transition structures exhibit twist mode asynchronicity. The dienophile is twisted 17° in the *endo* direction in the *cis* transition structure (**159 *cis* TS**), and 15° in the *exo* direction in the *trans* transition structure (**159 *trans* TS**). There is residual torsional strain around the C4-C5-O6-C7 dihedral in the *trans* transition structure. The C4-C5 and O6-C7 bonds are staggered (31°) in the *cis* transition structure and eclipsed (7°) in the *trans* transition structure. There are also steric clashes similar to those seen in the parent transition structures (**150 *cis* TS**) and (**150 *trans* TS**), notably between the hydrogens at positions 4 and 8 (2.34 Å) in the *cis* transition structure, and positions 4 and 7 (2.45 Å) in the *trans* transition structure. The tether of triene (**159**) is a little shorter than the tether of the parent compound (**150**) as the C5-O6 and O6-C7 carbon-oxygen bonds (1.43 Å) of (**159**) are slightly shorter than the C5-C6 and C6-C7 carbon-carbon bonds (1.55 Å) of (**150**). As a consequence of the

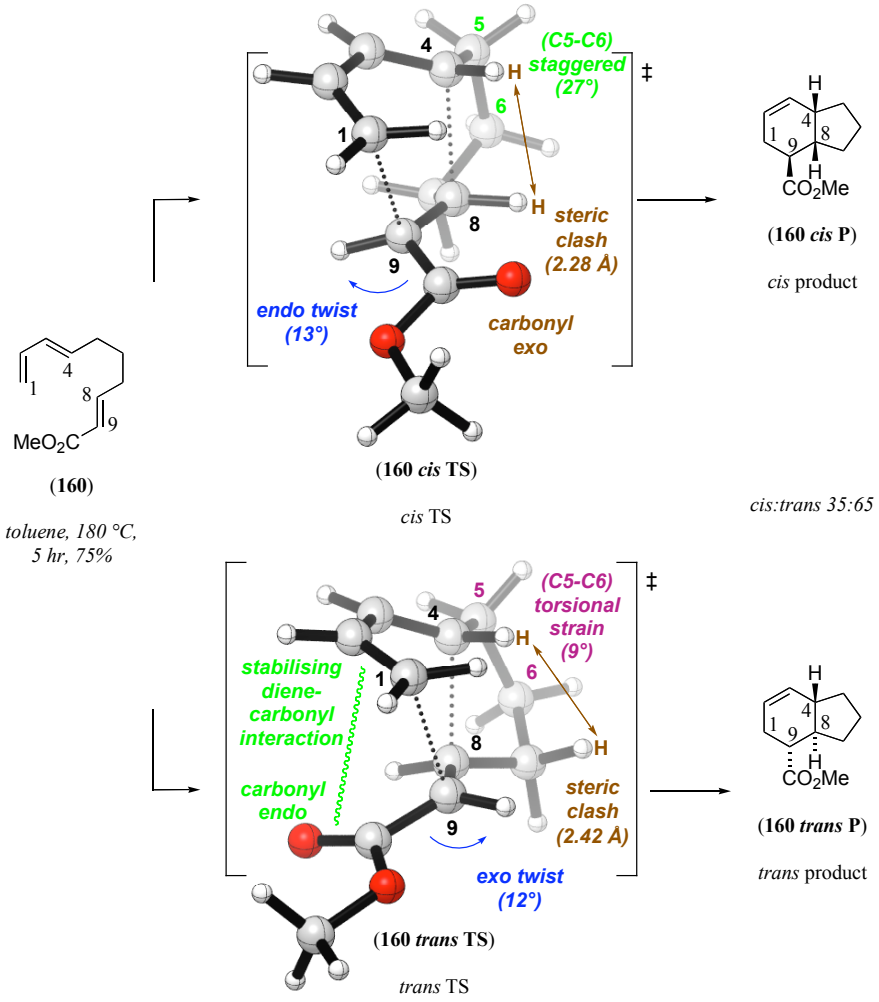
similarities between transition structures (**150 *cis* TS**) and (**150 *trans* TS**), and (**159 *cis* TS**) and (**159 *trans* TS**), this triene undergoes IMDA reaction with the same stereoselectivity as that exhibited by the reaction of the parent 1,3,8-nonatriene (**150**), and again, the difference in energy between the diastereomeric transition structures is approximately 3.5 kJmol^{-1}. [89,142,143]

The Roush group synthesised and studied the IMDA reactions of the terminally activated, trimethylene tethered 1,3,8-nonatrienes (**160**) and (**161**). It was found that the configuration of the dienophile had little influence on the stereochemical outcome of the IMDA reactions; both trienes underwent IMDA reaction with weak *trans* selectivity (**Scheme 3.5**).[144]



Scheme 3.5 *Intramolecular Diels-Alder reactions of trimethylene tethered 1,3,8-nonatrienes (**160**) and (**161**). Conditions: (a) 180 °C, 5 hr, toluene, sealed tube, 75%, (b) 150 °C, 24 hr, toluene, sealed tube, 65%.*

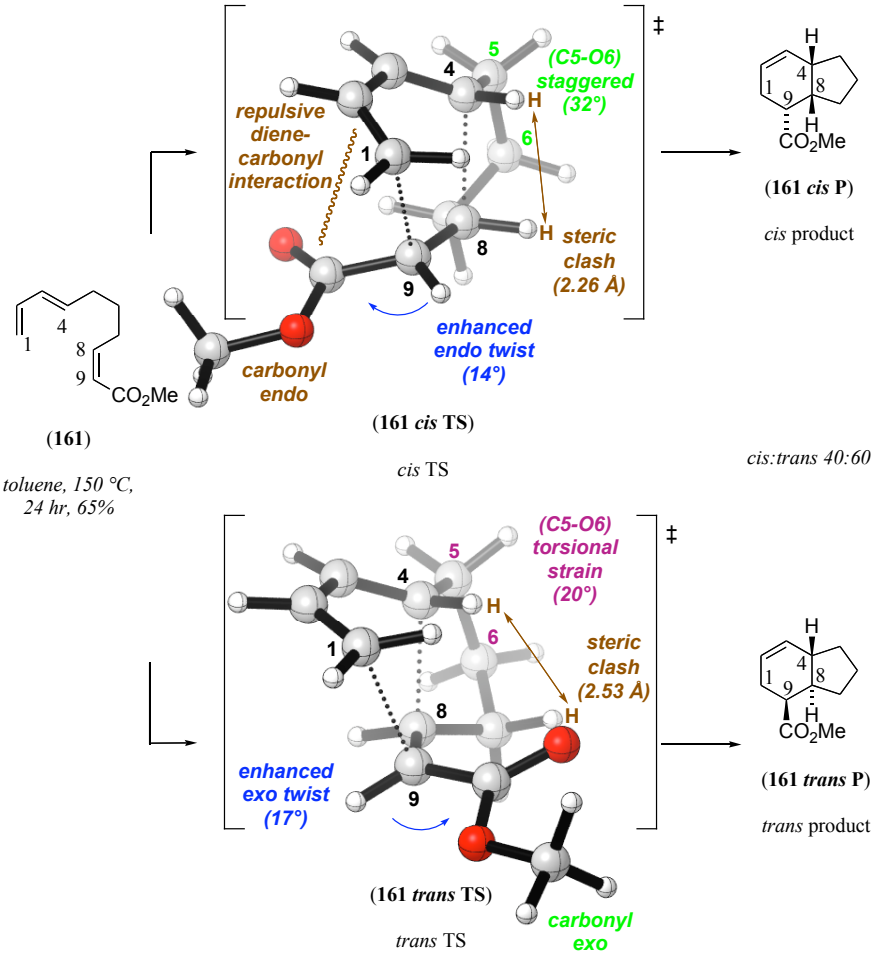
These reactions were investigated computationally by Prof. M. N. Paddon-Row. Calculations revealed that in the IMDA reaction of triene (**160**), the dienophile is twisted 13° in the *endo* direction in the *cis* transition structure (**160 *cis* TS**), and 12° in the *exo* direction in the *trans* transition structure (**160 *trans* TS**) (**Scheme 3.6**).



Scheme 3.6 *Intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**160**), gas phase cis and trans transition structures, and cis fused and trans fused cycloadducts. The gas phase B3LYP/6-31+G(d) transition structures were located by Prof. M. N. Paddon-Row.*[92]

The C4-C5-C6-C7 dihedral angle is 27° in the *cis* transition structure, but only 9° in the *trans* transition structure, and both transition structures exhibit steric clashes, between the hydrogens at positions 4 and 8 in the *cis* transition structure (2.28 Å), and between the hydrogens at positions 4 and 7 in the *trans* transition structure (2.42 Å). The *trans* transition structure is stabilised relative to the *cis* transition structure by a 1,3-diene-carbonyl interaction, which outweighs the energetic penalty associated with residual torsional strain around the C5-C6 bond. The greater stability of the *trans* transition structure (**160 *trans* TS**) is reinforced by the relative magnitudes of the steric clashes in the two transition structures, and the *trans* pathway is favoured by slightly less than 2.0 kJmol^{-1}.

The IMDA reaction of triene (**161**) is weakly *trans* selective, but in this case the terminal carbomethoxy group and tether adopt the *exo* orientation in the energetically favoured *trans* transition structure (**161 *trans* TS**) (**Scheme 3.7**).

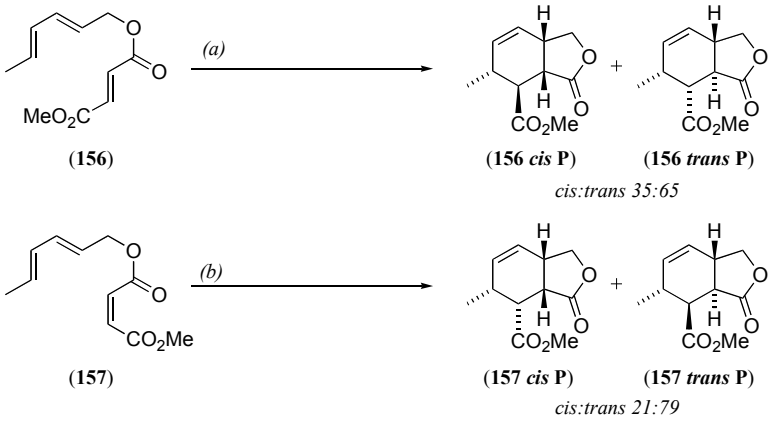


Scheme 3.7 *Intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**161**), gas phase cis and trans transition structures, and cis fused and trans fused cycloadducts. The gas phase B3LYP/6-31+G(d) transition structures were located by Prof. M. N. Paddon-Row.*[92]

The *Z* disposed tether and carbomethoxy group repel one another, and the twist mode asynchronicity of both the *cis* and *trans* transition structures are increased as a result of the repulsion, to 14° in the *endo* direction and 17° in the *exo* direction, respectively. In the *cis* transition structure (**161 *cis* TS**), the enhanced twist mode asynchronicity pushes the carbomethoxy group in the *endo* direction, into a region where destabilising, rather than stabilising, interactions with the 1,3-diene are dominant. In contrast, the enhanced twist mode asynchronicity of the *trans* transition structure (**161 *trans* TS**) pushes the terminal ester substituent further into the *exo* region, where interactions between the 1,3-diene and terminal carbomethoxy group are insignificant. Once again, the *cis*

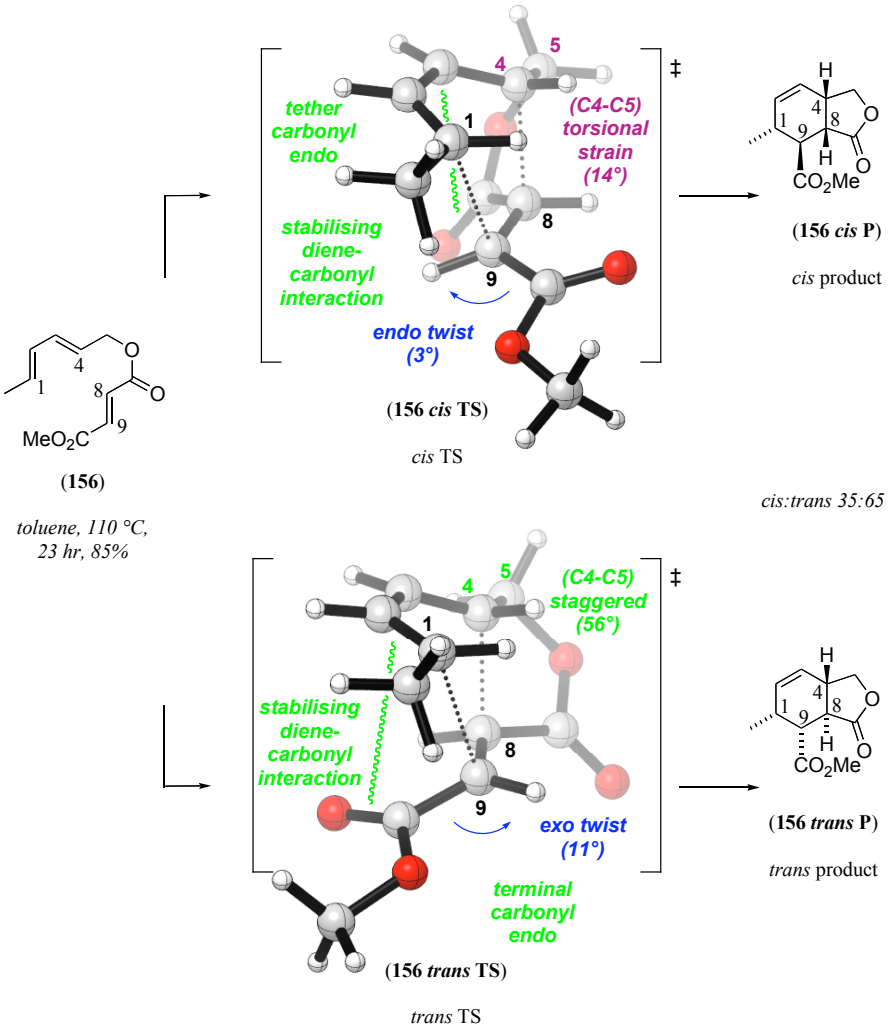
transition structure contains a steric clash between the hydrogens at positions 4 and 8 (2.26 Å), and the *trans* transition structure contains a steric clash between the hydrogens at positions 4 and 7 (2.45 Å). The C4-C5-C6-C7 dihedral angle is 32° in the *cis* transition structure, and 20° in the *trans* transition structure. The favourable staggered arrangement around the C5-C6 bond in the *cis* transition structure (**161 *cis* TS**) does not completely compensate for the destabilising interactions present in this transition structure, namely the repulsive 1,3-diene-carbonyl interaction and the steric clash between hydrogens at positions 4 and 8. In contrast, the *exo* oriented carbonyl group, residual torsional strain at C5-C6, and steric interaction between the hydrogens at positions 4 and 7 in the *trans* transition structure (**161 *trans* TS**) combine to stabilise the *trans* transition structure relative to the *cis* transition structure (**161 *cis* TS**) by approximately 1.3 kJmol^{-1}. The origin of the enhanced twist mode asynchronicity in the *trans* transition structure, and unexpected *trans* selectivity with *Z* configured, terminally substituted 1,3,8-nonatrienes has been named the "*Z* effect."[89]

The Sherburn group have demonstrated that substitution at the 9 position plays an important part in determining IMDA diastereoselectivity in ester linked 1,3,8-nonatriene systems,[92,145] (**Scheme 3.8**) and many these reactions have been studied computationally by Prof. M. N. Paddon-Row.[89]



Scheme 3.8 *Intramolecular Diels-Alder reactions of fumarate and maleate derived 1,3,8-nonatrienes, (**156**) and (**157**), respectively. Conditions: (a) 110 °C, 23 hr, toluene, 85%, (b) 110 °C, 2 hr, toluene, 79%.*

The stereoselectivity of the IMDA reaction of triene (**156**) (**Scheme 3.9**) is a consequence of competition between the two carbonyl groups in this triene for the *endo* orientation relative to the 1,3-diene.

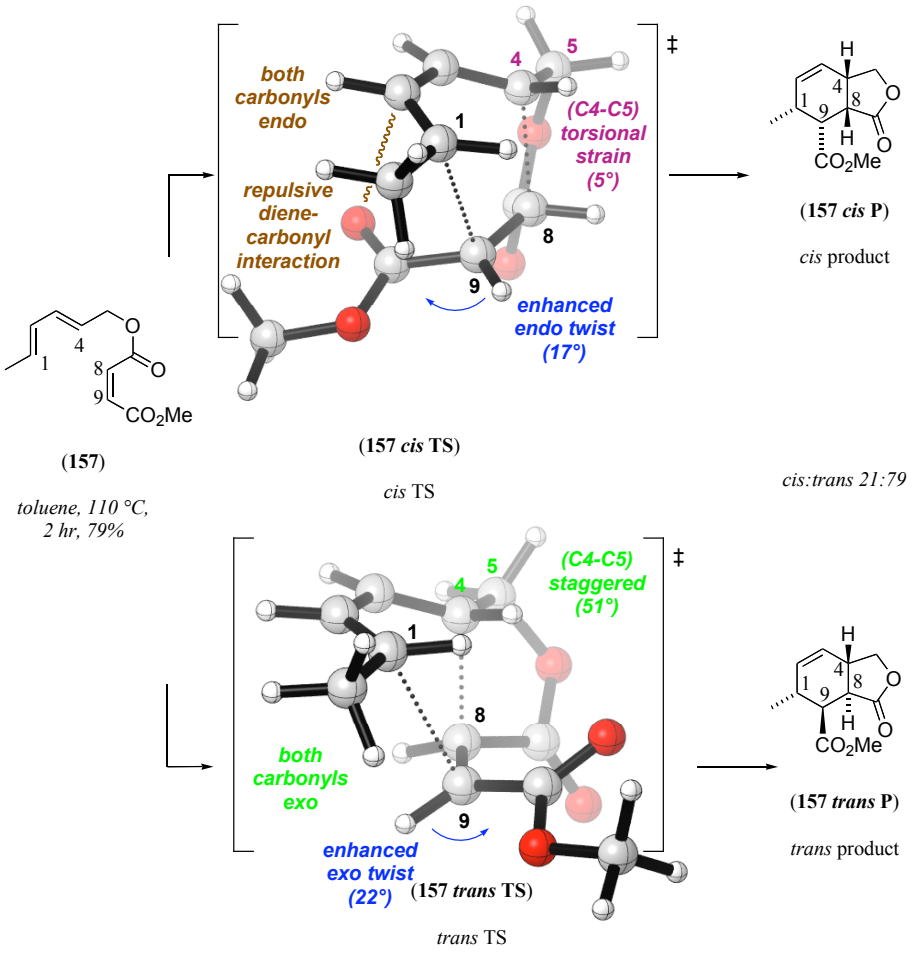


Scheme 3.9 *Intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**156**), gas phase cis and trans transition structures, and cis fused and trans fused cycloadducts. The gas phase B3LYP/6-31+G(d) transition structures were located by Prof. M. N. Paddon-Row.*[92]

The *cis* and *trans* transition structures for this transformation show marked bond forming asynchronicity. The internal developing bonds (C4-C8) are around 2.0 Å in length, while the external developing bonds (C1-C9) are around 2.6 Å in length. The ester tether of (**156**) is more rigid than the trimethylene tethers of (**150**), (**160**) and (**161**), as there is an energetic penalty associated with rotation of the alkoxy bond, and in both the *cis* and *trans* transition structures (**156 *cis* TS**) and (**156 *trans* TS**), respectively, the tether carbonyl group is twisted out of the plane occupied by the C8-C9 π-bond by approximately 30°. In addition, the *cis* transition structure (**156 *cis* TS**) displays little twist mode asynchronicity (3°), and is destabilised relative to the *trans* transition structure by residual torsional strain between C4 and C5, which is also a consequence of the rigidity of the tether. The H4-C4-C5-H5 dihedral angle is 14° in the

cis transition structure, and 56° in the *trans* transition structure. In the *cis* transition structure (**156 *cis* TS**), the tether carbonyl group adopts the *endo* orientation, but the geometrical requirements of the tether prevent it from assuming the optimum orientation for a stabilising interaction with the 1,3-diene, and it points down and away from the face of the 1,3-diene. In the *trans* transition structure (**156 *trans* TS**), however, the terminal carbomethoxy group adopts the *endo* orientation and it has the conformational freedom to maintain coplanarity with the C8-C9 π-bond (∠C8-C9-C=O = 9°) and to optimise the stabilising interaction with the 1,3-diene. In addition, there is a steric clash between the hydrogens at positions 4 and 8 in the *cis* transition structure (2.28 Å), but the steric clash often seen between the hydrogens at positions 4 and 7 in the *trans* transition structure is absent, as position 7 is a carbonyl group in this triene. Thus, the *cis* transition structure (**156 *cis* TS**) is destabilised relative to the *trans* transition structure (**156 *trans* TS**) by torsional strain between C4 and C5, a steric clash between the hydrogens at positions 4 and 8, and a less effective stabilising interaction between the 1,3-diene and the *endo* carbonyl group. These factors combine to favour the pathway leading to the *trans* product (**156 *trans* P**) by slightly under 2.0 $kJmol^{-1}$.[89]

The stereoselectivity of the IMDA reaction of triene (**157**) is remarkable in that the favoured *trans* transition structure (**157 *trans* TS**) is the one in which both carbonyl groups adopt the *exo* orientation relative to the 1,3-diene (**Scheme 3.10**).



Scheme 3.10 *Intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**157**), gas phase cis and trans transition structures, and cis fused and trans fused cycloadducts. The gas phase B3LYP/6-31+G(d) transition structures were located by Prof. M. N. Paddon-Row.*[92]

Once again, both the *cis* and *trans* transition structures (**157 *cis* TS**) and (**157 *cis* TS**), respectively, display marked bond forming asynchronicity. The internal forming bonds (C4-C8) are around 2.0 Å in length, while the external forming bonds (C1-C9) are around 2.7 Å in length. As is the case with triene (**156**), rotation about the alkoxy bond in the ester tether is energetically costly, making the tether quite rigid. This rigidity results in the tether carbonyl group being twisted out of the plane of the C8-C9 π-bond by 45° in both the *cis* and *trans* transition structures, and is the cause of torsional strain between C4 and C5 in the *cis* transition structure. The H4-C4-C5-H5 dihedral angle is 5° in the *cis* transition structure and 51° in the *trans* transition structure. There is a steric clash between the hydrogens at positions 4 and 8 in the *cis* transition structure (2.23 Å), but again the steric clash sometimes seen between the hydrogens at positions 4 and 7 in the *trans* transition structure is absent, as position 7 is occupied by a carbonyl

group in this triene. Steric and electrostatic repulsion between the *Z* disposed terminal carbomethoxy group and the tether carbonyl group enhances the twist mode asynchronicity of both the *cis* and *trans* transition structures, to 17° and 22°, respectively. In the *cis* transition structure (**157 *cis* TS**), the terminal carbomethoxy group is pushed in the *endo* direction, into a region where destabilising, rather than stabilising, interactions between the 1,3-diene and the carbonyl group are dominant. The enhanced twist mode asynchronicity of the *trans* transition structure (**157 *trans* TS**), moves the terminal carbomethoxy group in the *exo* direction, into a region where repulsive interactions with the 1,3-diene are minimal. The *cis* transition structure (**157 *cis* TS**), is destabilised by residual torsional strain between C4 and C5, an unfavourable interaction between the 1,3-diene and the terminal carbonyl group, and a steric clash between the hydrogens at positions 4 and 8, all of which are absent in the *trans* transition structure (**157 *trans* TS**). As a result, the *trans* transition structure is favoured by approximately 4.2 kJmol^{-1}, making the *trans* fused stereoisomer (**157 *trans* P**), the major product of this IMDA reaction.[89]

In this work, the heat and Lewis acid promoted IMDA reactions of the ether tethered trienes (**155**) and (**65**) were studied. One may anticipate the "*Z* effect" to be significant in the IMDA reactions of triene (**65**).

3.1.2 Lewis acid promotion and catalysis

Yates and Eaton were the first to report that DA reactions can be catalysed by Lewis acids.[146] In the original communication, rate accelerations of the DA reactions of anthracene (**62**) with a range of dienophiles including maleic anhydride (**54**), dimethyl maleate (**163**), dimethyl fumarate (**164**), *p*-benzoquinone (**165**), citraconic anhydride (**166**) and dichloromaleic anhydride (**167**) were described.

Lewis acids are chemical species with vacant, low energy atomic or molecular orbitals, which can accept a pair of electrons from suitable electron donors (Lewis bases), to form co-ordination complexes. They can promote or catalyse DA reactions by coordinating to Lewis basic electron withdrawing functional groups in conjugation with the dienophile, thereby lowering the energies of the molecular orbitals of the dienophile (**Figure 3.2**). Complexation of the dienophile by a Lewis acid generally results in an improved match between the LUMO energy of the dienophile and the HOMO energy of

the 1,3-diene, leading to more effective frontier orbital interactions and rate accelerations in normal electron demand DA reactions.[2,147]

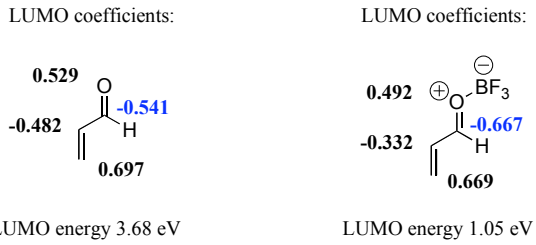


Figure 3.2 *STP-6G//4-31G LUMO coefficients and LUMO energies of acrolein and acrolein-boron trifluoride complex.*[148]

In addition to its effect on the energies of the molecular orbitals, complexation of the dienophile with a Lewis acid alters the distribution of the molecular orbital coefficients in the π-system of the dienophile (**Figure 3.3**). Co-ordination of Lewis acids to the carbonyl groups of α,β-unsaturated carbonyl dienophiles increases the magnitude of the LUMO coefficient at the carbonyl carbon. This effect, combined with the lowering of the LUMO energy of the dienophile, is thought to strengthen the SOI between the carbonyl carbon and the proximal carbon of the 1,3-diene, giving rise to enhanced *endo* stereoselectivity in Lewis acid promoted or Lewis acid catalysed DA reactions, when compared to the corresponding heat promoted DA reactions (**Figure 3.3**).[2,148,149]

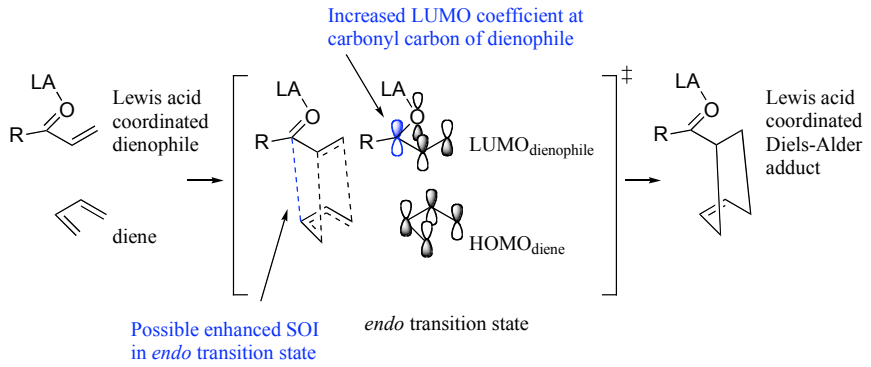


Figure 3.3 *Lewis acid complexation of carbonyl activated dienophiles decreases the dienophile LUMO energy and increases the molecular orbital coefficient at the carbon of the carbonyl group (blue).*

It has also been suggested that the *endo* stereoselectivity commonly observed in the DA reaction is a result of a repulsive electrostatic interaction between the carbon in the carbonyl group of the dienophile and the proximal inside hydrogen of the 1,3-diene in the *exo* transition state.[33] Both of these sites carry partial positive charges, and the

distance between them is greater in the *endo* transition state than in the *exo* transition state. This interaction has been used to rationalise the preferential formation of the *endo* product in kinetically controlled DA reactions (**Figure 3.4**). Further, an electrostatic interaction of this type will be augmented by co-ordination of a Lewis acid to the carbonyl group in question, as this will result in there being a greater partial positive charge at the carbon of the carbonyl group, and a stronger destabilising electrostatic interaction between this site and the inside hydrogen of the 1,3-diene. These ideas have not been thoroughly examined in a computational investigation, but are attractive in their simplicity and ability to account for the *endo* stereoselectivity observed in many DA reactions, and the tendency for Lewis acid promotion or catalysis to enhance *endo* stereoselectivity in DA reactions.

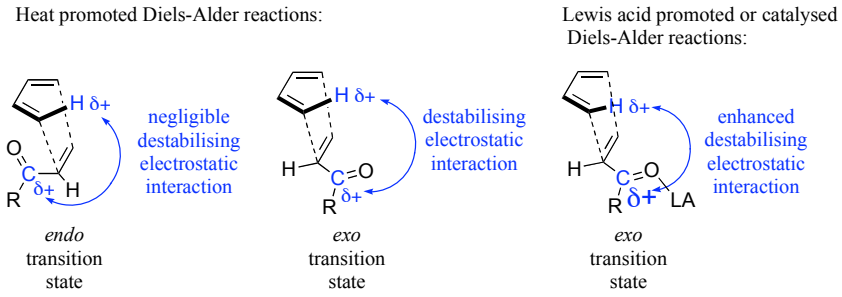


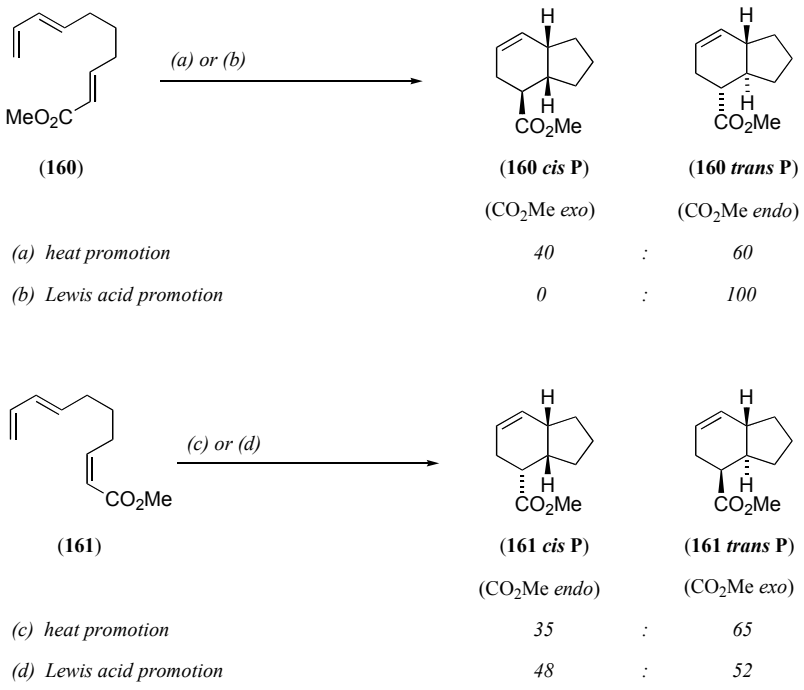
Figure 3.4 *Destabilising electrostatic interactions in the exo transition states of Diels-Alder reactions involving carbonyl activated dienophiles. The destabilising electrostatic interaction between the inside hydrogen of the 1,3-diene and the carbon of the carbonyl group is exacerbated by Lewis acid complexation of the carbonyl group, giving enhanced endo selectivity in Lewis acid promoted and Lewis acid catalysed Diels-Alder reactions.*

Lewis acid promoted and Lewis acid catalysed DA reactions have been studied in considerable detail, and asymmetric Lewis acid catalysed DA reactions have been developed by a number of research groups.[21]

Asymmetric IMDA reactions and diastereoselective IMDA reactions involving stereochemical controllers have also received considerable attention and a small number of examples are discussed here. The Roush group has studied the diastereoselective IMDA reactions of terminally activated chiral 1,3,8-nonatriene menthyl esters, observing variable chemical yields and low diastereoselectivities, and the enantioselective IMDA reactions of achiral, terminally activated 1,3,8-nonatriene methyl esters promoted by chiral bornyloxy and menthyloxy aluminium halide Lewis acids, observing very low asymmetric inductions.[150] The Evans group has studied the

dimethylaluminium chloride promoted IMDA reactions of a range of chiral, terminally activated N-acyloxazolidinone 1,3,8-nonatrienes, observing good chemical yields and diastereoselectivities,[151] and the IMDA reactions of a small number of achiral, terminally activated N-acyloxazolidinone 1,3,8-nonatrienes catalysed by chiral copper (II) complexes, observing high chemical yields and diastereoselectivities, and moderate asymmetric inductions.[152] The Corey group has studied the N-protonated oxazaborolidine catalysed enantioselective IMDA reactions of achiral, terminally activated 1,3,8-nonatrienes, observing good chemical yields, diastereoselectivities and asymmetric inductions.[153] The Yamamoto group has studied the chiral Brønsted acid assisted Lewis acid (BLA) catalysed enantioselective IMDA reaction of an achiral, terminally activated 1,3,8-nonatriene, obtaining the *endo* adduct exclusively, in high yield, with moderate asymmetric induction,[154] and the chiral acyloxyborane (CAB) catalysed enantioselective IMDA reactions of two achiral, terminally activated 1,3,8-nonatrienes, observing good chemical yields and excellent diastereoselectivities, but variable asymmetric inductions.[155]

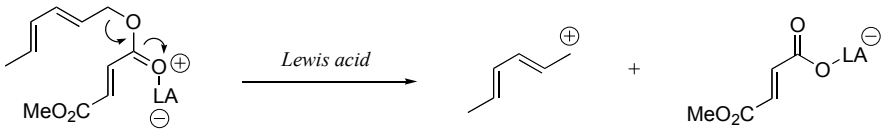
In the early 1980s, alkylaluminium halide Lewis acids were identified by the Roush group as particularly effective promoters of the IMDA reactions of 1,3,8-nonatrienes[150] and 1,3,9-decatrienes.[156] Complexation with alkylaluminium halide Lewis acids increases the IMDA reactivity of terminally activated 1,3,8-nonatrienes (**160**) and (**161**) by several orders of magnitude, allowing their IMDA reactions to be carried out at room temperature rather than at 150 °C to 180 °C **(Scheme 3.11)**.



Scheme 3.11 *Heat and Lewis acid promoted intramolecular Diels-Alder reactions of terminally activated 1,3,8-nonatrienes studied by the Roush group. Conditions: (a) toluene, sealed tube, 150 °C, 24 hr, cis:trans = 40:60, 65%; (b) Et_2AlCl (0.9 molar equiv.) CCl_4 23 °C, 36 hr, cis:trans = 0:100, 60% (c) toluene, sealed tube, 180 °C, 5 hr, cis:trans = 35:65, 75%; (d) Et_2AlCl (1.0 molar equiv.) CCl_4 23 °C, 40 hr, cis:trans = 48:52, 72%.*[150]

In the case of triene (**160**), where the *endo* stereoselectivity observed in the thermal IMDA reaction is enhanced by Lewis acid promotion, the Lewis acid promoted IMDA reaction gave the *endo* cycloadduct (**160 *trans* P**) exclusively. In the case of triene (**161**), the stereoselectivity is influenced by the "*Z* effect." The major product of the thermal reactions is the *exo* stereoisomer, and the Lewis acid promoted IMDA reactions gave roughly a one to one mixture of the *endo* and *exo* products (**161 *cis* P**) and (**161 *trans* P**), respectively.

The Sherburn group has recently carried out a detailed investigation of the IMDA reactions of ethylene-tethered and benzo-tethered, ester linked 1,3,9-decatrienes, using aluminium Lewis acids as either stoichiometric promoters or catalysts.[157] Previously, the Sherburn group had established that Lewis acid promotion of the IMDA reactions of ester linked 1,3,8-nonatrienes (**156**) and (**157**) was problematic, as the ester tethers are readily cleaved by the promoters, generating resonance stabilised pentadienyl cations of the type (**168**) by the mechanism shown (**Scheme 3.12**).[158] Similar behaviour in related systems has also been described by the Roush group[150] and the Toyota group.[159]



(**156**) (**168**) (**169**)

Scheme 3.12 *Lewis acid mediated cleavage of an ester linked 1,3,8-nonatriene (**160**).*

Aluminium tris(2,6-diphenylphenoxide) (ATPH) (**49**) is a sterically hindered aluminium Lewis acid developed by the Yamamoto group, which has been used to promote *exo* selective DA and IMDA reactions (**Figure 3.5**).[72,157]

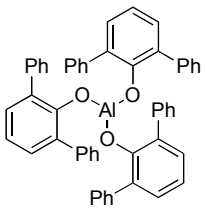


Figure 3.5 *Chemical structure of ATPH.*

The 2,6-diphenylphenoxide ligands crowd the aluminium centre, adopting a propeller-like arrangement and creating a pocket in which Lewis bases can co-ordinate to the metal. NMR experiments with the *iso*-propenyl methyl ketone - APTH complex showed that the ketone adopts the *s-trans* conformation and experiences substantial magnetic shielding from adjacent phenyl substituents when co-ordinated to the aluminium centre.

The Yamamoto group posit that co-ordinated dienophiles participate in a π-stacking interaction with one of the diphenylphenoxide ligands, and that the *endo* approach of 1,3-dienes to co-ordinated dienophiles is blocked by an adjacent phenyl group (**Figure 3.6**).

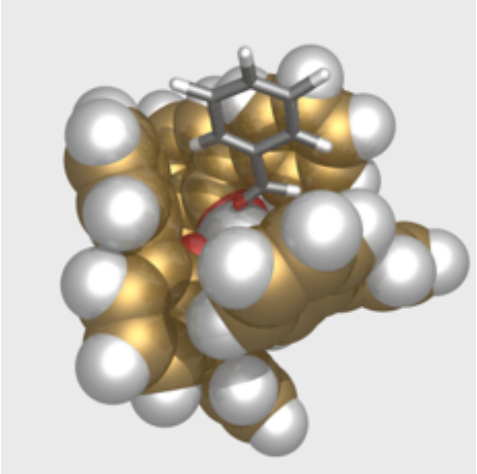
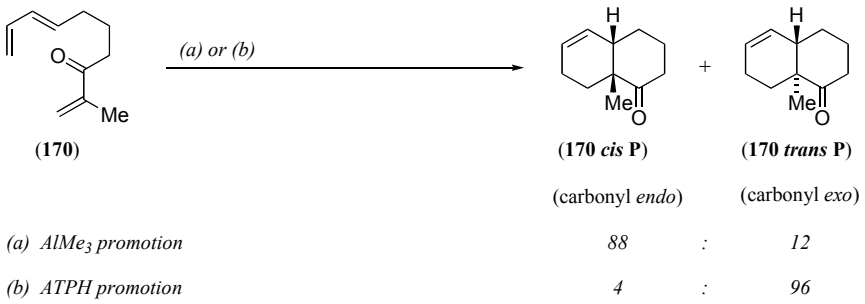


Figure 3.6 *Space filling model of ATPH benzaldehyde complex.*

The Yamamoto group reported that the promotion of the IMDA reaction of an internally activated 1,3,9-decatriene (**170**), with trimethylaluminium, a sterically unencumbered Lewis acid, and ATPH (**49**), gave synthetically useful yields of the *endo* and *exo* products, respectively (**Scheme 3.13**).



Scheme 3.13 *$AlMe_3$ and ATPH promoted intramolecular Diels-Alder reactions of triene (**170**).*[72] *Conditions (a) $AlMe_3$ (unspecified quantity), CH_2Cl_2, -78 °C to 0 °C, 75%; (b) ATPH (**49**) (1.1 mol. equiv.) CH_2Cl_2, -78 °C to 0 °C, 69%.*

The prospect of controlling the stereochemical outcomes of type 1 IMDA reactions by judicious choice of Lewis acid catalysts or promoters is very attractive. In principle, this can allow a single triene to be selectively transformed into either the *cis* fused adduct or the *trans* fused adduct, depending on the nature of the Lewis acid catalyst or promoter used.

The Sherburn group has investigated the IMDA reactions of a set of ten ester linked 1,3,9-decatrienes, using diethylaluminium chloride (**171**) and ATPH (**49**) as Lewis acid promoters.[157] Unlike the example reported by the Yamamoto group, in which

synthetically useful and complementary stereoselectivities were observed with ATPH (**49**) promotion and trimethylaluminium promotion,[72] the effects of the Lewis acid promoters on these IMDA reactions were rather modest. In most instances, the apposite Lewis acid promoter was able to enhance the selectivity observed in the thermal IMDA reactions, but no synthetically useful reversals in stereoselectivity were observed. In addition, in three of the ten cases, ATPH (**49**) promotion unexpectedly resulted in enhanced *endo* selectivity when compared to the corresponding heat promoted IMDA reactions.

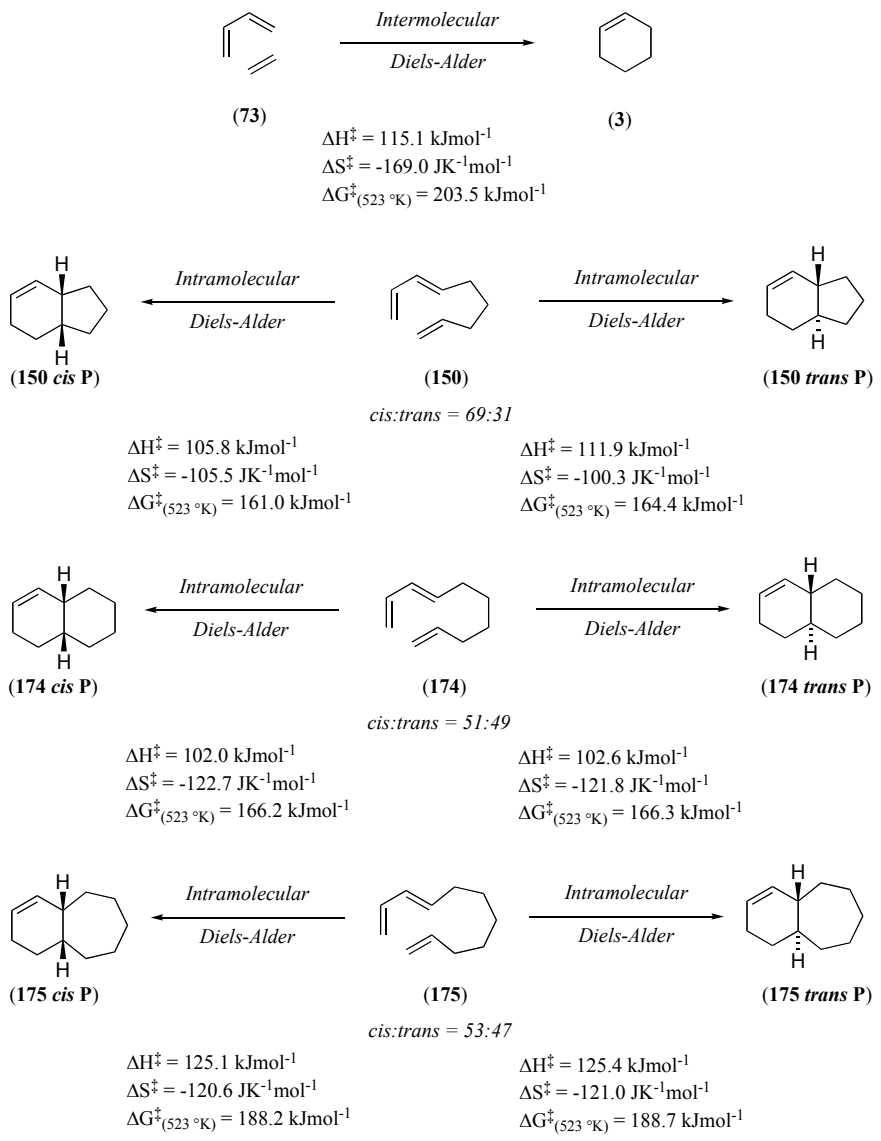
3.1.3 Thermodynamics and kinetics of the intramolecular Diels-Alder reaction

The thermodynamic driving force in an IMDA reaction is the same as that of an intermolecular DA reaction; the net conversion of two carbon-carbon π-bonds to two carbon-carbon σ-bonds. Both reactions are exergonic and strongly exothermic, and both have negative entropies of reaction (ΔS_R). In the intermolecular DA reaction, the negative entropy of reaction (ΔS_R) is a consequence of forming a single, cyclic product from two acyclic reactant molecules. In the IMDA reaction, it is a consequence of forming a fused, bicyclic product from a single acyclic precursor molecule.[2,160,161]

The activation barriers of IMDA reactions are determined by the nature and substitution pattern of the IMDA precursor, but the enthalpic component ($\Delta H^{\ddagger}$) is largely a consequence of a sharp rise in the magnitude of closed shell repulsions as the reaction co-ordinate approaches the transition state. These are quickly overwhelmed by the energetic benefits of bond formation and geometrical reorganisation beyond the transition state.[162] IMDA reactions generally exhibit less negative entropies of activation ($\Delta S^{\ddagger}$) than the corresponding intermolecular DA reactions, significantly reducing the free energy of activation ($\Delta G^{\ddagger}$) of the intramolecular processes relative to the intermolecular processes. This allows many IMDA reactions to be carried out under milder conditions than the analogous intermolecular DA reactions, with a corresponding increase in stereoselectivity for a given $\Delta\Delta G^{\ddagger}$ between competing reaction pathways.[2,9,163,164]

The chemical literature contains a number of kinetic studies involving IMDA reactions, which are summarised in the following pages. A variety of triene architectures have been examined, including precursors to type one and type two IMDA reactions, and almost every study has examined the effect of tether substitution on the rates of IMDA

reactions. The reactive rotamer and Thorpe-Ingold effects[51] are discussed relatively frequently in the references. The stereoselectivities and gas phase kinetics of the IMDA reactions of the parent trienes, 1,3,8-nonatriene (**150**), 1,3,9-decatriene (**174**) and 1,3,10-undecatriene (**175**) were the subject of an experimental and computational study by the Houk and Klarner groups (**Scheme 3.14**).

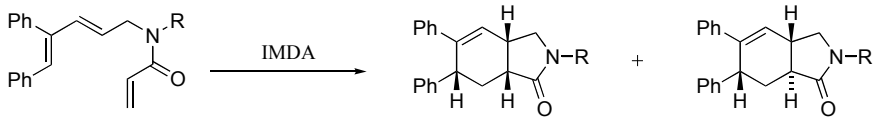


Scheme 3.14 *Gas phase experimental activation parameters for the Diels-Alder reaction of 1,3-butadiene with ethylene, giving cyclohexene,[161,165] and gas phase experimental activation parameters and stereoselectivities for the intramolecular Diels-Alder reactions of 1,3,8-nonatriene (**150**), 1,3,9-decatriene (**174**) and 1,3,10-undecatriene (**175**) at 523 °K, giving cis fused and trans fused adducts.[164]*

Experimentally, it was found that the IMDA reactions have enthalpic barriers comparable to that of the intermolecular DA reaction of 1,3-butadiene with ethylene,

but that the intramolecular processes are entropically favoured compared to the intermolecular reaction by between 45 and 70 $JK^{-1}mol^{-1}$. This entropic effect corresponds to a lowering of the free energy of activation ($\Delta G^{\ddagger}$) of between 25 and 37 $kJmol^{-1}$ at 250 °C. As a consequence, the absolute activation barriers of the IMDA reactions of all three trienes (**150**), (**174**) and (**175**), are significantly smaller than that of the intermolecular DA reaction. The activation barriers of the IMDA reactions of 1,3,10-undecatriene (**175**), giving both the *cis* fused and *trans* fused products (**175 *cis* P**) and (**175 *trans* P**), respectively, are 22 to 28 $kJmol^{-1}$ higher than those of the intramolecular reactions of the other trienes (**150**) and (**174**), due primarily to the relatively high enthalpies of activation ($\Delta H^{\ddagger}$) of the cycloadditions of (**175**).[164,166]

The Gschwend group has studied the rates of the IMDA reactions of a group of pentadienyl acrylamides carrying a range of alkyl groups on the amide nitrogen (**176a**) to (**176d**) (**Scheme 3.15**). Triene (**1**) gave 49:51 mixture of the *cis* fused and *trans* fused IMDA adducts. The stereoselectivities of the other IMDA reactions were not reported. The enthalpies of activation ($\Delta H^{\ddagger}$) ranged from 87.8 to 103.3 $kJmol^{-1}$ and the entropies of activation ($\Delta S^{\ddagger}$) ranged from -56.1 to -88.7 $JK^{-1}mol^{-1}$. There was no clear pattern in the enthalpy of activation or entropy of activation data, but the free energies of activation ($\Delta G^{\ddagger}$) decreased with increasing size of the substituent, from 120.1 to 105.9 $kJmol^{-1}$ along the series from (**176a**) to (**176d**).[167]



(**176a**) R= CH_3
(**176b**) R= CH_2CH_3
(**176c**) R= $CH(CH_3)_2$
(**176d**) R= $C(CH_3)_3$

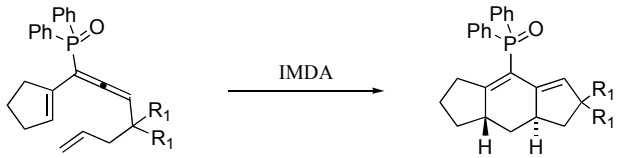
(**176a *cis* P**) R= CH_3
(**176b *cis* P**) R= CH_2CH_3
(**176c *cis* P**) R= $CH(CH_3)_2$
(**176d *cis* P**) R= $C(CH_3)_3$

(**176a *trans* P**) R= CH_3
(**176b *trans* P**) R= CH_2CH_3
(**176c *trans* P**) R= $CH(CH_3)_2$
(**176d *trans* P**) R= $C(CH_3)_3$

Scheme 3.15 *Intramolecular Diels-Alder reactions studied by the Gschwend group.*

The Okamura group studied the IMDA reactions of a number of tether substituted allenyl phosphine oxides, calculating thermodynamic activation parameters for the IMDA reactions of (**177a**), (**177b**) and (**177c**) (**Scheme 3.16**). Each of these trienes gave a single IMDA adduct. Once again, while the was no discernable trend in enthalpy of activation ($\Delta H^{\ddagger}$) or entropy of activation ($\Delta S^{\ddagger}$) data, the free energies of activation ($\Delta G^{\ddagger}$) decreased gradually from 100.0 to 92.5 $kJmol^{-1}$ through the series (**177a**) to

(**177c**). The authors stated that the activation parameters reflected a complex combination of small factors, which were difficult to interpret in chemical terms.[168]

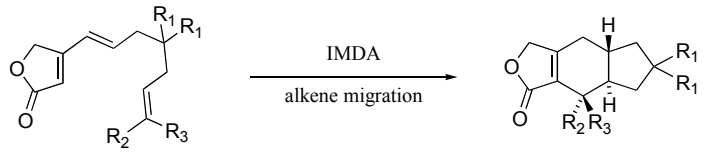


(**177a**) R_1 = H
(**177b**) R_1 = Me
(**177c**) R_1 = Et

(**177a P**) R_1 = H
(**117b P**) R_1 = Me
(**177c P**) R_1 = Et

Scheme 3.16 *Intramolecular Diels-Alder reactions studied by the Okamura group.*

The Boeckman group have studied the IMDA reactions of a set of trienes with varied substitution patterns in the tether and at the dienophile (**Scheme 3.17**), determining product stereochemistries and measuring rate constants at 110 °C. It was found that the IMDA reaction of each triene was followed by alkene migration, and exclusively gave the adduct containing a *trans* fused ring junction between the newly formed five and six membered rings. Geminal dimethyl substitution in the tether increased the rate of IMDA reaction by approximately four, which the authors assumed corresponds to a decrease in the entropy of activation ($\Delta S^{\ddagger}$) of around 12.5 $JK^{-1}mol^{-1}$. The relationship between geminal dimethyl substitution in the tether of a triene and the entropy of activation ($\Delta S^{\ddagger}$) of its IMDA reaction is by no means certain, however, as thermodynamic activation parameters were not obtained in this study. In a number of cases, the authors observed that steric interactions between the electron withdrawing groups appended to the dienophile forced one of those groups to rotate out of the plane occupied by the dienophilic alkene, diminishing the conjugative interaction with the alkene and the IMDA reactivity of the triene. The relative rates of reaction in toluene-d_8 at 110 °C are (**178g**) 1; (**178b**) 2.1; (**178a**) 8.6; (**178e**) 10.6; (**178c**) 20.0; (**178d**) 33.6; (**178f**) 88.7; (**178i**) 169.4; (**178h**) 286.7.[169]

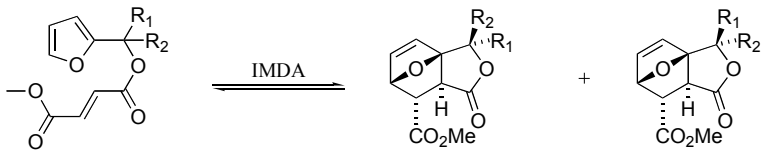


(**178a**) R_1 = H, R_2 = CO_2Me, R_3 = CO_2Me
(**178b**) R_1 = H, R_2 = CO_2Me, R_3 = H
(**178c**) R_1 = H, R_2 = CO_2t-Bu, R_3 = CN
(**178d**) R_1 = Me, R_2 = CO_2Me, R_3 = CO_2Me
(**178e**) R_1 = Me, R_2 = CO_2Me, R_3 = H
(**178f**) R_1 = Me, R_2 = CO_2t-Bu, R_3 = CN
(**178g**) R_1 = Me, R_2 = CN, R_3 = H
(**178h**) R_1 = Me, R_2 = CN, R_3 = CN
(**178i**) R_1 = Me, R_2 = CO_2Me, R_3 = CN

(**178a P**) R_1 = H, R_2 = CO_2Me, R_3 = CO_2Me
(**178b P**) R_1 = H, R_2 = CO_2Me, R_3 = H
(**178c P**) R_1 = H, R_2 = CO_2t-Bu, R_3 = CN
(**178d P**) R_1 = Me, R_2 = CO_2Me, R_3 = CO_2Me
(**178e P**) R_1 = Me, R_2 = CO_2Me, R_3 = H
(**178f P**) R_1 = Me, R_2 = CO_2t-Bu, R_3 = CN
(**178g P**) R_1 = Me, R_2 = CN, R_3 = H
(**178h P**) R_1 = Me, R_2 = CN, R_3 = CN
(**178i P**) R_1 = Me, R_2 = CO_2Me, R_3 = CN

Scheme 3.17 *Intramolecular Diels-Alder reactions studied by the Boeckman group.*

The Jung group has used the IMDA reaction to probe the relative magnitudes of the reactive rotamer and Thorpe-Ingold effects,[170] using the reversible IMDA reactions of trienes containing a furan 1,3-diene and carrying varying substituents at the tether (**Scheme 3.18**). All trienes gave exclusively the IMDA adducts in which the tether carbonyl group adopted the *exo* orientation. Triene (**179e**) gave a 1:1 mixture of diastereomers at the stereocentre carrying the methyl group, and triene (**179f**) gave a 20:1 mixture of diastereomers at the stereocentre carrying the *tert*-butyl group. The diastereomers obtained from trienes (**179e**) and (**179f**) were not assigned structures. Thermodynamic activation parameters were obtained for the trienes shown, and it was found that the observed variation in IMDA reactivity was almost entirely enthalpic in origin, refuting the assumption[169] that the *gem*-dialkyl effect is entropic in nature. The relative rates of the IMDA reactions were (**197a**) 1; (**179f**) 8.32; (**179e**) 8.35; (**179e**) 10.5; (**179d**) 208; (**179b**) 2123. This study also found that the reactive rotamer effect was more important than the Thorpe-Ingold effect in enhancing IMDA reactivity in tether substituted trienes.[171,172]



(**179a**) R_1= R_2 = H
(**179b**) R_1= R_2 = Me
(**179c**) R_1= R_2 = -$(CH_2)_2$-
(**179d**) R_1= R_2 = -$(CH_2)_3$-

(**179e**) R_1= Me, R_2 = H
(**179f**) R_1= *t*-Bu, R_2 = H

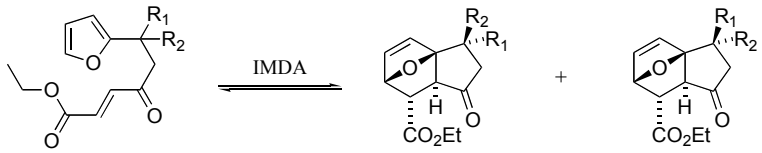
(**179a P**) R_1= R_2 = H
(**179b P**) R_1= R_2 = Me
(**179c P**) R_1= R_2 = -$(CH_2)_2$-
(**179d P**) R_1= R_2 = -$(CH_2)_3$-

(**179e P1**) R_1= Me, R_2 = H
(**179f P1**) R_1= *t*-Bu, R_2 = H

(**179e P2**) R_1= Me, R_2 = H
(**179f P2**) R_1= *t*-Bu, R_2 = H

Scheme 3.18 *Intramolecular Diels-Alder reactions studied by the Jung group.*

Another study by the Jung group investigated the reversible IMDA reactions of three tether substituted 6-furylhexenoates (**Scheme 3.19**).[173] Data from the study discussed above[172] allowed the relationship between tether substitution and composition, and IMDA reaction rates to be explored. Rate constant data were reported, but IMDA stereoselectivities and thermodynamic activation parameters were not reported. The authors found that the rates of the IMDA reactions of three ester tethered trienes (**179a**), (**179b**) and (**179e**) (**Scheme 3.18**), were more sensitive to alkyl substitution in the tether than those of the corresponding ketone tethered trienes (**180a**) to (**180c**).



(**180a**) $R_1 = R_2 = H$
(**180b**) $R_1 = R_2 = Me$

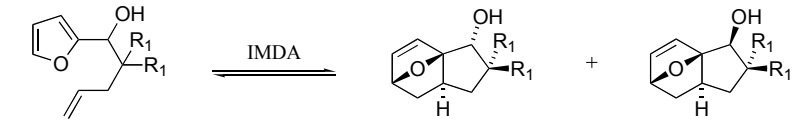
(**180a P**) $R_1 = R_2 = H$
(**180b P**) $R_1 = R_2 = Me$

(**180c**) $R_1 = Me$, $R_2 = H$

(**180c P1**) $R_1 = Me$, $R_2 = H$ (**180c P2**) $R_1 = Me$, $R_2 = H$

Scheme 3.19 *Intramolecular Diels-Alder reactions studied by the Jung group.*

The Sternbach group have studied the effects of tether substitution on the rates and equilibria of the reversible IMDA reactions of a set of trienes containing furan 1,3-dienes and unactivated dienophiles (**Scheme 3.20**). IMDA stereoselectivity was not discussed, and it appears the authors assumed the tether adopted the *exo* orientation with respect to the 1,3-diene in every IMDA reaction. Once again, the trienes studied carried varied substituents at the tether, and the rate constants obtained in this study were discussed in terms of the Thorpe-Ingold and reactive rotamer effects. The authors found a number of small factors contributed to the rate differences between trienes. Properties of the trienes which disfavoured unreactive rotamers without increasing eclipsing interactions were identified as important. The relative rates of the IMDA reactions were (**181c**) 1; (**181d**) 1.8; (**181e**) 4.1; (**181f**) 4.8; (**181g**) 9.8.[174]



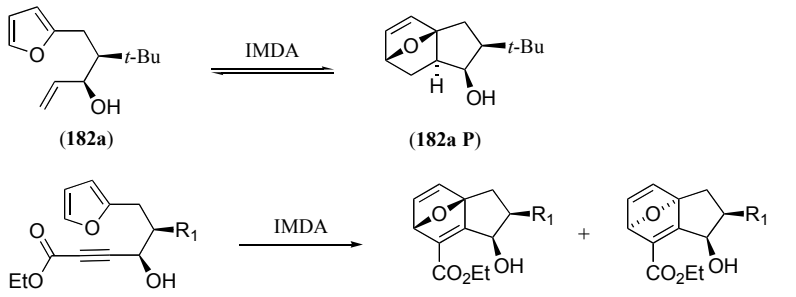
(**181a**) R_1 = H
(**181b**) R_1= Me
(**181c**) R_1= -$(CH_2)_5$-
(**181d**) R_1= Pr
(**181e**) R_1= -$S(CH_2)_3S$-
(**181f**) R_1= SCH_2CH_3
(**181g**) R_1= OCH_2CH_3

(**181a P1**) R_1 = H
(**181b P1**) R_1= Me
(**181c P1**) R_1= -$(CH_2)_5$-
(**181d P1**) R_1= Pr
(**181e P1**) R_1= -$S(CH_2)_3S$-
(**181f P1**) R_1= SCH_2CH_3
(**181g P1**) R_1= OCH_2CH_3

(**181a P2**) R_1 = H
(**181b P2**) R_1= Me
(**181c P2**) R_1= -$(CH_2)_5$-
(**181d P2**) R_1= Pr
(**181e P2**) R_1= -$S(CH_2)_3S$-
(**181f P2**) R_1= SCH_2CH_3
(**181g P2**) R_1= OCH_2CH_3

Scheme 3.20 *Intramolecular Diels-Alder reactions studied by the Sternbach group.*

The de Clercq group have obtained rate constants for the IMDA reactions of three tether substituted trienes containing furan 1,3-dienes (**Scheme 3.21**). The IMDA reaction of triene (**182a**) is reversible in benzene at 80 °C, and gave exclusively the IMDA adduct (**182a P**). The IMDA reactions of trienes (**182b**) and (**182c**) are not reversible in benzene at 80 °C. Triene (**182b**) gave a mixture of adducts (**182b P1**) and (**182b P2**), the major product being (**182b P2**), and triene (**182c**) gave exclusively adduct (**182c P**). The relative rates of the IMDA reactions of these trienes in benzene solution at 80 °C were (**182b**) 1.00; (**182a**) 14.7; (**182c**) 237. The authors stated that the origin of the large rate enhancement with triene (**182c**) could not be identified without more detailed kinetic data.[175]



(**182a**)

(**182a P**)

(**182b**) R_1 = H
(**182c**) R_1= *t*-Bu

(**182b P1**) R_1 = H

(**182b P2**) R_1 = H
(**182c P**) R_1= *t*-Bu

Scheme 3.21 *Intramolecular Diels-Alder reactions studied by the de Clercq group.*

In a related study, the de Clercq group compared the IMDA reactions of trienes (**183a**) and (**183b**) (**Scheme 3.22**). Each IMDA reaction gave a single product diastereomer, but the relative stereochemistry of the oxa-bridge with respect to the *tert*-butyl group in adduct (**183a P**) was not determined. The relative rates of the IMDA reactions of these trienes in *o*-xylene solution at 90 °C were (**183a**) 1.00 and (**183b**) 61.4, and thermodynamic activation parameters for the IMDA reaction of the more reactive

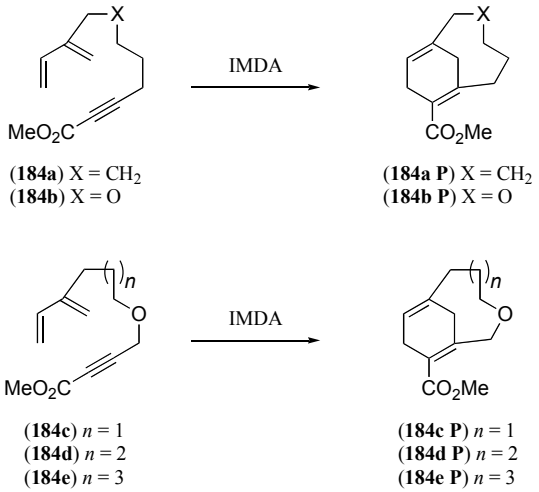
triene, (**183b**), were obtained. The enthalpy of activation ($\Delta H^{\ddagger}$) and the entropy of activation ($\Delta S^{\ddagger}$) for this transformation are 83.9 $kJmol^{-1}$ and -71.1 $JK^{-1}mol^{-1}$, respectively. The authors remarked that as the entropy of activation is quite large for an IMDA reaction, it appears the enhanced reactivity of this triene is unlikely to be due to entropic effects.

(**183a**) R_1 = H
(**183b**) R_1= OH

(**183a P**) R_1 = H
(**183b P**) R_1= OH

Scheme 3.22 *Intramolecular Diels-Alder reactions studied by the de Clercq group.*

The Shea group has studied the IMDA reactions of five type two trienes, (**184a**), (**184b**), (**184c**), (**184d**) and (**184e**), obtaining rate constants and thermodynamic activation parameters for each transformation (**Scheme 3.23**). The free energy of activation ($\Delta G^{\ddagger}$) of each of these IMDA reactions is significantly higher than those observed for type one trienes carrying activating groups at the dienophile. The IMDA reactions of trienes (**184a**) and (**184b**) have almost identical thermodynamic activation parameters; enthalpies of activation ($\Delta H^{\ddagger}$) of 109 $kJmol^{-1}$, entropies of activation ($\Delta S^{\ddagger}$) of 121 $JK^{-1}mol^{-1}$, and free energies of activation ($\Delta G^{\ddagger}$) of 168 $kJmol^{-1}$. There was no clear pattern in the enthalpy of activation or entropy of activation data, and the relationship between entropy of activation and tether length in the IMDA reactions of otherwise similar trienes was complex. The free energies of activation, ($\Delta G^{\ddagger}$), do increase from 151 $kJmol^{-1}$ to 159 $kJmol^{-1}$ with increasing tether length along the series (**184c**), (**184d**), (**184e**).[176]



(**184a**) X = CH_2 (**184a P**) X = CH_2
(**184b**) X = O (**184b P**) X = O

(**184c**) *n* = 1 (**184c P**) *n* = 1
(**184d**) *n* = 2 (**184d P**) *n* = 2
(**184e**) *n* = 3 (**184e P**) *n* = 3

Scheme 3.23 *Type two intramolecular Diels-Alder reactions studied by the Shea group.*

IMDA reactivity has been investigated by number of research groups using a diverse array of trienes. The parent trienes (**150**), (**174**) and (**175**) were the subject of a detailed study by the Houk and Klarner groups,[164] but many other studies have been very limited in scope and applicability.[167-169] In some cases, IMDA adducts were not assigned structures,[175] only rate constant data were obtained,[169,175] or the IMDA reactions studied were reversible under the chosen reaction conditions.[172,174] Most groups have examined the effect of tether substitution on reactivity, with mixed and sometimes conflicting results. One group assumed the *gem*-dialkyl effect was entropic in nature,[169] another found it was almost entirely enthalpic in nature,[171,172] and a third found it was neither entropic nor enthalpic in nature.[168] Missing from the literature are thorough and systematic investigations of the IMDA reactions of easily synthesised and synthetically useful 1,3,8-nonatrienes.

3.1.4 Rate studies involving 1,3,8-nonatrienes

In collaboration with Prof. M. N. Paddon-Row, we are interested in developing the computational tools needed to predict the stereoselectivities and activation barriers of the IMDA reactions of 1,3,8-nonatrienes, as this approach has the potential to eliminate many of the uncertainties currently hampering the use of these reactions in chemical synthesis. After having considerable success predicting IMDA stereoselectivities using DFT modelling,[89,92] attention moved to the prediction of IMDA activation barriers.[92,177]

Whereas the successful prediction of IMDA stereoselectivities requires the accurate evaluation of relative activation barriers, successful prediction of IMDA reactivities

requires the accurate evaluation of absolute activation barriers, which is a considerably more challenging objective. The IMDA reactions of five trienes (**155**), (**65**), (**156**), (**157**) and (**158**) (**Scheme 3.24**) were modelled by Prof. M. N. Paddon-Row using the B3LYP/6-31+G(d) level of theory, and the IMDA reactions of the three ester tethered trienes, (**156**), (**157**) and (**158**), were the subjects of rate studies carried out within the Sherburn group.[92,177]

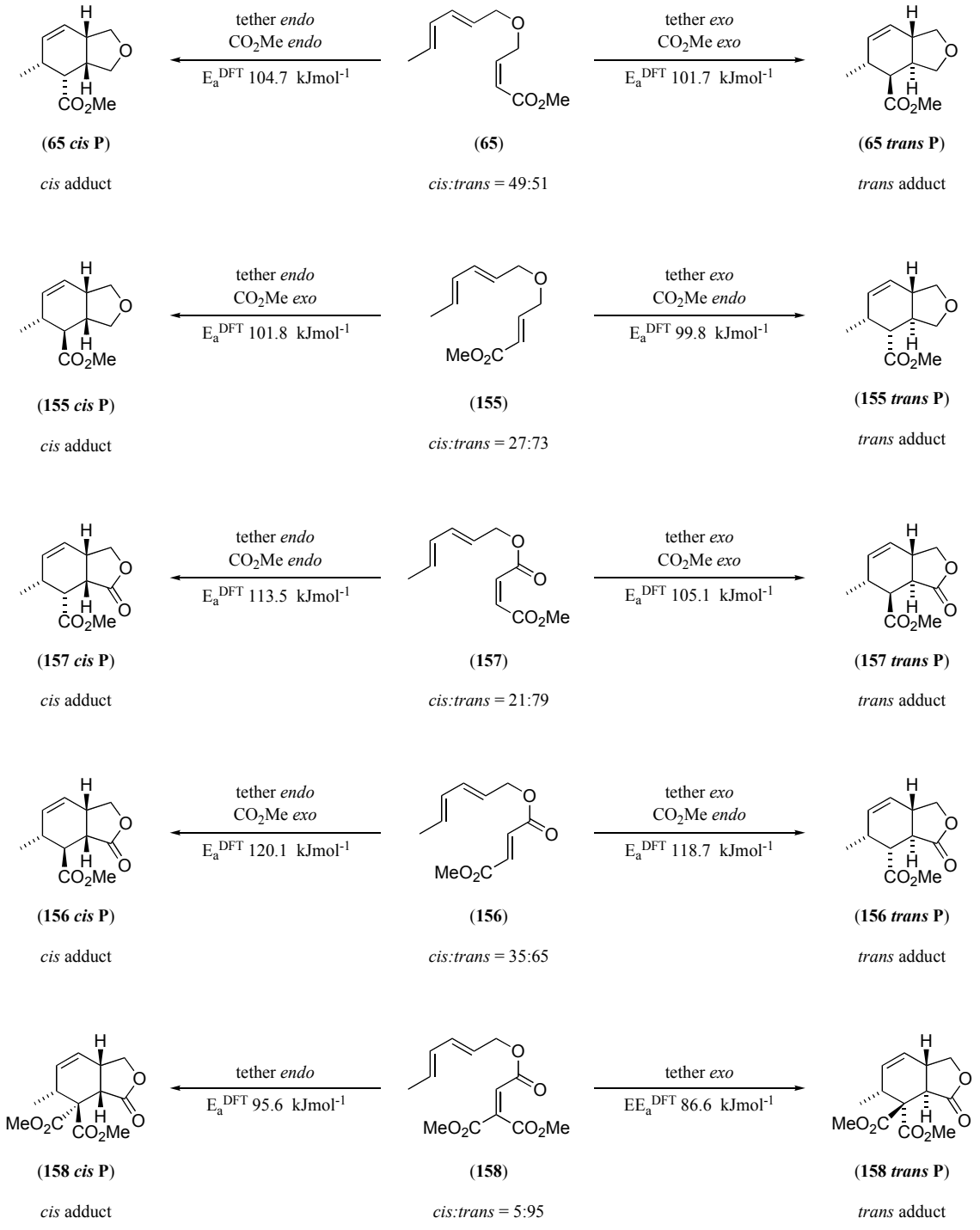


Figure 3.24 *B3LYP/6-31+G(d) calculated cis and trans intramolecular Diels-Alder activation barriers for a series of 1,3,8-nonatrienes studied within the Sherburn group.*[178]

These rate studies found that the uncatalysed IMDA reactions of the three ester tethered 1,3,8-nonatrienes (**156**), (**157**), and (**158**), were simple unimolecular processes which obeyed first order kinetics. Each rate study was carried out in a non-polar solvent, at five experimental temperatures, employing high dilution to minimise oligomerisation of the trienes through intermolecular DA processes. The consumption of the trienes and

production of the IMDA adducts was monitored by ^{1}H NMR spectroscopy relative to an internal standard.[160,177]

The activation energies obtained from the DFT calculations were consistently higher than those derived from the empirical rate data.[92] Initially it was thought that the DFT modelling was overestimating the degree of conjugation in the ester tethers of the trienes (**156**), (**157**) and (**158**), and attention shifted to the ether tethered trienes (**155**) and (**65**). The rate data obtained from the IMDA reactions of all five trienes, (**155**), (**65**), (**156**), (**157**) and (**158**) will be discussed in this chapter of the thesis.

3.1.5 Kinetic isotope effects

Kinetic isotope effects (KIEs) arise when isotopomeric compounds take part in chemical reactions at different rates, and they are a rich source of mechanistic and geometrical information about the rate determining steps and transition states of many chemical reactions. They are defined as the quotient of rates of reaction of two isotopomers, where the rate of reaction with the light isotopomer is the numerator, and the rate of reaction with the heavy isotopomer is the denominator.[179]

$$KIE = \frac{k_{light\ isotope}}{k_{heavy\ isotope}}$$

The assumption that the potential energy surfaces of chemical reactions are unaffected by isotopic substitution has a solid theoretical basis. Isotopic substitution does, however, affect the mass dependent properties of chemical systems, notably the quantised vibrational states of chemical bonds, which in turn affect the rates of chemical reactions. The vibrational energy of a chemical bond is proportional to its reduced mass, μ, which can be calculated from the masses, m, of the atoms involved in the bonding interaction.[179,180]

$$\mu = \frac{m_1 \times m_2}{m_1 + m_2}$$

Isotopomeric compounds, intermediates and transition states have slightly different zero point vibrational energies (ZPE), due to the differences in the masses of the isotopes they contain. KIEs occur in the chemical reactions of these systems because the differences in the ZPEs of the isotopomeric compounds and transition states give rise to

differences in the free energies of activation ($\Delta G^{\ddagger}$) of the rate determining steps of the reactions.[181,182]

$$\Delta\Delta G^{\ddagger} = \Delta ZPE_{GS} - \Delta ZPE_{TS}$$

Hydrogen KIEs are widely used in organic chemistry for a number of reasons. The relative difference in mass between protium and deuterium is large compared to the relative differences in the masses of the stable isotopes of heavier elements; substitution of deuterium for protium in a ^{12}C - protium bond nearly doubles the reduced mass, μ, of the system, whereas substitution of ^{13}C for ^{12}C changes μ by less than one percent. For this reason, primary hydrogen KIEs are often large in magnitude, allowing their measurement by relatively simple means, and even secondary hydrogen KIEs can yield useful mechanistic information on a wide range of chemical reactions.[181] Further, hydrogen is ubiquitous in organic compounds, and many deuterium enriched reagents are either commercially available or readily accessible from commercial compounds.

The mechanisms of a number of intermolecular DA reactions have been investigated using deuterium KIEs. Early work by Seltzer on the retro DA reactions of mixtures of deuterium labelled and unlabelled DA adducts derived from 2-methylfuran (**185**) and maleic anhydride (**54**) demonstrated that the retro DA reactions of the compounds studied and, by the principle of microscopic reversibility, the forward DA reaction of 2-methylfuran (**185**) with maleic anhydride (**54**), were concerted processes.[183,184]

The Van Sickle group observed small deuterium KIEs in the DA reactions of mixtures of unlabelled and deuterium labelled maleic anhydride (**54**) with 1,3-butadiene (**1**), cyclopentadiene (**23**) and anthracene (**162**). They also studied the reaction of unlabelled maleic anhydride (**54**) with mixtures of unlabelled and deuterium labelled 1,3-butadiene (**1**), and unlabelled and deuterium labelled anthracene, (**162**), concluding that all of the reactions studied were concerted processes.[185]

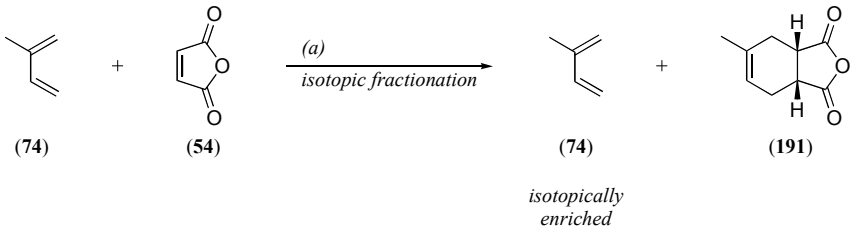
The retro DA reactions of mixtures of unlabelled and deuterium labelled 9,10-dihydro-9,10-ethanoanthracenes, were the subject of a detailed KIE study by the Thornton group. The authors found that the retro DA reactions, and their forward counterparts, proceeded through concerted and nearly synchronous transition states.[186]

The Gajewski group determined KIEs for the DA reactions of mixtures of unlabelled and deuterium labelled isoprene (**74**) with acrylonitrile (**36**), fumaronitrile (**186**), 1,1-dicyanoethylene (**187**), dimethyl fumarate (**164**), dimethyl maleate (**163**) and methyl *trans*-β-cyanoacrylate (**188**). It was found that the DA reactions of symmetrical dienophiles proceeded through nearly symmetrical transition states, whereas the DA reactions of unsymmetrical dienophiles proceeded through concerted but asynchronous transition states.[187]

The Shine group studied the DA reactions of ^{14}C labelled β-nitrostyrenes with 2,3-dimethyl-1,3-butadiene (**190**). Comparison of the experimentally determined ^{14}C KIEs with computational predictions indicated that the DA reactions were concerted.[188]

With the advent of high field NMR, it has become possible to obtain position specific information on the relative abundances of the different isotopes of carbon and hydrogen within organic compounds. While carbon and secondary deuterium kinetic isotope effects are generally much too small to measure by simple, quantitative high field NMR techniques, methods combining an isotopic fractionation event with high field NMR analysis are capable of extracting KIE data from systems with natural isotopic abundances. Isotopic fractionation experiments at natural abundance warrant some discussion. As a chemical reaction takes place, the starting materials will become enriched in their slower reacting isotopomers, which are initially present at natural abundance. In suitable systems allowed to react until close to complete conversion, the degree of enrichment caused even by small KIEs can be detected by comparing the quantitative NMR spectra of the starting material with the quantitative NMR spectra of the isotopically enriched starting material recovered from the isotopic fractionation event. To achieve high accuracy in a KIE determination of this sort, the degree of completion of the reaction must be determined with high precision, as the magnitudes of the observed KIEs depend on this variable. These methods do not require the synthesis of isotopically labelled material, and a single experiment can yield position specific KIE data at many sites in a compound of interest.[94,179,189]

A KIE study of the DA reaction of isoprene (**74**) with maleic anhydride (**54**) has been reported by the Singleton group (**Scheme 3.25**).[94]



Scheme 3.25 *Large scale isotopic fractionation event using the Diels-Alder reaction of isoprene (**74**) with maleic anhydride (**54**). (a) 25 °C, 7 d, xylenes, 98.9% conversion, >10 mole scale.*[94]

The authors took the DA reaction of isoprene (**74**) with maleic anhydride (**54**) to 98.9% conversion, as measured by GC, and assumed the ^{13}C and ^{2}H KIEs at the methyl position of isoprene were equal to one. Using the methyl group as an internal standard, hydrogen and carbon KIEs were obtained for each position in the 1,3-diene. (**Figure 3.7**). The KIE data gathered in this manner were sufficiently precise to exclude stepwise and synchronous DA reaction mechanisms, and the authors concluded that the DA reaction of isoprene (**74**) with maleic anhydride (**54**) is concerted and proceeds through an asynchronous transition state.[94]

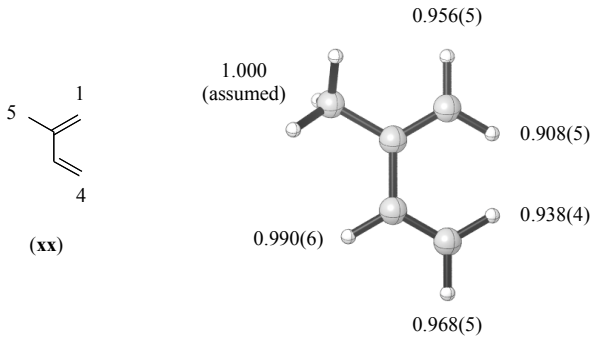


Figure 3.7 *Secondary hydrogen kinetic isotope effects and experimental uncertainties for isoprene in the Diels-Alder reaction of isoprene (**74**) with maleic anhydride (**54**).*

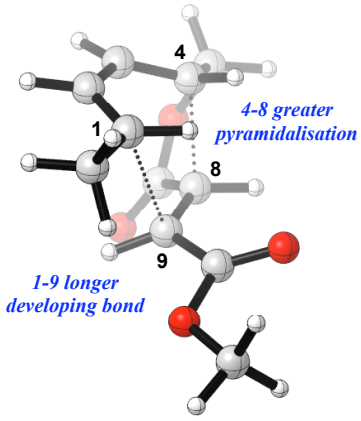
KIE data have long been a valuable source of information about the mechanisms and transition state geometries of chemical reactions[181,182] and, where available, provide one of the most rigorous empirical verifications of the geometries of computationally generated transition structures. In 1994 the Houk group surveyed the literature, comparing experimental KIE data for DA reactions with calculated KIEs corresponding to concerted and stepwise reaction channels. The reactions investigated in this manner include the retro DA reactions studied by Seltzer,[183,184] the DA reactions of maleic anhydride (**54**) studied by the Van Sickle group,[185] the retro DA reactions of 9,10-

dihydro-9,10-ethanoanthracenes studied by the Thornton group,[186], the DA reactions of isoprene (**74**) studied by the Gajewski group,[187] and the DA reactions of ^{14}C labelled β-nitrostyrenes with 2,3-dimethyl-1,3-butadiene (**190**) studied by the Shine group.[188] In all cases, strong correlations between the experimental KIEs and those calculated for the concerted reaction channels were found. In subsequent publications, the Houk group explored the use of KIE data in determining the mechanism of the DA reaction of 1,3-butadiene (**1**) with ethylene (**2**)[161], and the mechanisms of a selection of fundamental pericyclic reactions.[190]

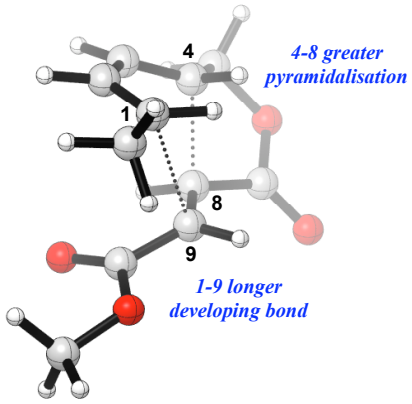
High precision natural abundance KIE data have since been reported by the Singleton group for a range of DA reactions, including the diethylaluminium chloride (**171**) catalysed DA reactions of isoprene (**74**) with methyl vinyl ketone (**33**), ethyl acrylate (**10**) and acrolein (**32**);[191] the inverse electron demand DA reaction of hexachlorocyclopentadiene (**192**) with ether vinyl ether (**193**);[192] the DA reactions of isoprene (**74**) with dimethyl acetylenedicarboxylate (**194**) and dimethyl maleate (**163**); the DA reaction of 2-*tert*-butyl-1,3-butadiene (**195**) with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (**196**); and the retro DA reaction of norbornene (**197**), generating cyclopentadiene (**23**) and ethylene (**2**).[193] All of these publications included impressive comparisons between experimental and computed KIEs, and supported concerted and asynchronous mechanisms for the transformations studied.

The transition structures located by Prof. M. N. Paddon-Row for the IMDA reactions of the ester tethered trienes, (**156**) and (**157**), giving the *cis* fused and *trans* fused IMDA adducts, (**156 *cis* P**), (**156 *trans* P**), (**157 *cis* P**) and (**157 *trans* P**), all exhibit marked bond forming asynchronicity. The internal developing bonds, at approximately 2.0 Å in length, are consistently shorter than the peripheral developing bonds, which are closer to 2.6 Å in length. The sums of the lengths of the developing bonds in all four transition structures are a little over 4.6 Å, indicating that an extension (contraction) in one of the two developing bonds is generally accompanied by a contraction (extension) in its counterpart. The asynchronicity of the IMDA reactions of 1,3,8-nonatrienes can be gauged by examining the lengths of the developing bonds and the pyramidalisation of the carbons at positions 1, 4, 8 and 9 in the transition structures (**Figures 3.8 and 3.9**). These carbons are sp^2 hybridised in the trienes and sp^3 hybridised in the IMDA adducts, as they are the sites in the dienophile and at the termini of the 1,3-diene where new carbon-carbon σ-bonds are formed in the IMDA reaction. At an idealised sp^2

hybridised carbon, the three substituents are 120° apart, and the sum of the three angles is 360°. At an idealised sp^3 hybridised carbon, the four substituents are 109.5° apart, and the sum of three of these angles is 328.5°. As the new carbon-carbon σ-bonds are formed in the IMDA reaction, the sites in question gradually become pyramidalised, with the apex of the pyramid pointing in the direction of the site to which the developing carbon-carbon bond is forming. The angles made by the original three substituents around each of these carbon centres in the IMDA transition structures give an indication of the degree of rehybridisation which has occurred at each site upon moving from the triene to the transition structure. It was expected that the largest secondary deuterium KIEs for the IMDA reactions of the 1,3,8-nonatrienes (**156**) and (**157**) would be a consequence of the rehybridisation of these carbon centres. It was later found that electrostatic and steric interactions also made significant contributions to the secondary deuterium KIEs at these sites.



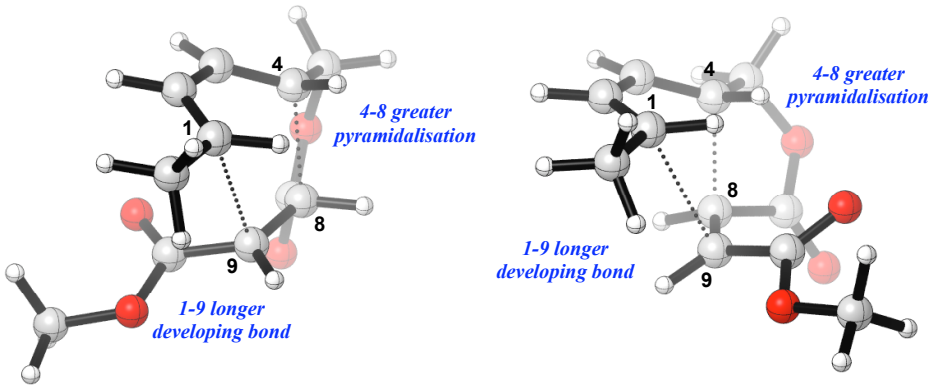
(**156** ***cis*** **TS**)



(**156** ***trans*** **TS**)

transition structure	*cis*				**transition structure**	*trans*			
developing bond location (length Å)	**C1 - C9** (2.600)		**C4 - C8** (2.010)		**developing bond location (length Å)**	**C1 - C9** (2.706)		**C4 - C8** (1.950)	
atom	**C1**	**C9**	**C4**	**C8**	**atom**	**C1**	**C9**	**C4**	**C8**
sum of angles at carbon (°)	358.36	357.97	354.93	349.83	**sum of angles at carbon (°)**	358.85	358.50	352.89	348.30

Figure 3.8 *Bond forming asynchronicity reflected in the developing bond lengths and pyramidalisation of carbons at positions 1, 4, 8 and 9 in the gas phase B3LYP/6-31+G(d) transition structures located by Prof. M. N. Paddon-Row for the intramolecular Diels-Alder reaction of triene* ***(156)****.*[92]



(**157** ***cis*** **TS**)

transition structure	*cis*			
developing bond location (length Å)	**C1 - C9** (2.651)		**C4 - C8** (2.001)	
atom	**C1**	**C9**	**C4**	**C8**
sum of angles at carbon (°)	359.03	359.63	352.41	349.18

(**157** ***trans*** **TS**)

transition structure	*trans*			
developing bond location (length Å)	**C1 - C9** (2.791)		**C4 - C8** (1.952)	
atom	**C1**	**C9**	**C4**	**C8**
sum of angles at carbon (°)	359.13	359.70	352.97	346.46

Figure 3.9 *Bond forming asynchronicity reflected in the developing bond lengths and pyramidalisation of carbons at positions 1, 4, 8 and 9 in the gas phase B3LYP/6-31+G(d) transition structures located by Prof. M. N. Paddon-Row for the intramolecular Diels-Alder reaction of triene* ***(157)***.[92]

As the carbons of the methine units at positions 1, 4, 8 and 9 of a 1,3,8-nonatriene rehybridise during an IMDA reaction, the vibrational modes of the carbon-hydrogen bonds in the methine units undergo changes. Effects involving the stretching modes are negligible, but changes in the frequency of the out of plane bending modes are significant, and give rise to kinetic isotope effects. The in plane bending frequencies of sp^2 carbon-hydrogen bonds and sp^3 carbon-hydrogen bonds are nearly identical, both types of bonds absorb at around 1350 cm^{-1} in the IR (16.15 $kJmol^{-1}$), however the out of plane bending frequencies of sp^2 carbon-hydrogen bonds and sp^3 carbon-hydrogen bonds are quite different. Whereas sp^2 carbon-hydrogen bonds absorb at around 800 cm^{-1} in the IR (9.57 $kJmol^{-1}$) through the out of plane bending mode, the in plane and out of plane bending modes of sp^3 carbon-hydrogen bonds are degenerate; both absorb at around 1350 cm^{-1} in the IR (16.15 $kJmol^{-1}$). Overall, rehybridisation of a methine carbon from sp^2 to sp^3 is accompanied by an increase of approximately 6.6 $kJmol^{-1}$ in the energy of the out of plane bending vibrational mode of the carbon-hydrogen bond. This increase is brought about by the increase in steric hindrance in the environment of the carbon-hydrogen bond, which accompanies the rehybridisation from sp^2 to sp^3. The

vibrational amplitude and zero point energy (ZPE) of a carbon-deuterium bond are smaller than those of a carbon-protium bond. As the rehybridisation of carbons 1, 4, 8 and 9 takes place in the IMDA reactions of 1,3,8-nonatrienes, the zero point energies of the out of plane bends of the carbon-hydrogen bonds at these positions increase, as the force constants of those vibrational modes increase. This results in a difference in the zero point energies of the carbon-hydrogen bonds at positions 1, 4, 8 and 9 between the triene and the transition state, in which the carbons are pyramidalised, and between the transition state and the IMDA adduct, in which the carbons are sp^3 hybridised (**Figure 3.10**).

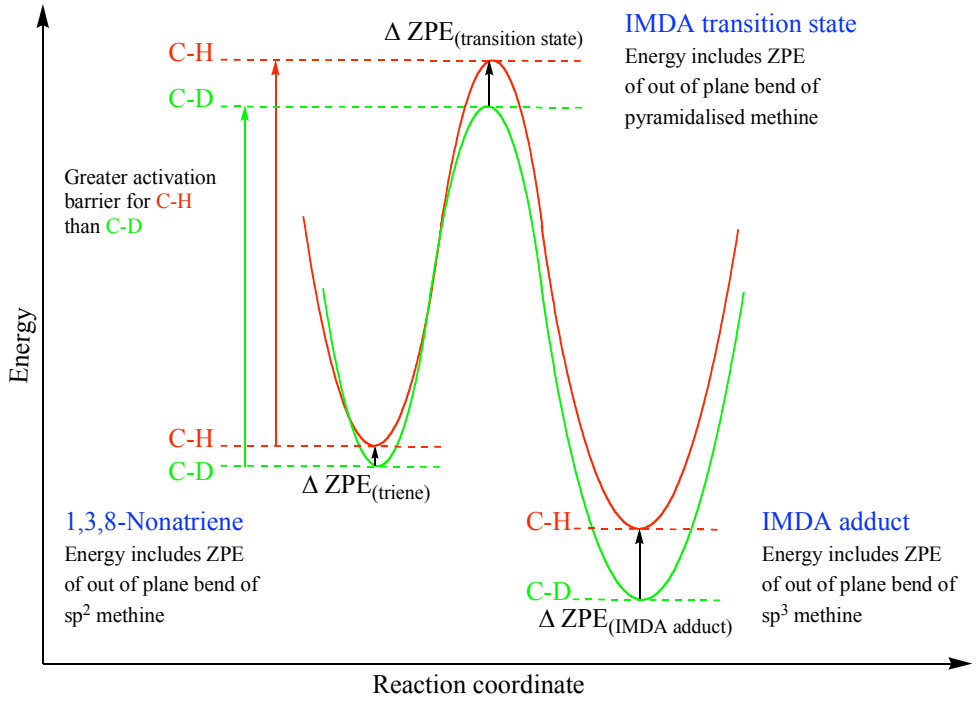


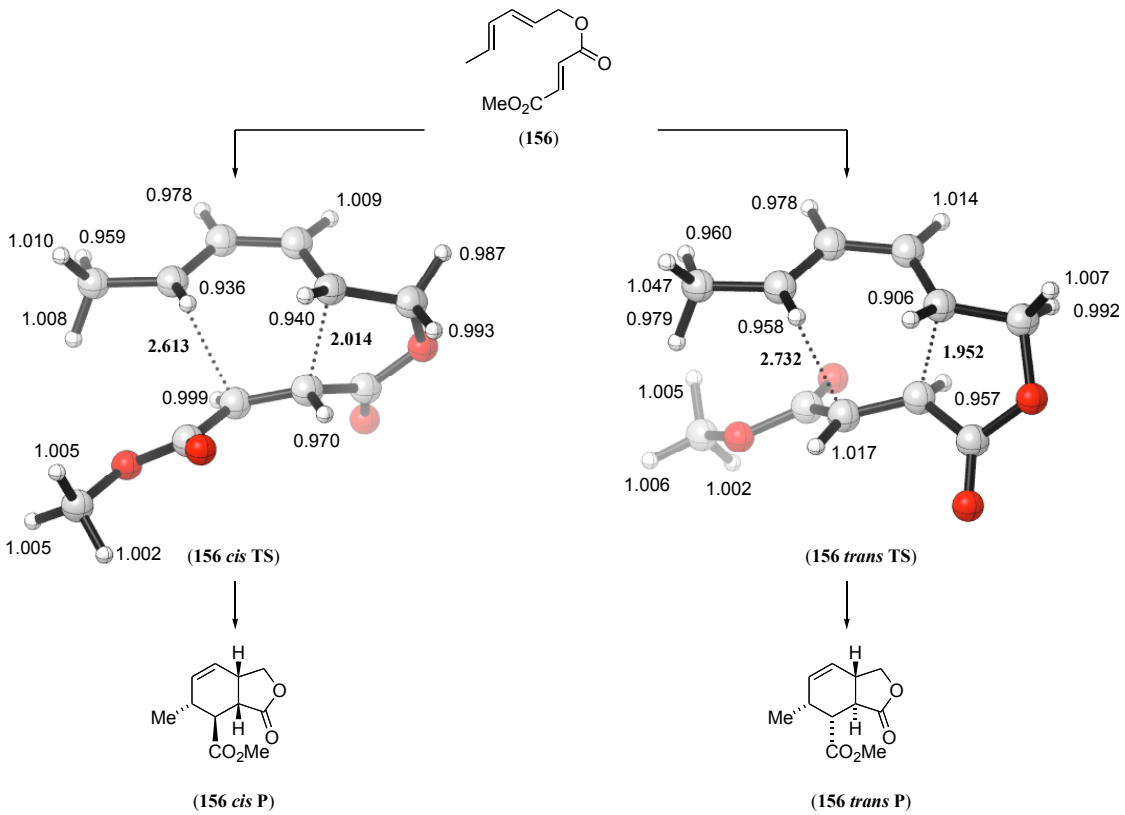
Figure 3.10 *The origins of kinetic isotope effects in the intramolecular Diels-Alder reactions of 1,3,8-nonatrienes. Differences in the zero-point energies of carbon-protium and carbon-deuterium out of plane bending vibrational modes are amplified as the reaction coordinate approaches the transition state. The intramolecular Diels-Alder reactions of isotopomeric trienes have slightly different activation barriers.*

The zero point energies of the out of plane bending modes increase more through the transition from sp^2 hybridisation, to pyramidalisation, to sp^3 hybridisation for carbon-protium bonds than they do for carbon-deuterium bonds, making the difference in ZPE between the isotopomeric transition states greater than that between the isotopomeric trienes. This gives rise to slightly different activation barriers for the protium and deuterium isotopomers of the trienes, as expressed by the equation.

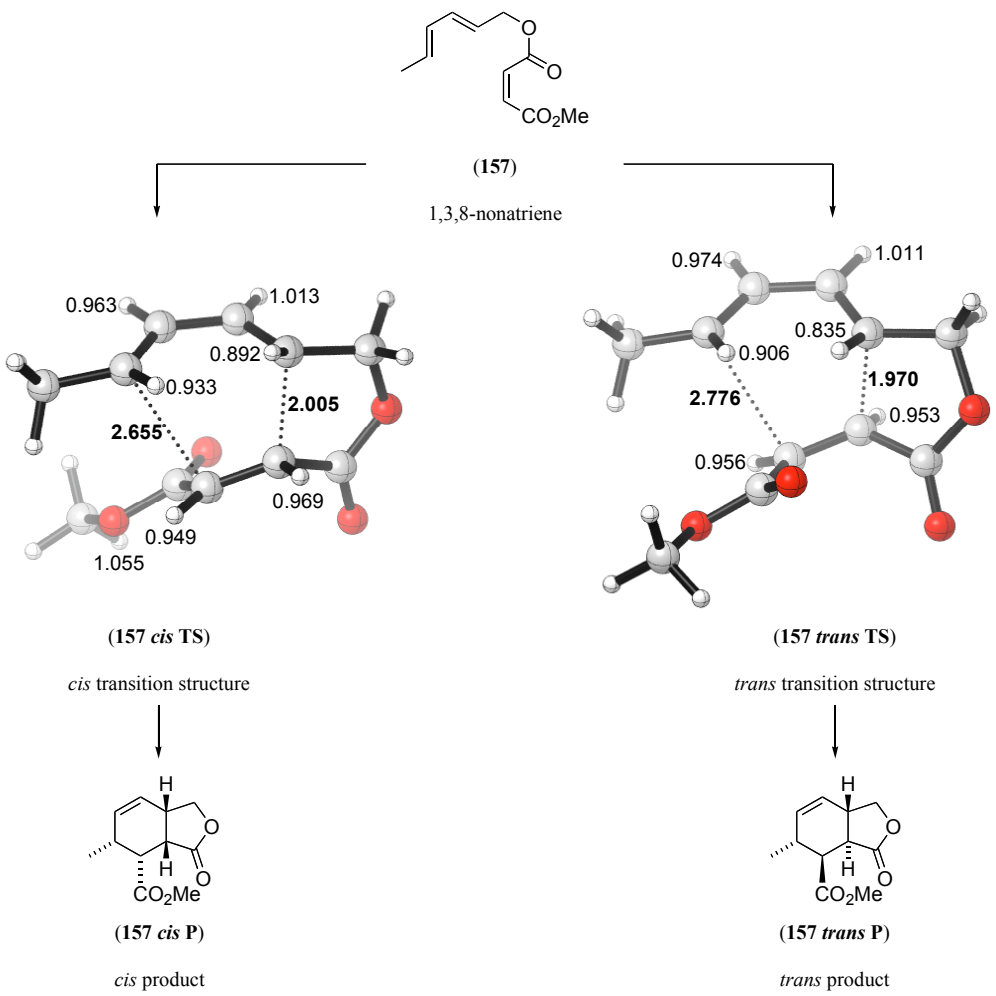
$$\Delta\Delta G^{\ddagger} = \Delta ZPE_{GS} - \Delta ZPE_{TS}$$

The rehybridisation of the carbons at positions 1, 4, 8 and 9 of 1,3,8-nonatrienes (**156**) and (**157**) which has taken place in moving from the triene to the transition state manifests in the transition structures, located by Prof. M. N. Paddon-Row, as pyramidalisation at the carbons. It can be seen that the transition structures are reactant-like, as would be expected for exothermic reactions, and the degree of rehybridisation which has taken place in the transition structure is small, particularly at C1 and C9, where the developing bonds are in excess of 2.6 Å in length, and the sum of the angles at the carbon centres are within three degrees of 360°. The geometries of the transition structures give a rough indication of the relative magnitudes of the KIEs to be expected at the sites of interest, where greater pyramidalisation in the transition structure is correlated with larger KIEs.

Prof. M. N. Paddon-Row has calculated KIEs for the IMDA reactions of a series of 1,3,8-nonatrienes. The calculated KIEs for the IMDA reactions of triene (**156**) (**Scheme 3.26**) and triene (**157**) (**Scheme 3.27**) are shown here. Through bond rotations, the KIEs for the different hydrogen positions in the methyl and methylene groups of trienes (**156**) and (**157**) average to approximately 1.000, as is evident from (**Scheme 3.26**), and are omitted from (**Scheme 3.27**) for clarity.



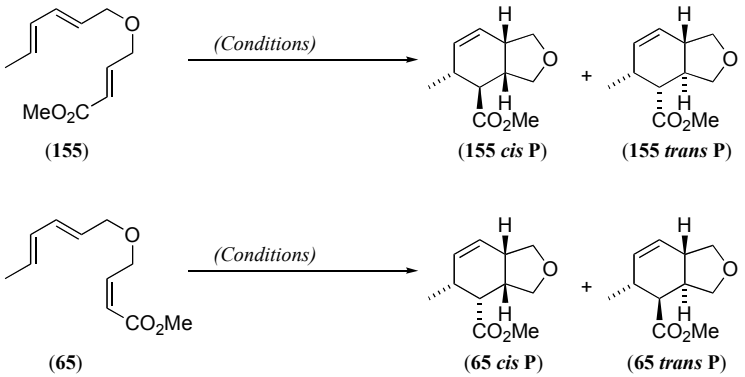
Scheme 3.26 *B3LYP/6-31+G(d) transition structure geometries, developing bond lengths (bold), and calculated kinetic isotope effect values for the intramolecular Diels-Alder reaction of triene (**156**) at 405.15 K.*[178]



Scheme 3.27 *B3LYP/6-31+G(d) transition structure geometries, developing bond lengths (bold), and calculated kinetic isotope effect values for the intramolecular Diels-Alder reaction of triene (**157**) at 298.15 K.*[178]

3.1.6 Summary and research objectives

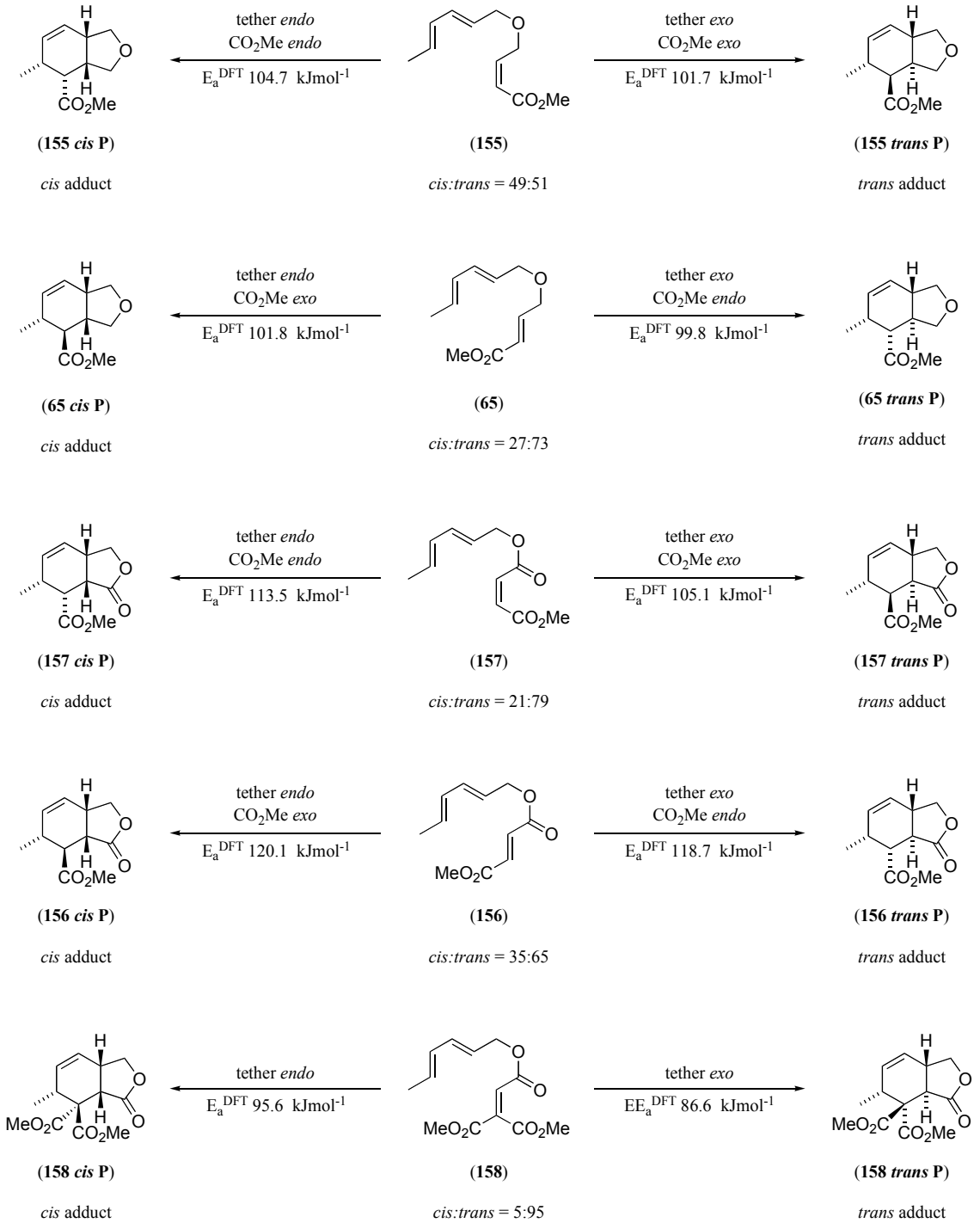
The work presented in this chapter had a number of aims, and can be viewed as an extension of work done previously in the Sherburn group.[89,91,92] The diastereoselectivities of the IMDA reactions of the terminally activated, ether tethered 1,3,8-nonatrienes (**155**) and (**65**) (**Scheme 3.28**), under thermal reaction conditions and under different types of Lewis acid promotion were studied.



Scheme 3.28 *Intramolecular Diels-Alder reactions of ether tethered 1,3,8-nonatrienes (**155**) and (**65**) studied in the course of this work.*

Goals of this work included determining the stereoselectivities of the heat promoted IMDA reactions of trienes (**155**) and (**65**). These could then be compared with predictions derived from B3LYP/6-31+G(d) modelling carried out by Prof. M. N. Paddon-Row, and used to refine previously developed approaches to predicting IMDA stereoselectivities. In addition, reaction conditions were sought under which these trienes could be selectively and efficiently transformed into either the *cis* or *trans* fused IMDA adducts, depending on the choice of reaction conditions and Lewis acid promoters. The ability to obtain either IMDA adduct in high yield by careful choice of reaction conditions makes these trienes attractive intermediates for the synthesis of complex molecules.

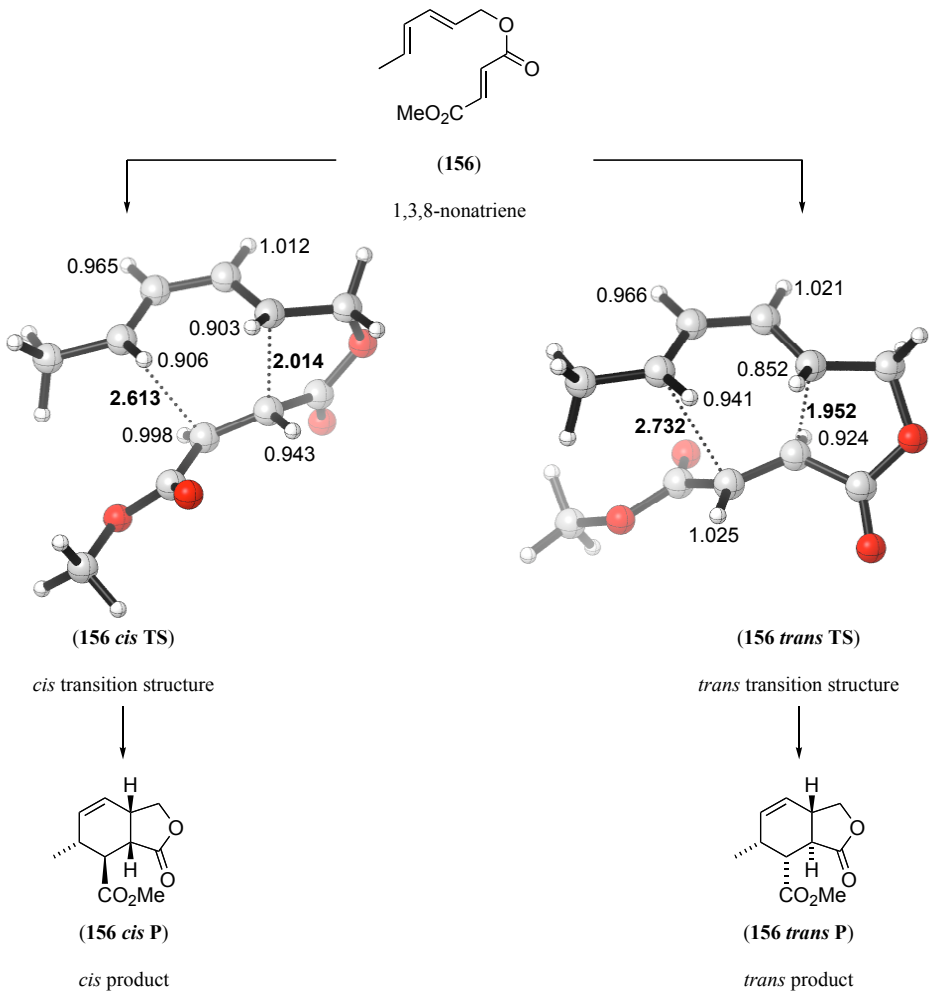
Another goal of this work was to perform a rate study on triene (**65**) (**Scheme 3.29**), allowing the Arrhenius parameters, activation energy, E_a, and frequency factor, A, and the thermodynamic activation parameters, enthalpy of activation, $\Delta H^{\ddagger}$, entropy of activation, $\Delta S^{\ddagger}$, and free energy of activation, $\Delta G^{\ddagger}$, to be compared with those of other trienes, and with activation energies calculated at the B3LYP/6-31+G(d) level of theory by Prof. M. N. Paddon-Row. This is an important part of developing the theoretical tools necessary for predicting IMDA activation barriers.



Scheme 3.29 *B3LYP/6-31+G(d) calculated cis and trans intramolecular Diels-Alder activation barriers calculated by Prof. M. N. Paddon-Row for a series of 1,3,8-nonatrienes studied within the Sherburn group.*[178]

Finally, attempts were made to investigate IMDA transition state geometries through the measurement of KIEs in the IMDA reactions of the ester tethered trienes (**155**) and (**65**) (**Scheme 3.30**). The experimental KIE data were compared with KIE data calculated by Prof. M. N. Paddon-Row at the B3LYP/6-31+G(d) level of theory. KIEs

are sensitive to transition state geometry and experimental KIE values can be used to verify computationally generated transition structures for many types of chemical reaction. Once computationally generated transition structures have received experimental verification through KIE analysis, they can be used with greater confidence in the identification of factors controlling the stereochemical outcomes and reaction rates of the corresponding reactions.

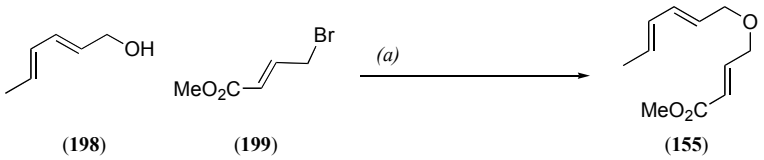


Scheme 3.30 *B3LYP/6-31+G(d) transition structure geometries, developing bond lengths, and calculated deuterium kinetic isotope effect values for the intramolecular Diels-Alder reaction of triene (**156**) at 298.15 K. The kinetic isotope effect values at the methyl and methylene positions average to approximately 1.000, and are omitted for clarity.*[178]

3.2 Results and Discussion

3.2.1 Synthesis of trienes (155) and (65)

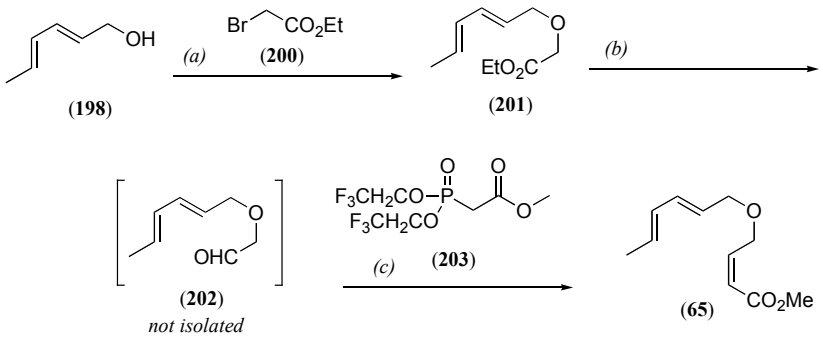
Triene (**155**) was synthesised by a silver (I) oxide promoted Williamson etherification from commercial sorbyl alcohol (**198**) and methyl bromocrotonate (**199**) through a modified literature procedure (**Scheme 3.31**).[177,194] An excess of the dienol (**198**) was used, and the reaction gave the triene in 44% yield based upon the electrophile. The triene was isolated in pure form by column chromatography.



(**198**) (**199**) (**155**)

Scheme 3.31 *Synthesis of triene (**155**). Conditions: (a) (**198**) (3.6 molar equiv.) (**199**) (1.0 molar equiv.), Ag_2O (0.6 molar equiv.), 84 hr, 44%, E:Z 100:0.*

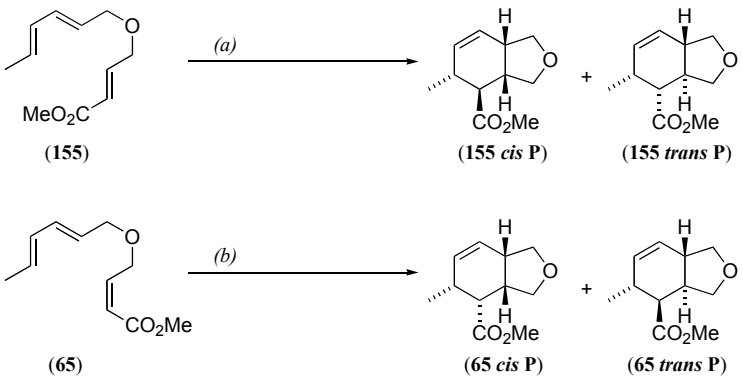
Triene (**65**) was synthesised in three steps from commercial sorbyl alcohol (**198**) (**Scheme 3.32**). An iodide catalysed Williamson etherification between the lithium alkoxide of sorbyl alcohol and ethyl bromoacetate (**200**)[195] gave the ethyl ester (**201**) in 42% yield. Similar results were obtained with the sodium alkoxide. The ethyl ester (**201**) was isolated in pure form by column chromatography. The ester group was then reduced to the aldehyde with DIBAL-H at -78 °C,[195] and the crude aldehyde was used directly in a *Z*-selective Still-Gennari modified Horner-Wadsworth-Emmons reaction[196] which gave the (1*E*,3*E*,8*Z*)-triene (**65**) and the (1*E*,3*E*,8*E*)-triene (**155**) as a 87:13 mixture of geometrical isomers at the newly formed alkene, in 63% yield over two steps. The isomeric trienes (**65**) and (**155**) were isolated in pure form by column chromatography.



Scheme 3.32 *Synthesis of triene (**65**). Conditions: (a) n-BuLi (1.0 molar equiv.), -78 °C, 30 min, (**200**) (5.0 molar equiv.), n-Bu_4NI (0.2 molar equiv.), THF, -78 °C to RT, 20 hr, 42%. (b) DIBAL-H (1.5 molar equiv.), CH_2Cl_2, -78 °C, 45 min. (c) (**203**) (1.1 molar equiv.), $KN(TMS)_2$,(1.1 molar equiv.) 18-crown-6 (5.0 molar equiv.), -78 °C, 40 min, 63% (2 steps), E:Z 13:87.*

3.2.2 Stereochemistry of intramolecular Diels-Alder adducts (155 cis P), (155 trans P), (65 cis P) and (65 trans P)

The thermal and Lewis acid promoted IMDA reactions of the two terminally activated, ether tethered trienes (**155**) and (**65**), were investigated. Before discussing the IMDA reactions of these trienes in detail, the stereochemistry of the IMDA adducts obtained from them (**155 *cis* P**), (**155 *trans* P**), (**65 *cis* P**) and (**65 *trans* P**), will be examined. When heated to reflux in toluene, the (1*E*,3*E*,8*E*)-triene (**155**) gave the *cis* and *trans* fused adducts (**155 *cis* P**) and (**155 *trans* P**), in a 27:73 ratio, and the (1*E*,3*E*,8*Z*)-triene (**65**) gave the *cis* and *trans* fused adducts (**65 *cis* P**) and (**65 *trans* P**), in a 51:49 ratio (**Scheme 3.33**).



Scheme 3.33 *Heat promoted intramolecular Diels-Alder reactions of ether linked trienes (**155**) and (**65**). Conditions: (a) toluene, 10 mM in triene, BHT (1 mol. %) reflux, 20 hr, 66%, (**155 cis P**):(**155 trans P**) 27:73. (b) toluene, 10 mM in triene, BHT (1 mol. %), reflux, 6 hr, 93%, (**65 cis P**):(**65 trans P**) 51:49.*

The stereoselectivity of the DA reaction was discussed in some detail in Chapter 1. The reaction is strictly suprafacial with respect to each reactant, hence the stereochemistry of the reactants is conserved in the adducts, in accord with Alder's *cis* principle.[31] The adducts of some intermolecular[53] and intramolecular[197] DA reactions have been found to epimerise under relatively mild conditions. In both cases, epimerisation occurred at stereocentres bearing carbonyl groups and acidic hydrogens. The IMDA adducts derived from trienes (**155**) and (**65**) all contain stereocentres bearing carbomethoxy groups and acidic hydrogens, and the geometry of ring fusion and stereochemical integrity of these compounds were established by 800 MHz ^{1}H NMR and 200 MHz ^{13}C NMR spectroscopy, including one dimensional ^{1}H, one dimensional ^{13}C, one dimensional NOE, ^{1}H COSY, ^{13}C HSQC and ^{13}C HMBC experiments.

In the characterisation of these compounds, one dimensional NOE experiments gave significantly better results than two dimensional NOESY experiments. Compounds of molecular weight below 200 Da, such as the IMDA adducts of these simple trienes, have inherently weak NOE correlations. One dimensional NOE experiments are generally more sensitive than two dimensional NOESY experiments, and the use of the one dimensional experiments is often advantageous when working with molecules of this size.[114]

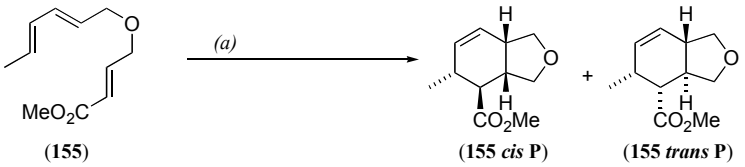
A useful indicator of the geometry of ring fusion in systems such as these is the size of the coupling constant between the protons at the site of ring fusion. These, however, were difficult to obtain by conventional means, as the resonances in question were complex multiplets. The coupling constants were eventually obtained using F1-decoupled DQF-COSY spectra, incorporating a semiselective 180° pulse to decouple the spins of interest. Assistance with these experiments, which appear to be unpublished, was kindly provided by Prof. Gottfried Otting, Research School of Chemistry, Australian National University.[198] In all cases, the geometries of the IMDA adducts, including the configurations of the stereocentres bearing carbomethoxy groups and acidic hydrogens, faithfully reflected those of the trienes from which they were formed.

The ^{1}H NMR spectra of each of the four stereoisomeric IMDA adducts contains two resonances at around 5.7 ppm, corresponding to the two olefinic protons in each adduct; five resonances between 4.2 and 3.2 ppm, corresponding to the methylene groups

flanking the ether oxygen, and the methyl group of the methyl ester; four resonances between 3.2 and 2.0 ppm, corresponding to the protons of the four sp^3 methine units which, together with the endocyclic olefin, comprise the six membered ring; and one resonance at approximately 1.0 ppm, which is a doublet in all adducts, and corresponds to the methyl group bonded directly to the six membered ring.

The ^{13}C NMR spectra of each of the four stereoisomeric IMDA adducts contains one resonance at around 175 ppm, corresponding to the ester carbonyl group; two resonances at around 130 ppm, corresponding to the methine carbons of the olefin; two resonances at around 70 ppm, corresponding to the methylene carbons adjacent to the ether oxygen; one resonance at around 50 ppm, corresponding the methoxy group; four resonances between 50 and 30 ppm, corresponding to the four sp^3 methine carbons in the carbocyclic ring; and one resonance at around 20 ppm, corresponding to the methyl group bonded to one of the four sp^3 methine carbons.

The adducts obtained from IMDA reactions of (1*E*,3*E*,8*E*)-triene (**155**) (**Scheme 3.34**) were isolated in pure form by flash column chromatography and characterised. $CDCl_3$ solutions of IMDA adduct (**155 *cis* P**) were analysed by 800 MHz ^1H NMR and 200 MHz ^{13}C NMR spectroscopy.



Scheme 3.34 *Heat promoted intramolecular Diels-Alder reaction of triene (**155**), producing adducts (**155 cis P**) and (**155 trans P**). Conditions: (a) toluene, 10 mM in triene, BHT (1 mol.%) reflux, 20 hr, 66%, (**155 cis P**):(**155 trans P**) 27:73.*

The atom connectivity of (**155 *cis* P**) was confirmed by inspection of the 800 MHz ^1H COSY spectrum of the compound in $CDCl_3$ solution (**Figure 3.11**).

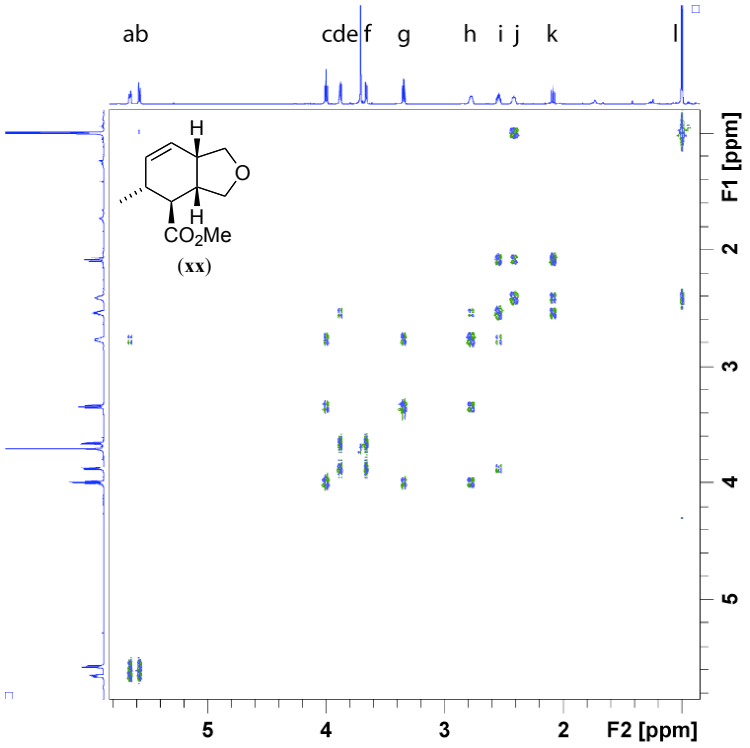
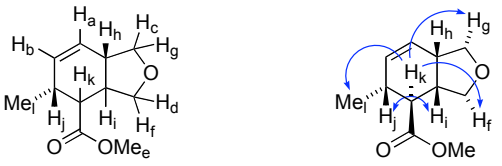


Figure 3.11 *800 MHz ^{1}H COSY spectrum of intramolecular Diels-Alder adduct (**155 cis P**), obtained from intramolecular Diels-Alder reactions of triene (**155**).*

The proton signals were assigned letters of the alphabet. The doublet corresponding to the methyl group at 1.0 ppm, H_l, is linked to the signals corresponding to the ring junction methine units, H_i and H_h, by three bond couplings; H_l couples to H_j, H_j couples to H_k, H_k couples to H_i, and H_i couples to H_h. The signals corresponding to the methylene units adjacent to H_h and H_i in the tetrahydrofuran ring, the alkene interposed between H_j and H_h, and the methyl ester, H_e, are well resolved and easily identified.

The atom connectivity of this compound is depicted in the left hand structure of (**Figure 3.12**). The coupling constant between the protons at the site of ring fusion, H_h and H_i, is 7.7 Hz, indicative of a *cis* fused ring junction. The stereochemical information missing from the left hand structure was obtained from coupling constant data and one dimensional NOE experiments summarised in the right hand structure. NOEs were observed between H_k and H_f, H_k and H_g, and H_k and H_l, confirming that the ring junction is *cis* fused, and these data and the NOE observed between H_j and H_i, demonstrate that the configuration of the triene is conserved in the IMDA adduct.

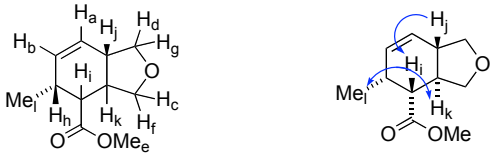


(**155** ***cis*** **P**) (**155** ***cis*** **P**)

Figure 3.12 *Left: Connectivity of intramolecular Diels-Alder adduct (**155 cis P**) derived from inspection of the 800 MHz ^{1}H COSY spectrum of (**155 cis P**) in $CDCl_3$. Right: Nuclear Overhauser effect data obtained from one dimensional nOe experiments with adduct (**155 cis P**) in $CDCl_3$.*

$CDCl_3$ solutions of IMDA adduct (**155** ***trans*** **P**) were analysed by 800 MHz ^{1}H NMR and 200 MHz ^{13}C NMR spectroscopy (**Scheme 3.34**).

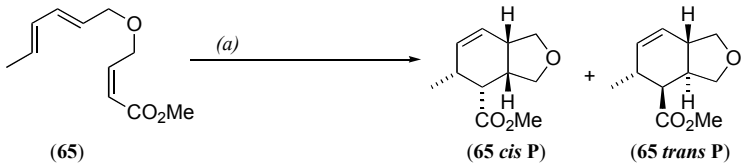
The atom connectivity of IMDA adduct (**155** ***trans*** **P**) was confirmed by inspection of its 800 MHz ^{1}H COSY spectrum in $CDCl_3$ solution (**Appendix Figure 6.3**), and is depicted in the left hand structure in (**Figure 3.13**). The coupling constant between the protons at the site of ring fusion, H_j and H_k, is 12.5 Hz. The stereochemical information missing from the left hand structure was obtained from coupling constant data and through one dimensional NOE experiments summarised in the right hand structure. The magnitude of the coupling constant between H_j and H_k and the NOE data, in particular the NOE observed between H_k and H_l, indicate that the ring system in this IMDA adduct is *trans* fused. A NOE was also observed between H_j and H_i, indicating that the configuration of the triene is conserved in the IMDA adduct.



(**155** ***trans*** **P**) (**155** ***trans*** **P**)

Figure 3.13 *Left: Connectivity of intramolecular Diels-Alder adduct (**155 trans P**) derived from inspection of the 800 MHz ^{1}H COSY spectrum of (**155 trans P**) in $CDCl_3$. Right: Nuclear Overhauser effect data obtained from one dimensional nOe experiments with (**155 trans P**) in $CDCl_3$.*

The adducts obtained from IMDA reactions of (1*E*,3*E*,8*Z*)-triene (**65**) (**Scheme 3.35**) were isolated in pure form by preparative normal phase HPLC and characterised. A number of solvents were screened for the NMR analysis of adduct (**65** ***cis*** **P**). CD_3OD solutions of IMDA adduct (**65** ***cis*** **P**) were analysed by 800 MHz ^{1}H NMR and 200 MHz ^{13}C NMR spectroscopy.



Scheme 3.35 *Heat promoted intramolecular Diels-Alder reaction of triene (**65**), producing adducts (**65 cis P**) and (**65 trans P**). Conditions: (a) toluene, 10 mM in triene, BHT (1 mol. %) reflux, 6 hr, 93%, (**65 cis P**):(**65 trans P**) 51:49.*

The atom connectivity of IMDA adduct (**65 *cis* P**) was deduced from its 800 MHz ^{1}H COSY spectrum in CD_3OD solution (**Appendix Figure 6.5**), and is depicted in the left hand structure in (**Figure 3.14**). The coupling constant between the protons at the site of ring fusion, H_h and H_i, is 8.3 Hz. The stereochemical information omitted from the left hand structure was obtained from one dimensional NOE experiments and coupling constant data summarised in the right hand structure. The NOE observed between H_i and H_j indicates that the ring system in this adduct is *cis* fused, and this conclusion is confirmed by the observation of a NOE between H_h and H_g, and the size of the coupling constant at the site of ring fusion. Further, the NOE between H_h and H_g demonstrates that the geometry of the triene is conserved in the IMDA adduct.

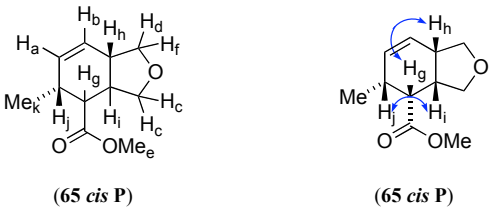
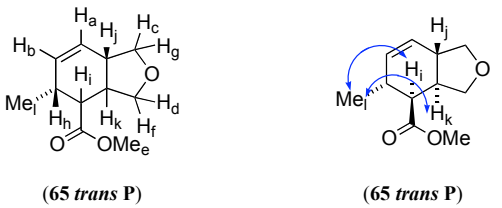


Figure 3.14 *Left: Connectivity of intramolecular Diels-Alder adduct (**65 cis P**) derived from inspection of the 800 MHz ^{1}H COSY spectrum of (**65 cis P**) in CD_3OD. Right: Nuclear Overhauser effect data obtained from one dimensional nOe experiments with adduct (**65 cis P**) in CD_3OD solution.*

$CDCl_3$ solutions of IMDA adduct (**65 *trans* P**) were analysed by 800 MHz ^{1}H NMR and 200 MHz ^{13}C NMR spectroscopy (**Scheme 3.35**).

Analysis of the 800 MHz ^{1}H COSY spectrum of IMDA adduct (**65 *trans* P**) (**Appendix Figure 7**) yielded the atom connectivity depicted in the left hand structure in (**Figure 3.15**). The coupling constant between the protons at the site of ring fusion, H_j and H_k, is 12.8 Hz. The stereochemical information absent in the left hand structure was obtained from coupling constant data and through one dimensional NOE experiments summarised in the right hand structure. The NOE observed between H_k and H_l, and the

magnitude of the coupling constant observed between H_j and H_k indicate that the ring system in this IMDA adduct is *trans* fused. Further, the NOE between H_i and H_l demonstrates that the geometry of the triene is conserved in the adduct.

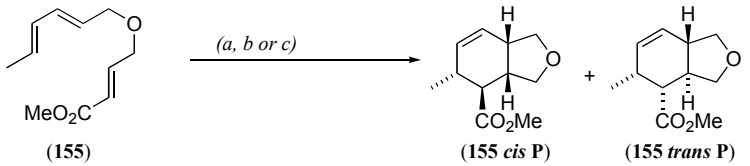


(**65** ***trans*** **P**) (**65** ***trans*** **P**)

Figure 3.15 *Left: Connectivity of intramolecular Diels-Alder adduct (**65 trans P**) derived from inspection of the 800 MHz ^{1}H COSY spectrum of (**65 trans P**) in $CDCl_3$. Right: Nuclear Overhauser effect data obtained from one dimensional nOe experiments with adduct (**65 trans P**) in $CDCl_3$.*

3.2.3 Intramolecular Diels-Alder reactions of 1,3,8-nonatrienes (155) and (65)

The heat promoted IMDA reactions of trienes (**155**) and (**65**) took place at reflux in toluene in the presence of 1 mol.% BHT, a radical inhibitor. Intermolecular reactions were suppressed by carrying out the reactions at a triene concentration of 10 mM. The ratios of diastereomers produced by these reactions were determined by 300 MHz ^{1}H NMR analysis of the crude and from the isolated yields of the cycloadducts. In all cases, the data from the two sources were in good agreement, and the uncertainties in the quoted ratios are smaller than 5%. The (1*E*,3*E*,8*E*)-triene (**155**) was heated to reflux for 20 hr and gave a 27:73 mixture of the *cis* and *trans* fused cycloadducts (**155** ***cis*** **P**) and (**155** ***trans*** **P**), respectively, in 66% yield. B3LYP/6-31+G(d) calculations predicted a 35:65 *cis:trans* ratio (**Scheme 3.36**).



(**155**) (**155 *cis* P**) (**155 *trans* P**)

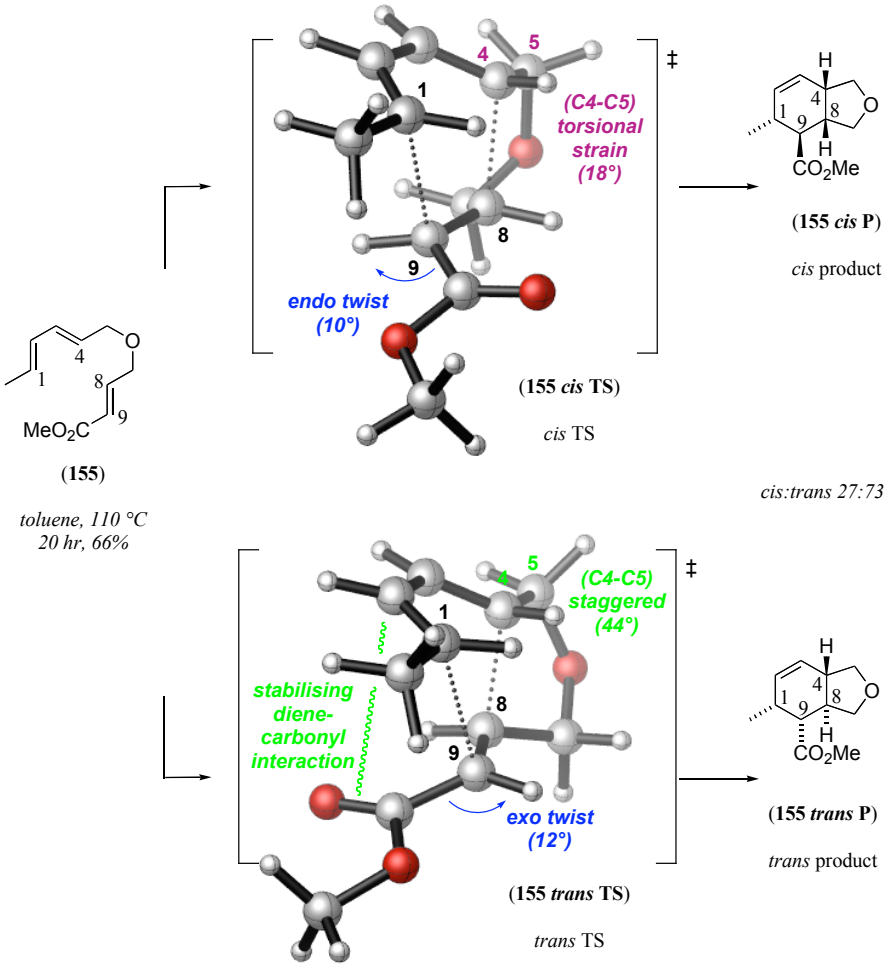
Scheme 3.36 *Heat and Lewis acid promoted intramolecular Diels-Alder reactions of (1E,3E,8E)-triene (**155**). Conditions:*

*Heat promoted reaction: (a) toluene, 10 mM in triene, BHT (1 mol.%) reflux, 20 hr, 66%, (**155 cis P**):(**155 trans P**) 27:73. B3LYP/6-31+G(d) gas phase calculated ratio: (**155 cis P**):(**155 trans P**) 35:65.*

*$EtAlCl_2$ promoted reaction: (b) CH_2Cl_2, 20 mM in triene, $EtAlCl_2$, (2.0 molar equiv.), 20 °C, 5 hr, 87%, (**155 cis P**):(**155 trans P**) 4:96.*

*ATPH promoted reaction: (c) CH_2Cl_2, 100 mM in triene, Me_3Al (2.0 molar equiv.), 2,6-diphenylphenol (6.0 molar equiv.), 25 °C, 21 hr, 81%, (**155 cis P**):(**155 trans P**) 1:99.*

The transition structures (**155 *cis* TS**) and (**155 *trans* TS**), located for the IMDA reaction of triene (**155**), both display pronounced bond forming and twist-mode asynchronicity (**Scheme 3.37**).

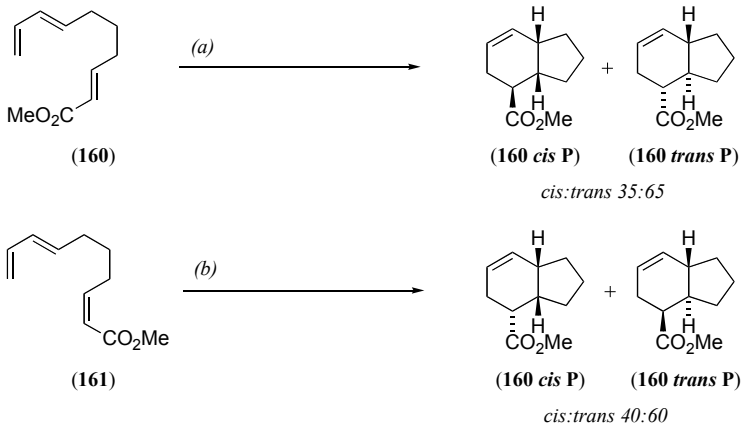


Scheme 3.37 *Intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**155**), gas phase cis and trans transition structures, and cis fused and trans fused cycloadducts. Gas phase B3LYP/6-31+G(d) transition structures were located by Prof. M. N. Paddon-Row.*[178]

In the *cis* transition structure (**155 *cis* TS**), the developing bonds are 2.017 and 2.511 Å in length, and in the *trans* transition structure (**155 *trans* TS**), the developing bonds are 1.929 and 2.686 Å in length. The dienophile is twisted 10° in the *endo* direction in the *cis* transition structure (**155 *cis* TS**) and 12° in the *exo* direction in the *trans* transition structure (**155 *trans* TS**). This twisting helps reduce strain in the forming five membered rings. The carbonyl group adopts the *exo* orientation in the *cis* transition structure (**155 *cis* TS**) and the *endo* orientation in the *trans* transition structure (**155 *trans* TS**), and there appears to be a stabilising 1,3-diene-carbonyl interaction in the *trans* transition structure (**155 *trans* TS**). The *cis* transition structure (**155 *cis* TS**) is further destabilised relative to the *trans* transition structure (**155 *trans* TS**) by residual torsional strain around the C4-C5 bond; the hydrogens at positions 4 and 5 are eclipsed in the *cis* transition structure (**155 *cis* TS**) (18°) and staggered in the *trans* transition

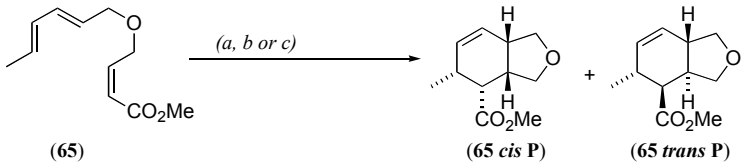
structure (**155 *trans* TS**) (44°). There are a number of steric clashes in the *cis* transition structure; between the hydrogens at positions 4 and 8 (2.26 Å), between the C1 methyl group and the alkoxy oxygen in the terminal ester group (2.52 Å), and between the carbonyl oxygen and the hydrogen at position 8 (2.51 Å). There is only one identifiable steric clash in the *trans* transition structure; between the C1 methyl group and the carbonyl oxygen (2.51 Å). The favourable 1,3-diene-carbonyl interaction in the *trans* transition structure (**155 *trans* TS**), and residual torsional strain and steric clashes in the *cis* transition structure (**155 *cis* TS**) are offset by an eclipsing interaction about the C4-C5-O6-C7 dihedral in the *trans* transition structure (0°), which is minimised in the *cis* transition structure C4-C5-O6-C7 (22°). This triene gave a 27:73 *cis:trans* product ratio when heated to 110 °C in toluene, indicating that the *trans* transition structure (**155 *trans* TS**) is favoured by 3.16 $kJmol^{-1}$. This figure is in very good agreement with energies calculated at the B3LYP/6-31+G(d) level of theory, which indicate the *trans* transition structure is favoured by 2.0 $kJmol^{-1}$, giving a predicted *cis:trans* ratio of 35:65.

The stereochemical outcome of this reaction is similar to that of the IMDA reaction of the corresponding trimethylene tethered triene (**160**), which was studied by the Roush group (**Scheme 3.38**). The trimethylene tethered triene (**160**) gave a 35:65 mixture of the *cis* and *trans* fused cycloadducts in 75% yield when heated to 180 °C in toluene for 5 hours. It appears that replacing the C6 methylene group in (**160**) with oxygen has only a small effect on the stereoselectivity of the IMDA reaction; the terminal carbomethoxy group adopts the *endo* orientation in the favoured transition states of the IMDA reactions of both trienes (**160**) and (**155**).[150]



Scheme 3.38 *Intramolecular Diels-Alder reactions of trimethylene tethered 1,3,8-nonatrienes (**160**) and (**161**) studied by the Roush group. Conditions: (a) 180 °C, 5 hr, toluene, sealed tube, 75%, (b) 150 °C, 24 hr, toluene, sealed tube, 65%.*[150]

The (1*E*,3*E*,8*Z*)-triene (**65**) was heated to reflux in toluene for 6 hr and gave a 51:49 mixture of the *cis* and *trans* fused cycloadducts (**65 *cis* P**) and (**65 *trans* P**), respectively, in 93% yield. This corresponds to a 51:49 *endo:exo* ratio with respect to the terminal carbomethoxy group. B3LYP/6-31+G(d) calculations predicted a 28:72 *cis:trans* ratio (**Scheme 3.39**).



Scheme 3.39 *Heat and Lewis acid promoted intramolecular Diels-Alder reactions of (1E,3E,8Z)-triene (**65**). Conditions:*

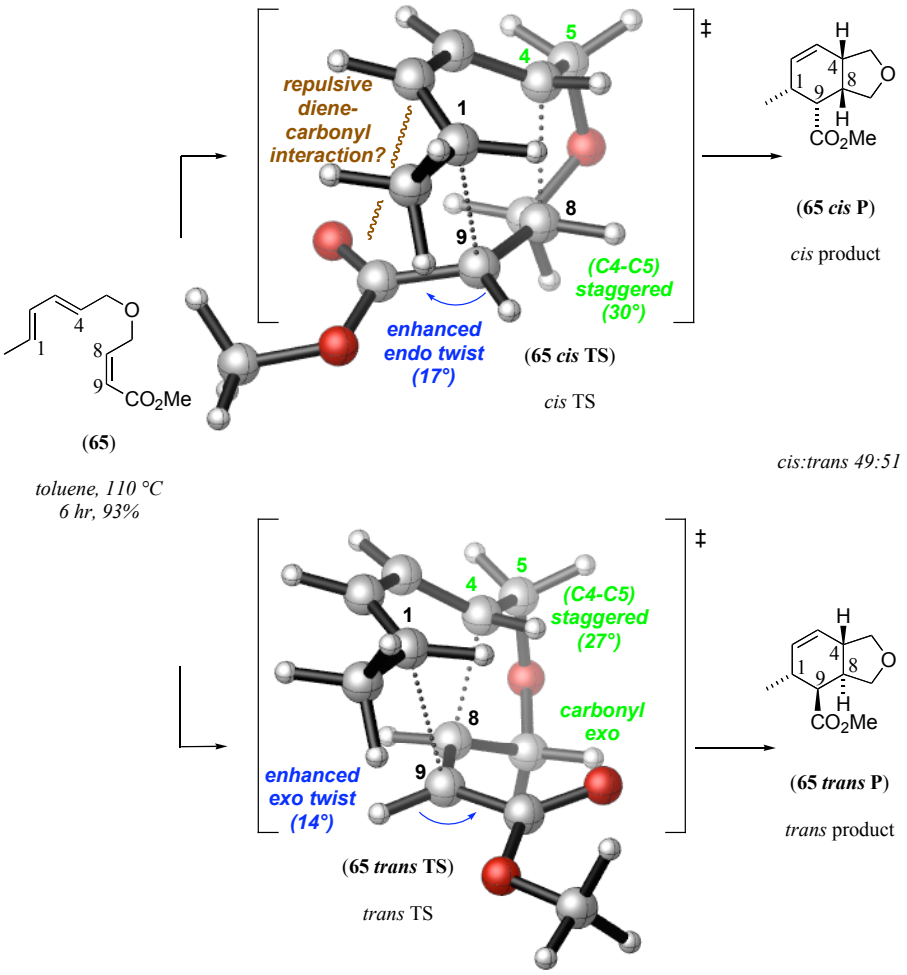
*Heat promoted reaction: (a) toluene, 10 mM in triene, BHT (1 mol.%), reflux, 6 hr, 93%, (**65 cis P**):(**65 trans P**) 51:49. B3LYP/6-31+G(d) gas phase calculated ratio: (**65 cis P**):(**65 trans P**) 28:72.*

*$EtAlCl_2$ promoted reaction: (b) CH_2Cl_2, 20 mM in triene, Et_2AlCl (2.0 molar equiv.), 20 °C, 2 hr, 44%, (**65 cis P**):(**65 trans P**) 82:18.*

*ATPH promoted reaction: (c) CH_2Cl_2, 100 mM in triene, Me_3Al (2.0 molar equiv.), 2,6-diphenylphenol (6.0 molar equiv.), 25 °C, 21 hr, 73%, (**65 cis P**):(**65 trans P**) 68:32.*

The transition structures (**65 *cis* TS**) and (**65 *trans* TS**), located for the IMDA reaction of triene (**65**), exhibit reasonably strong bond forming asynchronicity and enhanced twist-mode asynchronicity, due to the *Z*-effect. In the *cis* transition structure (**65 *cis***

TS), the developing bonds are 2.016 and 2.474 Å in length, and in the *trans* transition structure (**65 *trans* TS**), the developing bonds are 1.933 and 2.674 Å in length. As is the case with the IMDA reaction of triene (**155**), the *trans* transition structure is considerably more asynchronous than the *cis* transition structure (**Scheme 3.40**).



Scheme 3.40 *Intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**65**), gas phase cis and trans transition structures, and cis fused and trans fused cycloadducts. The gas phase B3LYP/6-31+G(d) transition structures were located by Prof. M. N. Paddon-Row.*

The dienophile is twisted 14° in the *endo* direction in the *cis* transition structure (**65 *cis* TS**) and 17° in the *exo* direction in the *trans* transition structure (**65 *trans* TS**). Again, this twisting helps reduce strain in the forming five membered rings. The carbonyl group adopts the *endo* orientation in the *cis* transition structure (**65 *cis* TS**) and the *exo* orientation in the *trans* transition structure (**65 *trans* TS**), and there appears to be a repulsive 1,3-diene-carbonyl interaction in the *cis* transition structure (**65 *cis* TS**). Both transition structures have little torsional strain around the C4-C5 bond. The hydrogens

at positions 4 and 5 are staggered in both transition structures; making angles of 28° in the *cis* transition structure (**65 *cis* TS**), and 30° in the *trans* transition structure (**65 *trans* TS**). There is one steric clash in the *cis* transition structure; between the hydrogens at positions 4 and 8 (2.24 Å), and there are two steric clashes in the *trans* transition structure; between the C1 methyl group and the carbonyl carbon (2.53 Å) and between the carbonyl oxygen and the C8 hydrogen (2.43 Å). Enhanced twist-mode asynchronicity and an unfavourable 1,3-diene-carbonyl interaction in the *cis* transition structure are hallmarks of the *Z*-effect. In some instances, the carbonyl group is pushed in the *endo* direction due to the enhanced twist mode asynchronicity of the *cis* transition structure, and occupies a region where repulsive rather than attractive interactions with the 1,3-diene are dominant. This triene gave a 49:51 *cis:trans* product ratio when heated to 110 °C in toluene, indicating that the *cis* and *trans* transition structures are isoenergetic within experimental error. This figure is in poor agreement with energies calculated at the B3LYP/6-31+G(d) level of theory, which indicate the *trans* transition structure is favoured by 3.0 $kJmol^{-1}$, giving a predicted *cis:trans* ratio of 28:72.

One may anticipate the anomalous *Z* effect to operate in this system, giving an excess of the *trans*, or *exo* product, as is predicted by the computational modelling. This is the case for the IMDA reaction of the corresponding trimethylene tethered triene (**161**), which was studied by the Roush group, and gave a 40:60 mixture of the *cis* and *trans* fused cycloadducts in 65% yield when heated to 150 °C in toluene for 24 hours (**Scheme 3.38**). In the case of the ether linked triene, where the C6 methylene group is replaced by an oxygen, however, no significant stereochemical preference was observed, and an additional factor appears to stabilise the *cis* or *endo* transition state relative to the *trans* or *exo* transition state, making the two transition states roughly isoenergetic.

To confirm that the observed *cis:trans* product ratios were kinetic in nature, each of the IMDA adducts derived from trienes (**155**) and (**65**), (**155 *cis* P**), (**155 *trans* P**), (**65 *cis* P**) and (**65 *trans* P**) was isolated and exposed to the IMDA reaction conditions used in its synthesis. No isomerisation of the adducts was observed, confirming that these IMDA reactions are irreversible in toluene at 110 °C.

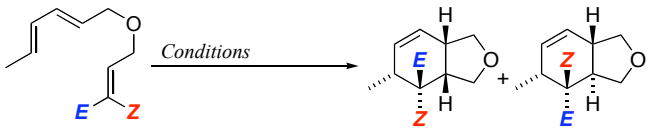
The heat promoted IMDA reactions of trienes (**155**) and (**65**) proceeded in 20 hours and 6 hours, respectively, at reflux in toluene. These conditions are significantly milder

than those used by the Roush group for the IMDA reactions of the trimethylene tethered trienes, (**160**) and (**161**), which were heated to 180 °C and 150 °C , respectively.

Diethylaluminium chloride (**171**) promoted IMDA reactions were carried out at 20 °C in CH_2Cl_2, at a triene concentration of 20 mM. Two molar equivalents of the Lewis acid promoter were used. The ratios of diastereomers produced by these reactions were determined by 300 MHz ^{1}H NMR analysis of the crude and from the isolated yields of the cycloadducts. In all cases, the data from the two sources were in good agreement, and the uncertainties in the quoted ratios are smaller than 5%. The reaction of the (1*E*,3*E*,8*E*)-triene (**155**) took 5 hr to consume the triene and gave a 4:96 mixture of the *cis* and *trans* fused cycloadducts (**155 *cis* P**) and (**155 *trans* P**), respectively, in 87% yield (**Scheme 3.36**). The (1*E*,3*E*,8*Z*)-triene (**65**) was unstable in the presence of the Lewis acid (**171**) at temperatures from -20 °C to reflux in CH_2Cl_2. A compromise between IMDA reactivity and triene stability was found at 20 °C, and the IMDA reaction was run at this temperature for 2 hr. It gave a 82:18 mixture of the *cis* and *trans* fused cycloadducts (**65 *cis* P**) and (**65 *trans* P**), respectively, in 44% yield. Both of these IMDA reactions exhibited enhanced *endo* selectivity with respect to the terminal carbomethoxy groups, when compared to the corresponding heat promoted IMDA reactions.

ATPH (**49**)[72] promoted IMDA reactions were carried out with a triene concentration of 100 mM at 25 °C in CH_2Cl_2.[157] Two molar equivalents of the Lewis acid, which was formed *in situ* from 2,6-diphenylphenol and trimethylaluminium, were used. The ratios of diastereomers produced by these reactions were determined by 300 MHz ^{1}H NMR analysis of the crude and from the isolated yields of the cycloadducts. In all cases, the data from the two sources were in good agreement, and the uncertainties in the quoted ratios are smaller than 5%. The reaction of the (1*E*,3*E*,8*E*)-triene (**155**) ran for 21 hr and gave a 1:99 mixture of the *cis* and *trans* fused cycloadducts (**155 *cis* P**) and (**155 *trans* P**), respectively, in 73% yield (**Scheme 3.36**). The (1*E*,3*E*,8*Z*)-triene (**65**) reacted smoothly over 21 hr in the presence of ATPH, to give a 68:32 mixture of the *cis* and *trans* fused cycloadducts (**65 *cis* P**) and (**65 *trans* P**), respectively, in 73% yield. Once again, both reactions proceeded with enhanced *endo* selectivity with respect to the terminal carbomethoxy groups of the trienes (**155**) and (**65**), when compared to the corresponding heat promoted IMDA reactions (**Scheme 3.39**).

The Lewis acid promoted IMDA reactions of (1*E*,3*E*,8*E*)-triene (**155**) are strongly *trans*, or *endo*, selective; diethyl aluminium chloride (**171**) promotion and ATPH (**49**) promotion both give *endo:exo* ratios in excess of 95:5, and these results are identical considering the limits of detection. The Lewis acid promoted IMDA reactions of the (1*E*,3*E*,8*Z*)-triene (**65**) are not as *endo* selective as the reactions of the (1*E*,3*E*,8*E*)-triene (**155**); diethyl aluminium chloride promotion gives a ratio of 82:18, *endo:exo*, and ATPH promotion gives a ratio of 68:32, *endo:exo*. Although diethylaluminium chloride (**171**) promotes a more *endo* selective reaction than does ATPH (**49**), both promoters give enhanced *endo* selectivity relative to the heat promoted IMDA reaction (**Scheme 3.41**).



(**203**) (**203 *cis* P**) (**203 *trans* P**)

Entry	*E* -	*Z* -	promoter	*cis* : *trans*^{EXP}	*cis* : *trans*^{DFT}	*endo* : *exo*	yield (%)
1	CO_2Me	H	heat	27:73	35:65	73:27	66
2	H	CO_2Me	heat	51:49	28:72	51:49	93
3	CO_2Me	H	Et_2AlCl	4:96	-	96:4	87
4	H	CO_2Me	Et_2AlCl	82:18	-	82:18	44
5	CO_2Me	H	ATPH	1:99	-	99:1	81
6	H	CO_2Me	ATPH	68:32	-	68:32	73

Scheme 3.41 *Summary of stereoselectivities of heat and Lewis acid promoted intramolecular Diels-Alder reactions of ether tethered trienes (155) and (65). DFT calculations were carried out by Prof. M. N. Paddon-Row at the B3LYP/6-31+G(d) level of theory. Note enhanced endo stereoselectivities relative to heat promoted reactions in all Lewis acid promoted reactions. Difference between runs ±3%.*

The Lewis acid promoted IMDA reactions of trienes (**155**) and (**65**) gave somewhat unexpected outcomes. It was anticipated that the diethylaluminium chloride (**171**) promoted reactions would give a preponderance of the *endo* stereoisomers; adduct (**155 *trans* P**) from triene (**155**), and adduct (**65 *cis* P**) from triene (**65**). However, at the time the reactions were carried out, it was not anticipated that the same stereoisomers would be the major products in the ATPH (**49**) promoted IMDA reactions of these trienes.

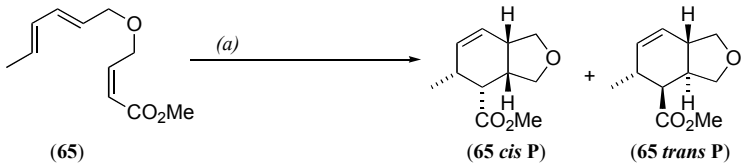
Subsequent studies with other trienes have shown that ATPH (**49**) does indeed promote *endo* selective IMDA reactions under certain circumstances.[157]

It is not known how ATPH promotes *endo* selective IMDA reactions, although one can speculate. The whole IMDA precursor may fit into the binding pocket of the intact complex, perhaps through complexation at the ether oxygen, or one or more diphenylphenoxide ligands may disassociate from the aluminium, producing a more sterically accessible Lewis acidic species.

3.2.4 Intramolecular Diels-Alder reactivity of ether and ester linked 1,3,8-nonatrienes

As part of a detailed experimental and computational investigation of the IMDA reactivity of a series of ether tethered and ester tethered trienes (**155**), (**65**), (**156**), (**157**) and (**158**), five rate studies were carried out in the Sherburn group.[177] This section describes the rate study carried out with triene (**65**), and calculations performed using data from all five rate studies carried out within the Sherburn group.

Triene (**65**) (**Scheme 3.42**) was synthesised and isolated in pure form by the method described earlier in this chapter, and 5 mM solutions of (**65**) and an internal standard (*t*-butyl benzene) in benzene-d_6 were sealed into ampoules and frozen.



(**65**) (**65** ***cis*** **P**) (**65** ***trans*** **P**)

Scheme 3.42 *Intramolecular Diels-Alder reaction of triene (**65**). Conditions: (a) benzene-d_6, 5 mM in triene, t-butyl benzene, sealed tubes, 55-95 °C, time.*

The ampoules were then placed in a preheated thermostat bath at 55 °C, 65 °C, 75 °C, 85 °C or 95 °C, ± 0.05 °C, (328.15 K, 338.15 K, 348.15 K, 358.15 K or 368.15 K) and removed at 15 regular intervals over at least two half lives ($t_{1/2}$) of reaction (**Figure 3.16**). Once removed, the ampoules were quickly cooled by immersion in a $CO_{2(s)}$/acetone bath. When they were opened, they were brought to room temperature, their contents were filtered through cotton wool and analysed by quantitative 300 MHz ^{1}H NMR. The T_1 relaxation times of the allylic methyl group in the triene and the corresponding methyl groups in the adducts were established. These resonances were

chosen as they were free from overlapping signals. 60 second relaxation delays were used as standard in data acquisition.

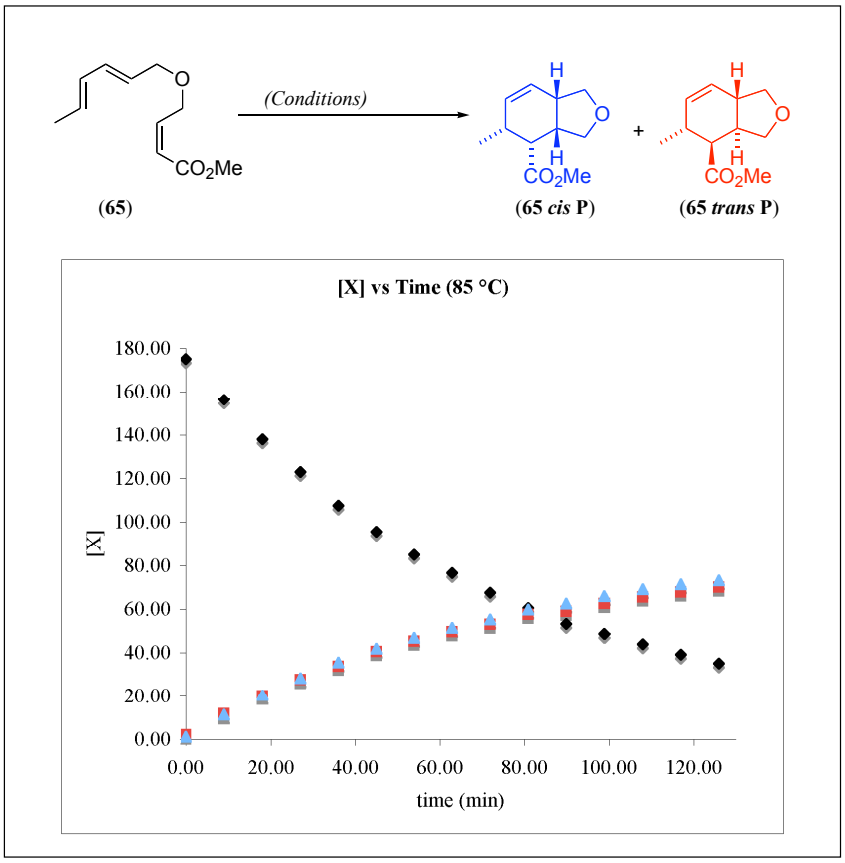


Figure 3.16 *Consumption of triene (**65**) (black) and production of cis (blue) and trans (red) cycloadducts (**65 cis P**) and (**65 trans P**), respectively. Conditions: 5 mM in triene, t-butyl benzene, 85 °C, benzene, sealed tubes, time.*

The consumption of the triene (**65**) and the production of the *cis* and *trans* fused IMDA adducts (**65 *cis* P**) and (**65 *trans* P**), respectively, were followed by 300 MHz ^{1}H NMR spectroscopy, and the experimental stereoselectivity was determined for each of the temperatures used. The stereoselectivity data were obtained from averages of up to 15 spectra per experimental temperature. It was important that the data were as accurate as possible, as they were used to partition the observed rate constants into rate constants for the cycloadditions giving the *cis* and *trans* products. The observed stereoselectivities are as follows:

55 °C: (**65** ***cis*** **P**):(**65** ***trans*** **P**) = (48.2:51.8)

65 °C: (**65** ***cis*** **P**):(**65** ***trans*** **P**) = (49.0:51.0)

75 °C: (**65** ***cis*** **P**):(**65** ***trans*** **P**) = (49.4:50.6)

85 °C: (**65** ***cis*** **P**):(**65** ***trans*** **P**) = (50.7:49.3)

95 °C: (**65** ***cis*** **P**):(**65** ***trans*** **P**) = (51.7:48.3)

The uncertainties in the ratios of rate constants were estimated to be less than 0.5%. Uncertainties in the stereoselectivity data (±0.5%), temperature (±0.02%) and time measurements (±0.2 to ±0.02%) were dwarfed by the uncertainties in the NMR integrals (±2%) obtained. Logarithmic curves were fitted to complete data sets for each experimental temperature, and plots of ln[triene (**65**)] versus time, generated with the Igor Pro software package,[199] were linear at each temperature, confirming the observed kinetic behaviour was first order (**Figure 3.17**).[200] Preliminary estimates of experimental uncertainties were obtained from plots of ln[triene (**65**)] versus time in the Igor Pro software package.[199]

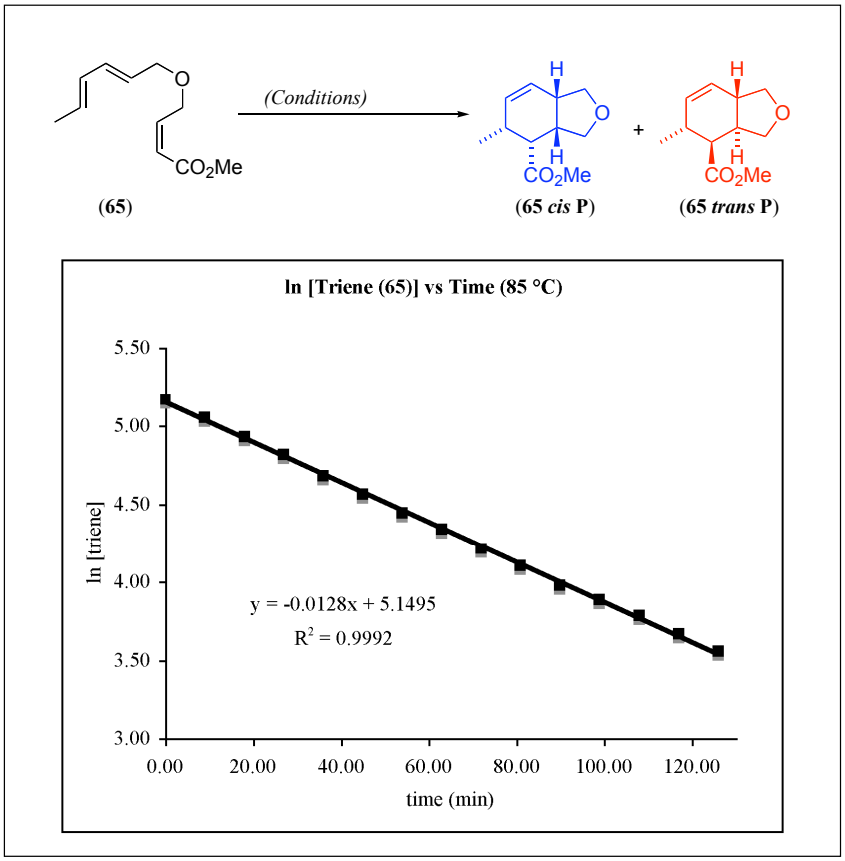


Figure 3.17 *Plot of ln [triene] (**65**) vs. time at 85 °C in benzene. The straight line fit indicates the intramolecular Diels-Alder reaction obeys first order kinetics. Conditions: 5 mM in triene, t-butyl benzene, 85 °C, benzene, sealed tubes, time.*

There are two chemical reactions occurring simultaneously under the experimental conditions; one consuming the triene (**65**) and producing the *cis* fused IMDA adduct (**65 *cis* P**), and one consuming the triene (**65**) and producing the *trans* fused IMDA adduct (**65 *trans* P**). Using the observed IMDA stereoselectivities at each of the five experimental temperatures, which it was assumed reflected ratios of rate constants, the observed rate constants were partitioned into separate rate constants for the cycloadditions yielding the *cis* and *trans* fused IMDA adducts, as shown below for data obtained at 85 °C.

$$y = mx + c$$
$$y = -0.0128x + 5.1495$$
$$k_{ob} = m = -0.0128$$
$$cis/trans = 1.041$$
$$k_{cis} = (1.041/2.041)k_{ob} = -0.00655$$
$$k_{trans} = (1.00/2.041)k_{ob} = -0.00629$$

In the Arrhenius analysis of the IMDA reactions of trienes (**155**), (**65**), (**156**), (**157**) and (**158**), the competing IMDA pathways producing the *cis* and *trans* fused IMDA adducts will be considered separately. The Arrhenius equation is an empirical kinetic model which relates the rate of a chemical reaction to an activation energy, E_a, and frequency factor, A. It is commonly used in the exponential form given here,

$$k = A \times e^{E_a / RT}$$

where k is a rate constant, E_a and A are the Arrhenius parameters, activation energy and frequency factor, respectively, R is the gas constant, and T is the absolute temperature. Arrhenius plots, of the natural logarithm of the rate constant versus the reciprocal of the absolute temperature were used to obtain E_a, and A for the IMDA reactions of trienes (**155**), (**65**), (**156**), (**157**) and (**158**), giving both the *cis* fused and *trans* fused IMDA adducts.[200] The Arrhenius plots for the cycloadditions giving the *cis* and *trans* fused IMDA adducts (**65 *cis* P**) and (**65 *trans* P**) from triene (**65**) are shown in (**Figure 3.18**).

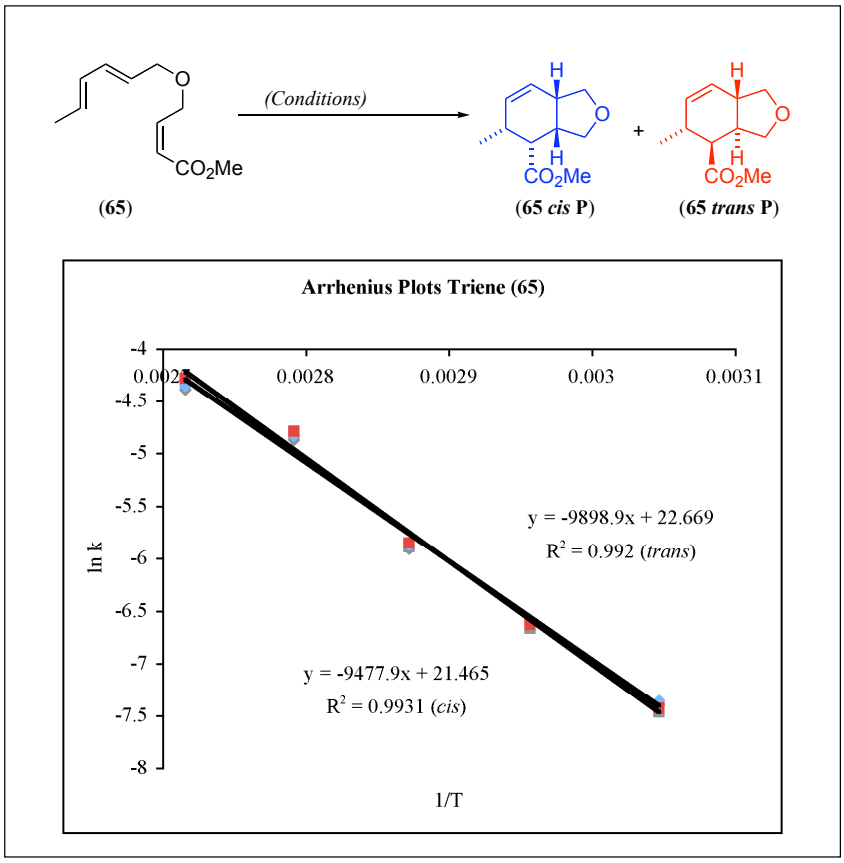


Figure 3.18 *Arrhenius plots for the intramolecular Diels-Alder reaction of triene (**65**), producing the cis and trans fused cycloadducts, (**65 cis P**) and (**65 trans P**). Conditions: 5 mM in triene, t-butyl benzene, 85 °C, benzene, sealed tubes, time.*

The activation energy, E_a, for the cycloaddition giving the *cis* fused adduct is obtained from the gradient of the Arrhenius plot and the gas constant, R. The activation energy of the IMDA reaction producing the *cis* fused IMDA adduct (**65** ***cis*** **P**) from triene (**65**) is calculated as follows.

$$y = mx + c$$
$$E_a = -m \times R$$
$$E_a = 9478 \times 8.314$$
$$E_a = 78.8 \ \ kJmol^{-1}$$

The frequency factor, A, for the cycloaddition giving the *cis* fused adduct is obtained from the y intercept of the Arrhenius plot. The frequency factor of the IMDA reaction producing the *cis* fused IMDA adduct (**65** ***cis*** **P**) from triene (**65**) is calculated as follows.

$$y = mx + c$$
$$A = e^{c}$$
$$A = e^{21.46}$$
$$A = 2.1 \times 10^{9}$$

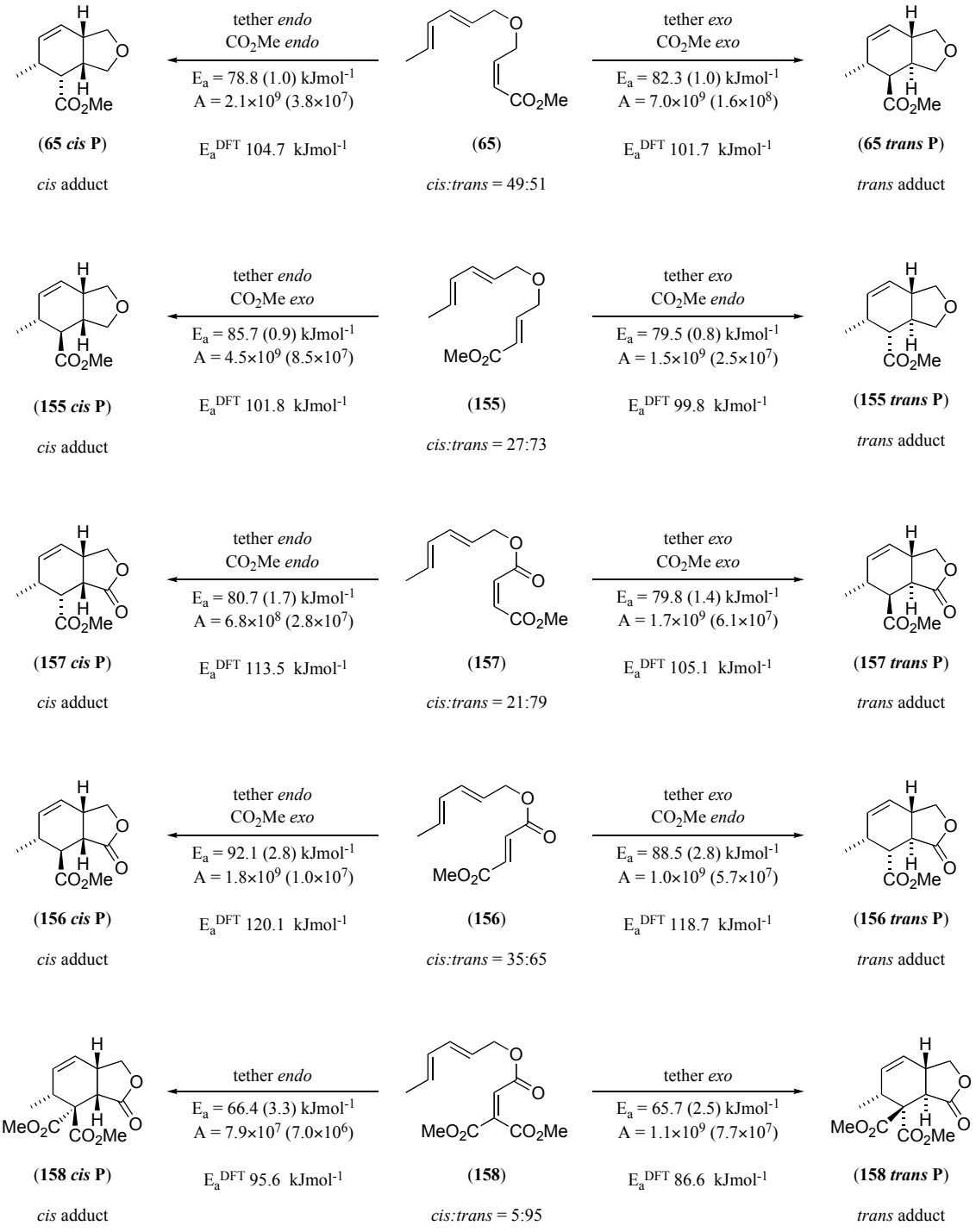
Experimental uncertainties are reported as standard deviations in each value of E_a and A, for the IMDA reactions of trienes (**155**), (**65**), (**156**), (**157**) and (**158**), giving both the *cis* and *trans* fused IMDA adducts. These values were obtained from the standard deviations of the gradients and y intercepts, respectively, of the corresponding Arrhenius plots in the Igor Pro software package.[199] The standard deviations of the activation energies, $\sigma(E_a)$, were obtained from the standard deviations of the gradients of the Arrhenius plots and the gas constant, R, as follows.

$$y = mx + c$$
$$E_a = -m \times R$$
$$\sigma(E_a) = \sigma(-m) \times R$$

The standard deviations of the frequency factors, $\sigma(A)$, were obtained from the standard deviations of the y intercepts of the Arrhenius plots as follows.

$$y = mx + c$$
$$A = e^{c}$$
$$\sigma(A) = e^{\sigma(c)}$$

The collected Arrhenius activation parameters, E_a and A, and the experimental uncertainties in the Arrhenius parameters expressed as standard deviations, $\sigma(E_a)$ and $\sigma(A)$ in parentheses, for the cycloadditions producing the *cis* and *trans* fused IMDA adducts from trienes (**155**), (**65**), (**156**), (**157**) and (**158**) are given in (**Scheme 3.43**).[201]



Scheme 3.43 *Collected Arrhenius parameters, activation energy, E_a, and frequency factor, A, and B3LYP/6-31+G(d) calculated activation energies[178] for intramolecular Diels-Alder reactions of trienes* ***(155)***, ***(65)***, ***(156)***, ***(157)*** *and* ***(158)****, giving the cis and trans fused cycloadducts. Experimental uncertainties associated with each value are presented as standard deviations, $\sigma(E_a)$ and $\sigma(A)$, in parentheses.*

Because the Arrhenius model has its basis in chemical kinetics, it treats the mechanism of a chemical reaction as something of a black box. The conceptual utility of this type

of analysis is limited, particularly for chemical reactions with complex, multi-step mechanisms. In these cases, the thermodynamic activation parameters available through the application of transition state theory, which can accommodate more complex reaction mechanisms, are likely to be more meaningful.[179] For single step, unimolecular reactions, such as the IMDA reactions considered here, the thermodynamic activation parameters of transition state theory, enthalpy of activation, $\Delta H^{\ddagger}$, and entropy of activation, $\Delta S^{\ddagger}$, relate to the Arrhenius parameters, activation energy, E_a, and frequency factor, A, respectively. The quantitative relationships are given here,

$$\Delta H^{\ddagger} = E_a - RT$$

$$\Delta S^{\ddagger} = R(\ln(A) - \ln(T) - 24.760)$$

where E_a and A are the Arrhenius parameters, activation energy and frequency factor, respectively, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are the thermodynamic activation parameters, enthalpy of activation and entropy of activation, respectively, R is the gas constant, and T is the absolute temperature.[179]

In the transition state theory analysis of the IMDA reactions of trienes (**155**), (**65**), (**156**), (**157**) and (**158**), the competing IMDA pathways, producing the *cis* and *trans* fused IMDA adducts, will be considered separately. Transition state theory assumes an equilibrium exists between the reactant and an activated complex, which permits analysis of the activation process in thermodynamic terms. When applied to single step, unimolecular processes, such as the IMDA reactions of trienes (**155**), (**65**), (**156**), (**157**) and (**158**), the expression for the equilibrium constant, $K^{\ddagger}$, is quite straightforward.

$$K^{\ddagger} = \frac{[activated\ complex]}{[triene]}$$

The Eyring equation relates the rate constant of a chemical reaction, k, to a transmission coefficient, κ, the Boltzmann constant, k_b, the absolute temperature, T, the Planck constant, h, and the equilibrium constant defined above, $K^{\ddagger}$. By substituting for $K^{\ddagger}$ in the Eyring equation, the rate constant of the reaction can be expressed in terms of the thermodynamic activation parameters, enthalpy of activation, $\Delta H^{\ddagger}$, entropy of activation, $\Delta S^{\ddagger}$, and free energy of activation, $\Delta G^{\ddagger}$.

$$k = \kappa \frac{k_b T}{h} K^{\ddagger}$$

$$k = \kappa \frac{k_b T}{h} e^{\left(-\Delta G^{\ddagger}/RT\right)}$$

$$k = \kappa \frac{k_b T}{h} e^{\left[\left(-\Delta H^{\ddagger}/RT\right)+\left(\Delta S^{\ddagger}/R\right)\right]}$$

Eyring plots, of the natural logarithm of the rate constant divided by the absolute temperature, versus the reciprocal of the absolute temperature, were constructed in the Kaleidagraph software package[202] and were used to obtain $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$ for the IMDA reactions of trienes (**155**), (**65**), (**156**), (**157**) and (**158**), giving both the *cis* fused and the *trans* fused IMDA adducts.[200] The Eyring plots for the IMDA reaction of triene (**65**), giving the *cis* and *trans* fused IMDA adducts, (**65 *cis* P**) and (**65 *trans* P**), are shown in (**Figure 3.19**).

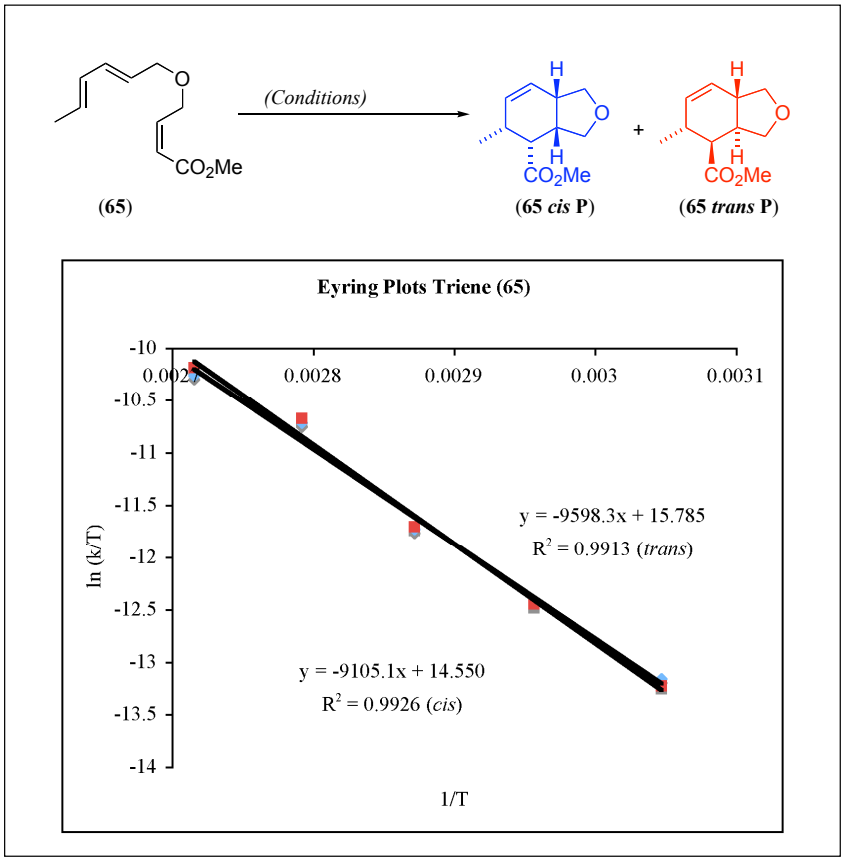


Figure 3.19 *Eyring plot for the intramolecular Diels-Alder reaction of triene (**65**), producing the cis and trans fused cycloadducts, (**65 cis P**) and (**65 trans P**). Conditions: 5 mM in triene, t-butyl benzene, 85 °C, benzene, sealed tubes, time.*

The enthalpy of activation, $\Delta H^{\ddagger}$, for the cycloaddition giving the *cis* fused adduct is obtained from the gradient of the Eyring plot and the gas constant, R, as follows.

$$y = mx + c$$
$$\Delta H^{\ddagger} = -m \times R$$
$$\Delta H^{\ddagger} = 9105.1 \times 8.314$$
$$\Delta H^{\ddagger} = 75.7 \ \ kJmol^{-1}$$

The entropy of activation, $\Delta S^{\ddagger}$, for the cycloaddition giving the *cis* fused adduct is obtained from the y intercept of the Eyring plot, the gas constant, R, the Boltzmann constant, k_b, and the Planck constant, h, as follows.

$$y = mx + c$$
$$\Delta S^{\ddagger} = R(c - \ln(k_b / h))$$
$$\Delta S^{\ddagger} = 8.314 \times (14.55 - \ln(1.381 \times 10^{-23} / 6.626 \times 10^{-34})$$
$$\Delta S^{\ddagger} = -76.6 \ \ JK^{-1}mol^{-1}$$

The free energy of activation, $\Delta G^{\ddagger}$, for the cycloaddition giving the *cis* fused adduct is calculated from the enthalpy of activation, $\Delta H^{\ddagger}$, the entropy of activation, $\Delta S^{\ddagger}$, and the absolute temperature, T, as follows.

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$
$$\Delta G^{\ddagger} = 75.7 - (348.15 \times -76.6)$$
$$\Delta G^{\ddagger} = 102.4 \ \ kJmol^{-1} \ \ at \ \ 75 \ \ ^{\circ}C$$

Experimental uncertainties are reported as the standard deviations of the values of enthalpy of activation, $\sigma(\Delta H^{\ddagger})$, entropy of activation, $\sigma(\Delta S^{\ddagger})$, and free energy of activation, $\sigma(\Delta G^{\ddagger})$, for the IMDA reactions of trienes (**155**), (**65**), (**156**), (**157**) and (**158**), giving both the *cis* and *trans* fused IMDA adducts. These uncertainties were obtained from the standard deviations of the gradients and y intercepts of the corresponding Eyring plots in the Igor Pro software package.[179,199,201]

The standard deviation of the enthalpy of activation, $\sigma(\Delta H^{\ddagger})$, is obtained from the standard deviation of the gradient of the Eyring plot and the gas constant, R, as follows.

$$y = mx + c$$
$$\Delta H^{\ddagger} = -m \times R$$
$$\sigma\left(\Delta H^{\ddagger}\right) = \sigma\left(-m\right) \times R$$

The standard deviation of the entropy of activation, $\sigma(\Delta S^{\ddagger})$, is obtained from the standard deviation of the y intercept of the Eyring plot, the gas constant, R, the Boltzmann constant, k_b, and the Planck constant, h, as follows.

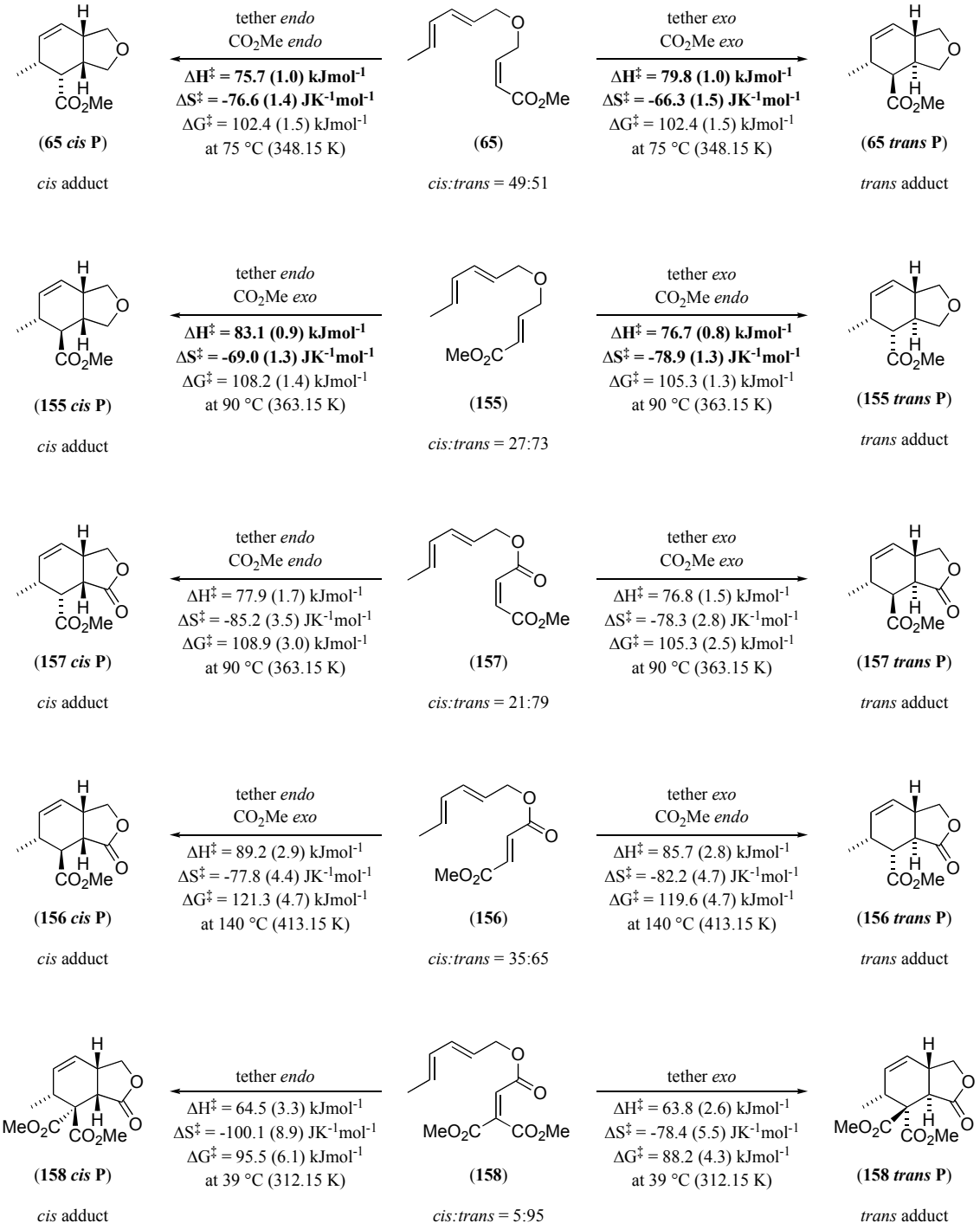
$$y = mx + c$$
$$\Delta S^{\ddagger} = R(c - \ln(k_b / h))$$
$$\sigma\left(\Delta S^{\ddagger}\right) = R(\sigma(c) - \ln(k_b / h))$$

The standard deviation in the free energy of activation, $\sigma(\Delta G^{\ddagger})$, is obtained from the standard deviations of the enthalpy of activation $\sigma(\Delta H^{\ddagger})$ and the entropy of activation $\sigma(\Delta S^{\ddagger})$, and the absolute temperature, T.

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

$$\sigma\left(\Delta G^{\ddagger}\right) = \sigma\left(\Delta H^{\ddagger}\right) + T\sigma\left(\Delta S^{\ddagger}\right)$$

The collected thermodynamic activation parameters, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$, for the cycloadditions producing the *cis* and *trans* fused IMDA adducts from trienes (**155**), (**65**), (**156**), (**157**) and (**158**), and the associated experimental uncertainties expressed as standard deviations, $\sigma(\Delta H^{\ddagger})$, $\sigma(\Delta S^{\ddagger})$, and $\sigma(\Delta G^{\ddagger})$, in parentheses, are listed in (**Scheme 3.44**).[201]



Scheme 3.44 *Collected experimental thermodynamic activation parameters, enthalpy of activation, $\Delta H^{\ddagger}$, entropy of activation, $\Delta S^{\ddagger}$, and free energy of activation, $\Delta G^{\ddagger}$, for intramolecular Diels-Alder reactions of trienes **(155)**, **(65)**, **(156)**, **(157)** and **(158)**, giving the cis and trans fused cycloadducts. Experimental uncertainties associated with each value are presented as standard deviations, $\sigma(\Delta X^{\ddagger})$, in parentheses. Entries in bold indicate that the 95% confidence intervals of the values for the cis and trans intramolecular Diels-Alder reaction pathways do not overlap.*

The stereoselectivities of the IMDA reactions of the trienes included in the rate studies range from nearly stereorandom to highly *trans* selective. Triene (**65**) gave a 51:49 mixture of the *cis* and *trans* fused IMDA adducts, respectively, whereas the IMDA reactions of the other four trienes, (**155**), (**156**), (**157**) and (**158**), are *trans* selective to varying degrees. The IMDA reaction of triene (**158**) is particularly *trans* selective, giving a *cis:trans* product ratio of 5:95. In a number of cases, the thermodynamic activation parameters of the competing *cis* and *trans* IMDA reaction pathways are very similar. The 95% confidence interval (95% CI) for the value of an activation parameter, ($\Delta X^{\ddagger}$), with a standard deviation $\sigma(\Delta X^{\ddagger})$, extends from [($\Delta X^{\ddagger}$) +1.96 $\sigma(\Delta X^{\ddagger})$] to [($\Delta X^{\ddagger}$) - 1.96 $\sigma(\Delta X^{\ddagger})$]. The 95% CIs of a pair of activation parameters, $(\Delta X^{\ddagger})_{(cis)}$ and $(\Delta X^{\ddagger})_{(trans)}$, do not overlap when they differ by nearly twice the sum of their standard deviations, $\sigma(\Delta X^{\ddagger})_{(cis)}$ and $\sigma(\Delta X^{\ddagger})_{(trans)}$, as expressed in the following equation.[201]

$$\sqrt{(\Delta X^{\ddagger}_{(cis)} - \Delta X^{\ddagger}_{(trans)})^2} \geq 1.96\left[\sigma(\Delta X^{\ddagger})_{(cis)} + \sigma(\Delta X^{\ddagger})_{(trans)}\right]$$

The activation parameters of the competing *cis* and *trans* IMDA reaction pathways, which do not overlap at the 95% CI are listed in bold in (**Scheme 3.44**). These are the enthalpies of activation, $\Delta H^{\ddagger}$, and entropies of activation, $\Delta S^{\ddagger}$, for the IMDA reactions of the ether tethered trienes, (**155**) and (**65**). The values of all the other activation parameters listed in (**Scheme 3.44**) overlap at the 95% CI, preventing the identification of meaningful trends in these parts of the data set. The enthalpy of activation, $\Delta H^{\ddagger}$, and entropy of activation, $\Delta S^{\ddagger}$, data for the IMDA reactions of trienes (**155**) and (**65**) are sufficiently precise give some insight into the factors controlling stereoselectivity in their IMDA reactions. In analysing the results of the rate studies, it is helpful to consider these factors in turn.

In the IMDA reactions of the ether tethered trienes (**155**) and (**65**), the enthalpically favoured transformations are those in which the terminal carbomethoxy groups adopt the *endo* orientation. It appears that any enthalpic factors associated with the ether tethers of these trienes are outweighed by effects involving the carbomethoxy groups appended to the dienophile. The precise nature of these effects are unknown, but a stabilising interaction between the *endo* disposed carbomethoxy group and the 1,3-diene in the IMDA transition state may account for the available data. The enthalpy of activation data for the ester tethered trienes (**156**), (**157**) and (**158**), are suggestive of a different trend. The enthalpically favoured transformations appear to be those in which

the ester tethers adopt the *exo* orientation. This pattern, however, is not statistically significant within the current data set.

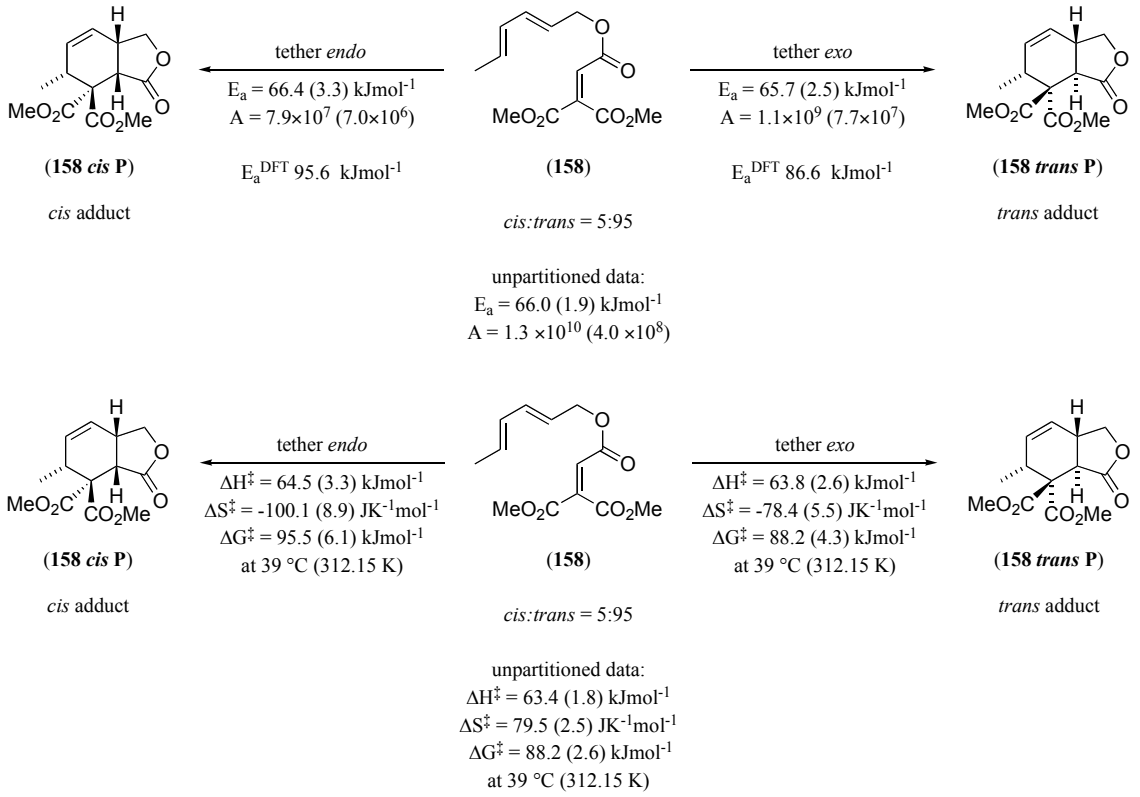
The entropic contribution to the free energy of activation, ($-T\Delta S^{\ddagger}$), is dependent on the temperature at which the reaction takes place, leading to small changes in stereoselectivity across the range of temperatures at which each rate study was carried out. In the IMDA reactions of the ether tethered trienes (**155**) and (**65**), the entropically favoured transformations are those in which the terminal carbomethoxy groups adopt the *exo* orientation. It appears that any entropic factors associated with the ether tethers of these trienes are again outweighed by effects involving the carbomethoxy groups appended to the dienophile. It seems plausible that the transition states in which the carbomethoxy groups adopt the *exo* orientation would have greater conformational freedom than those in which they adopt the *endo* orientation. In addition, the data for the IMDA reactions of the ester tethered trienes (**156**) and (**157**), are suggestive of a similar trend, although this trend is not statistically significant within the current data set.

Intuitively, one may expect transformations involving triene conformations with an *endo* disposed carbomethoxy group to be enthalpically favoured, due to stabilising interactions between the 1,3-diene and the carbomethoxy substituent, but entropically disfavoured by the relatively strict geometrical requirements such stabilising interactions may impose upon a molecule. Conversely, transformations involving triene conformations with an *exo* disposed carbomethoxy group may be enthalpically disfavoured due to the absence of a strong stabilising interaction between the carbomethoxy group and the 1,3-diene, but entropically favoured as the attendant geometrical requirements are relaxed.

Triene (**158**) undergoes IMDA reactions with very high *trans* stereoselectivity (5:95 *cis:trans*). The mixtures of cycloadducts produced by the IMDA reactions of this triene were analysed by ^{1}H NMR spectroscopy, and the relative amounts of the components of the mixture were obtained by integrating the ^{1}H NMR spectra. Such a procedure usually gives integral data with relative uncertainties of less than 2%, but the relative uncertainties in the measurements of the *cis* fused cycloadduct may have been as high as 40% in this instance, as the mixtures contained only small quantities of that compound. The integral data were used to partition the observed rate constants, giving

rate constants for the cycloadditions producing the *cis* fused and *trans* fused adducts. As a result, the partitioned rate constants, and the Arrhenius and thermodynamic activation parameters calculated from them, are likely to contain reasonably large errors.

Inspection of the Arrhenius data for the IMDA reactions of triene (**158**) derived from the partitioned rate constants shows that the *cis* and *trans* pathways have very similar activation energies and very different frequency factors (**Scheme 3.45**). Such a difference in frequency factors is thought to be unrealistic, given the degree of *trans* stereoselectivity.[178] For these reasons, the activation energy, E_a, frequency factor, A, and thermodynamic activation parameters, enthalpy of activation, $\Delta H^{\ddagger}$, entropy of activation, $\Delta S^{\ddagger}$, and free energy of activation, $\Delta G^{\ddagger}$, for the IMDA reaction of triene (**158**) were recalculated from unpartitioned rate data. This gives a weighted average of the activation parameters for the *cis* and *trans* reaction channels, without introducing the uncertainty associated with partitioning the observed rate constants. As would be expected, the figures calculated from the unpartitioned data are in very close agreement with the figures calculated from the partitioned data for the cycloaddition giving the *trans* adduct, (**158 *trans* P**).



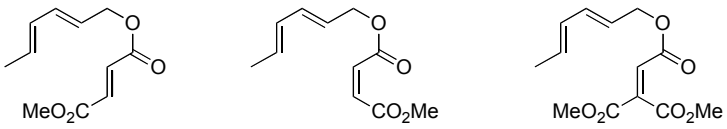
Scheme 3.45 *Top: Partitioned and unpartitioned experimental Arrhenius activation parameters, activation energy, E_a, and frequency factor, A, for intramolecular Diels-Alder reaction of triene (**158**), giving the cis and trans fused cycloadducts. Bottom: Partitioned and unpartitioned experimental thermodynamic activation parameters, enthalpy of activation, $\Delta H^{\ddagger}$, entropy of activation, $\Delta S^{\ddagger}$, and free energy of activation, $\Delta G^{\ddagger}$, for intramolecular Diels-Alder reaction of triene (**158**), giving the cis and trans fused cycloadducts. Experimental uncertainties associated with each value are presented as standard deviations, $\sigma(\Delta X^{\ddagger})$, in parentheses.*

The experimentally determined activation energies for the *cis* and *trans* pathways of the IMDA reactions of trienes (**155**), (**65**), (**156**), (**157**) and (**158**), can now be compared with the corresponding values calculated by Prof. M. N. Paddon-Row at the B3LYP/6-31+G(d) level of theory. It is clear from inspection of (**Scheme 3.43**) that the calculated values are consistently too large, but the reason for this discrepancy is unknown. Initially, it was thought that the DFT model was overestimating the degree of conjugation in the ester tethers of trienes (**156**), (**157**) and (**158**), and so rate studies were carried out with the two ether tethered trienes. The data for the ether tethered trienes (**155**) and (**65**), however, show that the problem is more general than was previously anticipated, as these trienes contain no functional groups capable of conjugative interactions in their tethers. It is thought that the experimental data

obtained in this study with allow the evaluation of the accuracy of calculations performed at higher levels of theory.[178,177,89,157]

3.2.5 Kinetic isotope effects and asynchronicity in the intramolecular Diels-Alder reaction

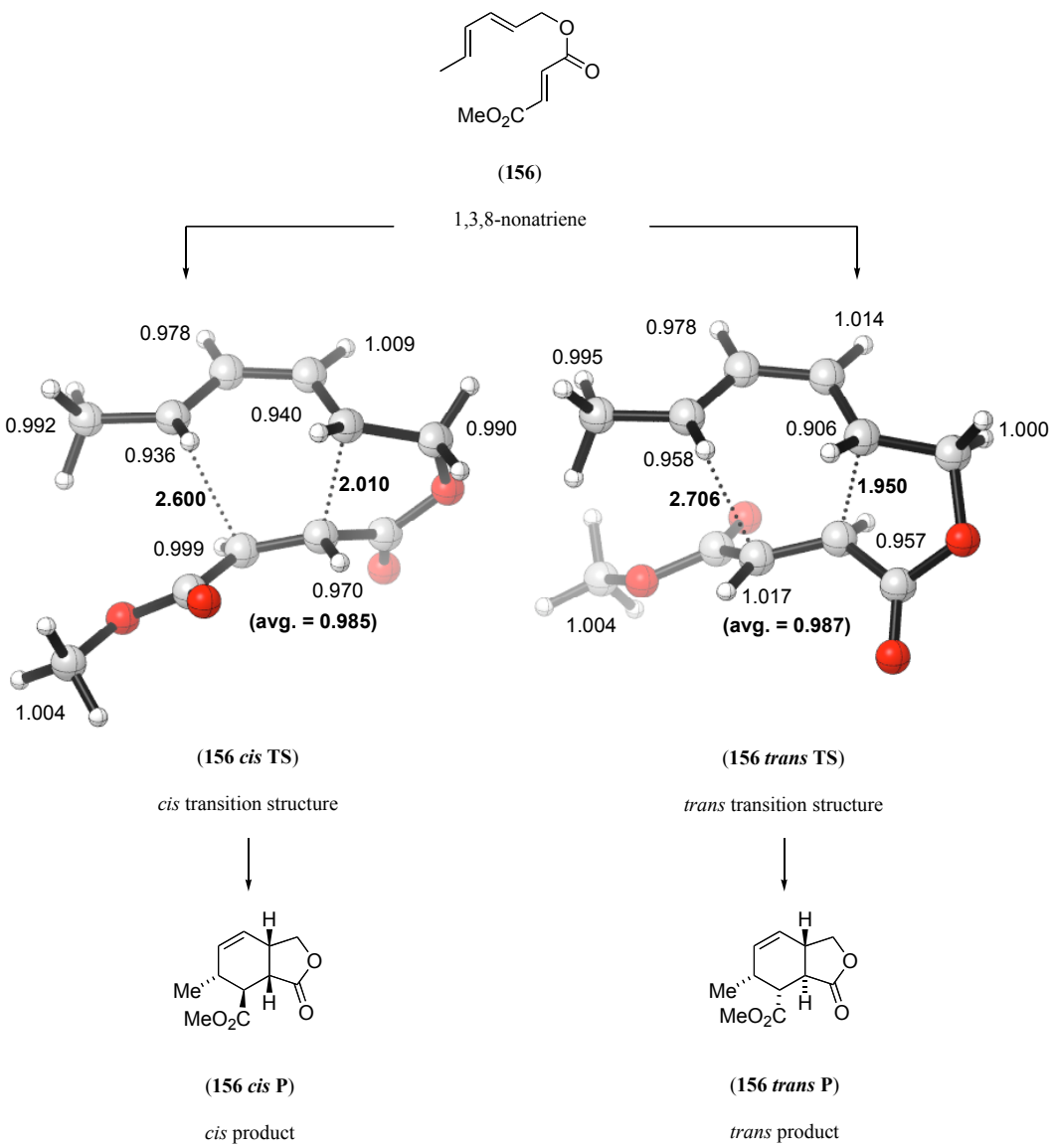
A gas phase B3LYP/6-31+G(d) computational investigation of the IMDA reactions of the ester tethered trienes (**156**), (**157**) and (**158**), carried out by Prof. M. N. Paddon-Row, found that the IMDA reactions of these trienes proceed with marked bond forming asynchronicity (**Figure 3.20**).



(**156**) (**157**) (**158**)

Figure 3.20 *1,3,8-nonatrienes chosen for kinetic isotope effect studies.*

The *cis* and *trans* transition structures located for the transformations of trienes (**156**), (**157**) and (**158**), have no diradical or zwitterionic character, but their peripheral developing bonds are greater than or equal to 2.6 Å in length, a large distance for an uncatalysed DA reaction. In addition, little rehybridisation of the carbons at either end of the peripheral developing bonds is evident in the transition structures; the geometry at these centres is almost trigonal planar (**Scheme 3.46**). KIE studies are one of the few experimental methods by which the transition structure geometries of chemical reactions can be investigated. In order to better understand why the DFT modelling fails to reproduce the absolute activation barriers of the IMDA reactions of trienes (**156**), (**157**) and (**158**), and to experimentally validate the transition structure geometries located for these transformations by computational methods, a study of secondary deuterium KIEs in the IMDA reactions of these trienes was considered.



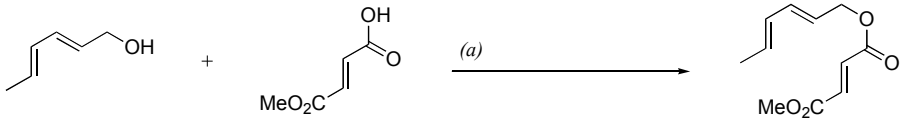
Scheme 3.46 *Deuterium kinetic isotope effects, developing bond lengths and B3LYP/6-31+G(d) transition structures located by Prof. M. N. Paddon-Row for the intramolecular Diels-Alder reaction of triene (**156**) in chlorobenzene at 405 K.*

KIEs can be an exceptionally sensitive probe of transition state geometry, and in numerous instances KIE data have provided definitive answers to long running mechanistic controversies, including those surrounding 3,3-sigmatropic shifts,[203,204] the dihydroxylation of alkenes involving osmium tetroxide,[205] and the intermolecular DA reaction.[94,206,207]

A thorough search of the literature found no references describing KIE studies of IMDA processes, but the application of the high precision natural abundance method, reported by Singleton and Thomas[94] and discussed in (**Section 3.1.3**), to the IMDA reactions of

trienes (**156**) and (**157**) appeared feasible and appealing. Triene (**158**) slowly undergoes IMDA reaction at room temperature, and it was thought that the reactivity of this compound would preclude its use in a high precision KIE determination, thus trienes (**156**) and (**157**) were the focus of the KIE study.

Trienes (**156**) and (**157**) are known compounds. Prior to the initiation of this project, they had been prepared on sub-gram scales in yields of around 40% through Steglich esterifications.[208] of the corresponding monomethyl esters (**204**) and (**205**) with sorbyl alcohol (**198**), and isolated in pure form by column chromatography.[92,145] The IMDA reactions of trienes (**156**) and (**157**) had been the subjects of rate studies, and their IMDA diastereoselectivities were known. The less reactive of the trienes, (**156**), was chosen for use in the development of a method for high precision IMDA KIE determinations at natural abundance. The Singleton group's approach for the measurement of KIEs at natural abundance uses a large scale isotopic fractionation event to amplify the effect of small KIEs, and requires that considerable amounts of the reactants be available.[94] Attempts were made to optimise and scale up the synthesis of triene (**156**) through Steglich esterification reactions with sorbyl alcohol (**198**) and methyl hydrogen fumarate (**204**), but they were largely unsuccessful (**Scheme 3.47**). Upon scale-up, it was particularly difficult to separate the dicyclohexyl urea byproduct from the triene (**156**) by column chromatography.



(**198**) (**204**) (**156**)

Scheme 3.47 *Synthesis of triene (**156**) from sorbyl alcohol (**198**) and methyl hydrogen fumarate (**204**) through Steglich esterification. Conditions: (a) DCC (1.5 molar equiv.), DMAP (0.2 molar equiv.), CH_2Cl_2, RT, 3 hr, 40%.*

Quantitative NMR data, obtained by integrating regions of NMR spectra, generally have relatively large uncertainties associated with them. The Singleton group's method[94] for natural abundance KIE determinations relies on an isotopic fractionation event to magnify the effects of the KIEs in the isotopic ratios observed by ^2H and ^{13}C NMR spectroscopy. The KIE can be calculated from F, the degree of completion of the reaction in the isotopic fractionation event, and R/R_0, the degree of isotopic enrichment at the site of interest.

$$KIE_{calc} = \frac{\ln(1-F)}{\ln[(1-F)R/R_0]}$$

The uncertainty in the calculated KIE is derived from uncertainty in the degree of completion of the reaction, F, and in the uncertainty in the degree of isotopic enrichment observed by NMR spectroscopy, R/R_0. If the degree of completion of the reaction, F, can be determined with high precision, then the contribution to the uncertainty in the calculated KIE from this source will be very small. Further, the uncertainty in the calculated KIE due to the uncertainty in the degree of isotopic enrichment decreases greatly as F approaches 1.000.[94]

^{1}H NMR spectroscopy is 6.7×10^5 times more sensitive than ^{2}H NMR spectroscopy at natural abundance,[209] and it was important to the overall precision of the technique that optimum conditions for the ^{2}H NMR spectroscopic analysis were found. Ideally, quantitative ^{2}H NMR spectra would be obtained from neat samples, giving the highest possible signal to noise ratio, as was done with isoprene (**74**) in many of the Singleton group's publication.[94] The triene (**156**) is, however, a solid, so this was not possible. Saturated solutions of the triene in $CHCl_3$ were approximately 4 M in triene. In these solutions, it was found the triene underwent oligomerisation during data acquisition by ^{2}H NMR spectroscopy at 25 °C on a time scale of hours. By reducing the sample temperature within the spectrometer to its minimum, 4 °C, the oligomerisation reactions were slowed but not halted. In addition, the solubility of the triene was somewhat reduced. The oligomerisation reactions could be suppressed by reducing the sample concentration, but this also caused a significant reduction in the signal to noise ratio of the ^{2}H NMR spectra generated. At 3 M in triene, with a sample temperature of 4 °C, the oligomerisation reactions proceeded, but did so reasonably slowly, and the window for data acquisition appeared to be around twelve hours. A 700 μL sample of a 3 M solution of the triene in $CHCl_3$ contains 430 mg of the triene dissolved in approximately 220 μL of solvent.

The isotopic fractionation event must be carried out on a scale large enough to permit the recovery of sufficient starting material for ^{2}H NMR spectroscopic analysis.[94] Approximately 430 mg of recovered triene (**156**) was needed for the ^{2}H NMR analysis under the optimised conditions, and this allowed the calculation of the initial quantity of the triene (**156**) required for the isotopic fractionation event. It was clear that relatively

large quantities of the trienes would be required for high precision KIE determinations. The reaction mixture obtained from an isotopic fractionation experiment beginning with 10 g triene (**156**) and taken to 95% conversion contains approximately 500 mg of the unreacted triene (**Figure 3.21**).

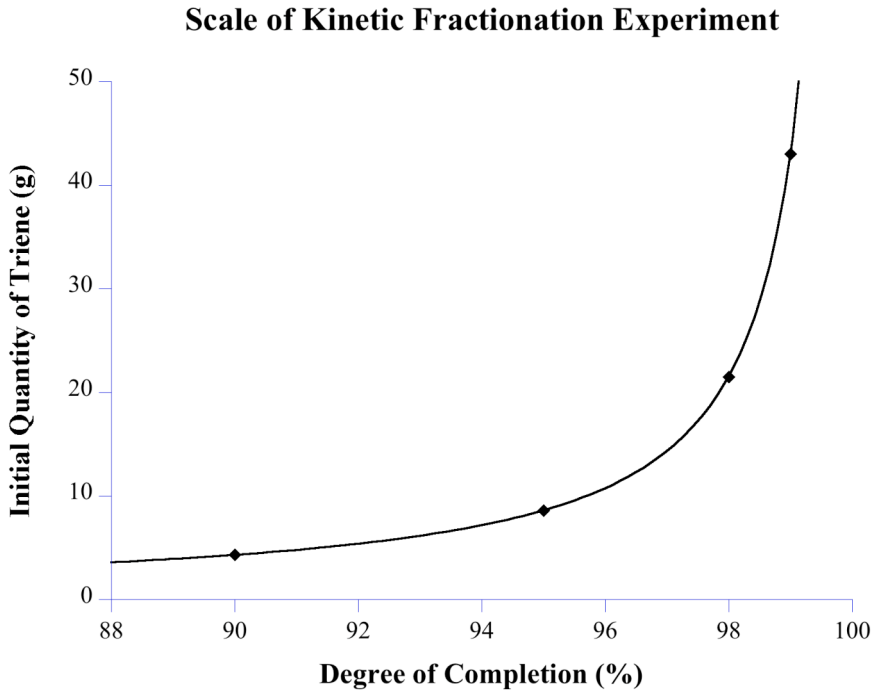
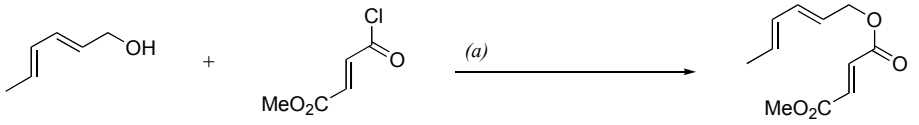


Figure 3.21 *Scale of the isotopic fractionation event necessary to obtain 430 mg of isotopically enriched triene (**156**).*

The Steglich esterifications of monomethyl fumarate (**204**) and monomethyl maleate (**205**) with sorbyl alcohol (**198**) were examined and found to be low yielding and inefficient. In addition, the trienes produced in this manner had to be purified by column chromatography, making the procedures very time consuming on the required scale. After considerable experimentation, a scaleable, efficient and high yielding synthesis of triene (**156**) from methyl fumaroyl chloride (**206**) and sorbyl alcohol (**198**) using Hunig's base (**207**) was developed (**Scheme 3.48**). A number of different bases and reaction temperatures were examined for this transformation. When the reaction was performed in the presence of less hindered amine bases, including 2,6-lutidine, pyridine and triethylamine, side reactions involving conjugate addition processes appeared to compete with the esterification reaction. Conducting the reaction at higher temperatures, or using NaH as the base also gave complex mixtures. Using Hunig's base (**207**) at low temperatures gave the cleanest reactions. It was important that the

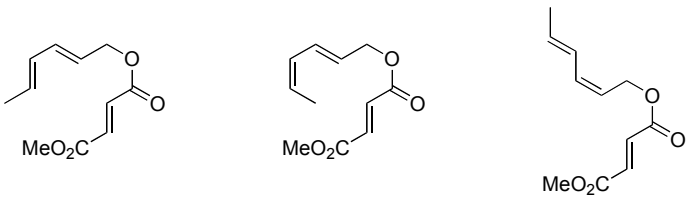
reaction was quenched with the addition of excess aqueous acid at 0 °C, and the reaction was run with a small excess of the acid chloride to ensure that all of the sorbyl alcohol was consumed. After all the sorbyl alcohol had reacted with the acid chloride, all of the byproducts in the reaction mixture could be removed with a series of acidic and basic aqueous washes, leaving reasonably pure triene (**156**) in the organic layer, which was then dried over $MgSO_4$ and concentrated under vacuum. Initially, the material obtained in this manner was used without further purification.



(**198**) (**206**) (**156**)

Scheme 3.48 *Efficient, large scale synthesis of triene (**156**) from methyl fumaroyl chloride (**206**) and sorbyl alcohol (**198**). Conditions: (a) Hunig's base (**207**), CH_2Cl_2, -78 to 0 °C, 1 hr, 87%.*

Test IMDA reactions with the triene (**156**), which served as isotopic fractionation events, were run on one gram scale to approximately 50%, 80% and 90% completion. Analysis of the ^{1}H NMR spectra of samples of the recovered triene (**156**) showed that they were contaminated with significant quantities of compounds thought to be geometrical isomers at the alkenes in the 1,3-diene unit, probably (1*Z*,3*E*,8*E*)-triene (**156a**) and (1*E*,3*Z*,8*E*)-triene (**156b**) (**Figure 3.22**).



(**156**) (**156a**) (**156b**)

Figure 3.22 *Isomeric fumarate trienes (**156**), (**156a**) and (**156b**).*

Careful examination of the ^{1}H NMR spectra of freshly prepared samples of triene (**156**) showed they contained small quantities of isomeric impurities, probably (1*Z*,3*E*,8*E*)-triene (**156a**) and (1*E*,3*Z*,8*E*)-triene (**156b**). The commercial sorbyl alcohol (**198**) used in the synthesis of the triene (**156**) was later found to contain the corresponding isomeric impurities. The impurities in the samples of triene (**156**) were less reactive than the triene (**156**) in an IMDA sense due to the *Z* configured alkenes in their 1,3-diene units, and they could not be separated from triene (**156**) by column

chromatography or HPLC. All isotopic fractionation experiments carried out on triene (**156**) led to enrichment of the unreactive isomeric trienes in the recovered starting material. It was clear that any benefits gained through an isotopic fractionation event were, in these cases, offset by the analytical difficulties caused by enrichment in the isomeric impurities. To overcome this problem, the sorbyl alcohol (**198**) used in preparing the triene (**156**) was recrystallised from *n*-pentane by cooling from 20 °C to 0 °C, and washing with *n*-pentane at 0 °C, in four cycles. The triene (**156**) was synthesised using recrystallised sorbyl alcohol (**198**) on 15 g (70 mmol) scale and was itself recrystallised from *n*-pentane by cooling slowly from 20 °C to -50 °C and washing with *n*-pentane at -50 °C, in five cycles. The recovery of material over the five iterations was 80%. This produced a batch of triene (**156**) weighing 11.95 g, with a purity of >99.95% by ^{1}H NMR analysis, using the ^{13}C satellite signals of the triene as an internal calibrant (**Figure 3.23**).[210]

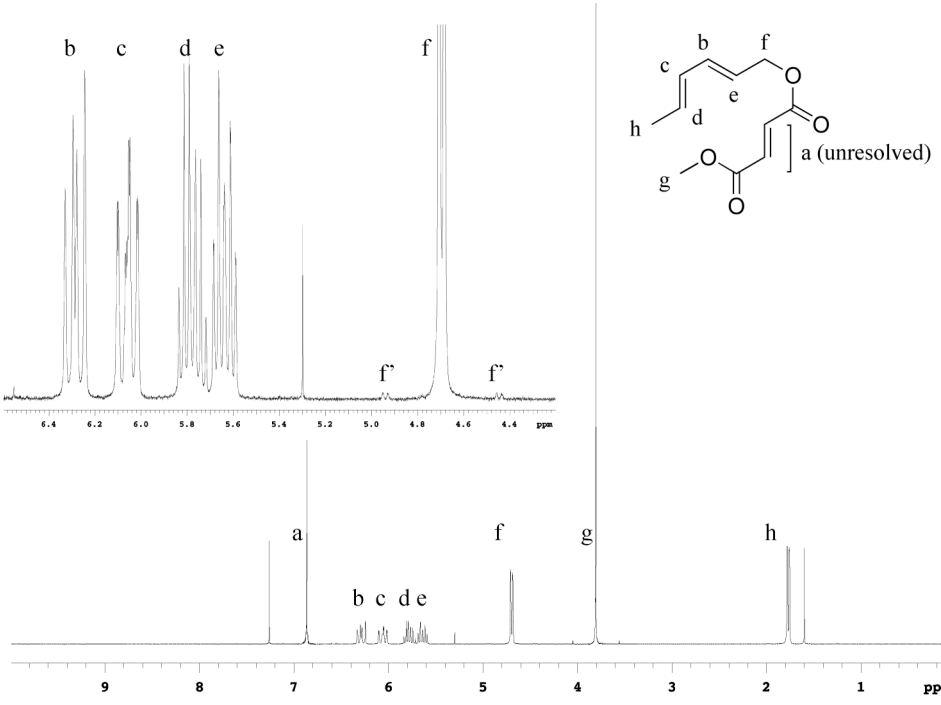
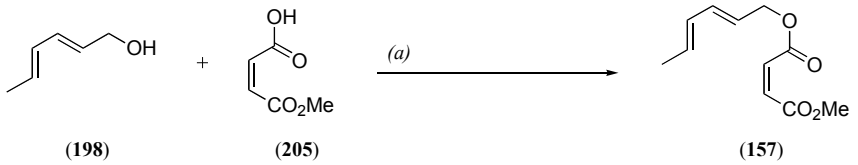


Figure 3.23 *^{1}H NMR spectrum of recrystallised triene (**156**) made using recrystallised sorbyl alcohol (**198**). The sample contains a small amount of CH_2Cl_2, visible as a singlet at δ = 5.30. Signals labelled **H_f'** are ^{13}C satellites of **H_f**, J (^{13}C - ^{1}H) = 148 Hz. Intensity ratio (**H_f:H_f'**) = (178.5:1).*

It was calculated that a sample of the triene (**156**) of this purity taken to 95% completion in an isotopic fractionation experiment would produce a sample of recovered triene (**156**) containing approximately 1% isomeric impurities, assuming that

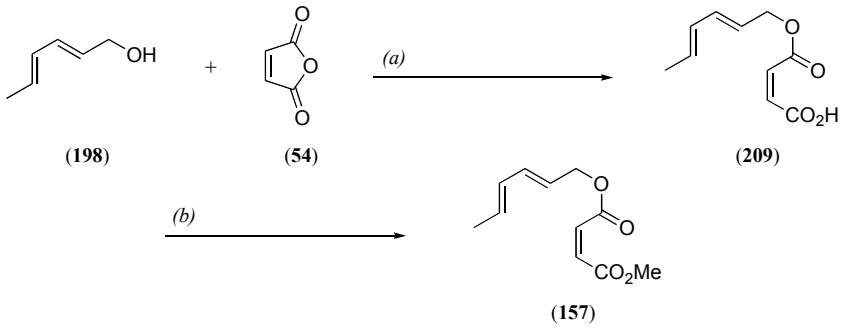
the impurities would not react during the experiment. The uncertainty in the measured KIEs due to this level of contamination was calculated and considered acceptable.

Triene (**157**) has previously been synthesised from sorbyl alcohol (**198**) and methyl hydrogen maleate (**205**) in a Steglich esterification, but this method was inefficient and required chromatographic purification of the product (**157**).[92,145] Attempts were made to optimise and scale this reaction up, but they were unsuccessful (**Scheme 3.49**).



Scheme 3.49 *Synthesis of triene (**157**) from sorbyl alcohol (**198**) and methyl hydrogen maleate (**205**) through Steglich esterification. Conditions: (a) DCC (1.5 molar equiv.), DMAP (0.2 molar equiv.), CH_2Cl_2, RT, 3 hr, 45%.*

An efficient and scaleable synthesis of triene (**157**) was developed (**Scheme 3.50**), starting from recrystallised sorbyl alcohol (**198**) and maleic anhydride (**54**). The reaction of sorbyl alcohol (**198**) with a small excess of maleic anhydride (**54**) in CH_2Cl_2, in the presence of Hunig's base (**207**), is rapid and exothermic at 0 °C. This reaction was conducted on 100 mmol (20 g) scale and the mixture obtained was carefully washed with acidic aqueous solutions and dried over $MgSO_4$, leaving the triene acid (**209**) in the organic phase. This acid (**209**) rapidly underwent IMDA reaction and oligomerisation, so it was methylated immediately with CH_3I (**210**) in the presence of Hunig's base (**207**) in DMF at RT. Conducting the methylation with diazomethane (**211**) in diethyl ether at -78 °C gave a mixture of triene (**157**) and compounds thought to be pyrazolines, formed through [3+2] cycloaddition reactions of the dienophile unit of the triene acid (**209**) or triene (**157**) with the diazomethane.



Scheme 3.50 *Efficient synthesis of triene (**157**) from recrystallised sorbyl alcohol (**198**) and maleic anhydride (**54**). Conditions: (a) Hunig's base (**207**), CH_2Cl_2, 0 °C to RT, 1 hr (b) CH_3I (**210**), Hunig's base (**207**), DMF, RT, 2 hr, 86% over two steps.*

The IMDA reactions of the free acid (**209**), and possibly triene (**157**), proceeded slowly during the methylation, and the triene (**157**) produced was contaminated with small amounts of the methylated cycloadducts (**157 *cis* P**) and (**157 *trans* P**). These could not be removed efficiently by recrystallisation, so the triene (**157**) was purified by column chromatography prior to recrystallisation. The recrystallisation was performed from *n*-pentane, between 0 °C and -70 °C, in three iterations. The recrystallisation was complicated by the fact that one crystal form had a melting point below -20 °C, and oligomerisation reactions slowly took place in concentrated solutions at -20 °C. The triene also slowly underwent IMDA reaction in dilute solution at 20 °C. ^{1}H NMR spectroscopic analysis using the ^{13}C satellite signals of the triene (**157**) as an internal calibrant[210] indicated that a 12 g batch of triene (**157**) produced in this way was >99.0% pure (**Figure 3.24**). From ^{1}H NMR spectroscopic analysis, the major contaminants appeared to be the IMDA adducts and compounds with isomeric configurations at the 1,3-diene unit of the triene. Assuming that the contaminants are unreactive in an IMDA sense, a kinetic fractionation experiment taken to 95% conversion using triene (**157**) of 99.0% isomeric purity will generate a sample of recovered triene (**157**) containing approximately 20% isomeric impurities, probably (1*Z*,3*E*,8*E*)-triene (**157a**) and (1*E*,3*Z*,8*E*)-triene (**157b**). In this case it was clear that the triene (**157**) was not of the purity required for the isotopic fractionation experiment, but improved recrystallisation conditions could not be found, and plans to perform a natural abundance KIE determination on triene (**157**) were abandoned.

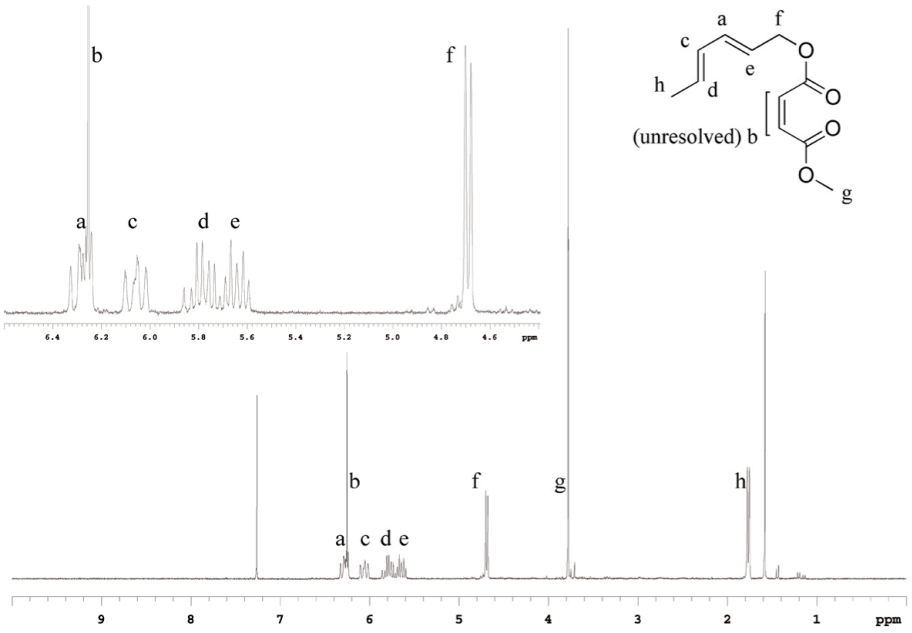


Figure 3.24 *^{1}H NMR spectrum of recrystallised triene (**157**) made from recrystallised sorbyl alcohol (**198**). The sample contains small quantities of isomeric impurities and the corresponding cycloadducts.*

It is noteworthy that the vast majority of the reported high precision KIE determinations using the natural abundance method described by Singleton and coworkers[94] and involving a DA reaction have been carried out using isoprene (**74**) as the 1,3-diene. The problems encountered in attempting to apply this method to the IMDA reaction of trienes (**156**) and (**157**), described above, are instructive and their implications are far reaching. No examples using acyclic 1,3-dienes with substituents at the 1 or 4 positions, of which *E* and *Z* isomers can exist, have been reported. This is a significant limitation of the technique, and it restricts its use in the investigation of DA reactions to just a handful of special cases. Unfortunately, this important limitation was completely ignored by the authors of the original publication, and the method was touted as enabling the determination of KIEs to "become a routine part of the characterization of chemical reactions."[94]

With 12 g of recrystallised, 99.95% pure triene (**156**) in hand, and knowing the optimum sample size for ^{2}H NMR spectroscopic analysis was 430 mg, a decision was made to carry out an isotopic fractionation experiment and KIE determination on 10 g of the material. The aim was to take the isotopic fractionation step to 95% conversion, leaving approximately 500 mg of the triene (**156**) to be recovered. This would allow

some margin for error in the recovery steps and time calculations, and ensure sufficient material remained for the final ^{2}H NMR spectroscopic analysis.

The IMDA reactions of triene (**156**) only occur when the tether of the triene folds back on itself, allowing the 1,3-diene and dienophile units to approach one another in space. The minimum energy conformation of the triene, however, is one in which the dienophile and the adjacent ester groups are coplanar, with conjugative interactions optimised through this moiety. Thus, the IMDA reactions of this triene incur an energetic penalty that its intermolecular DA reactions do not.[92] For these reasons, the concentration at which the IMDA reactions of this triene are carried out is critical, as oligomerisation can result if the concentration is too high. The prospect of carrying out a 50 mmol scale (10 g) isotopic fractionation experiment at high dilution was daunting, so the concentration at which the reaction became completely intramolecular, within the limits of detection, was determined. Test reactions showed that oligomerisation processes competed with the IMDA reaction at 20 mM and 15 mM, but not at or below 10 mM. An IMDA reaction using 50 mmol (10 g) of the triene at 10 mM concentration requires approximately 5 L of solvent.

The degree of completion in the isotopic fractionation step of a KIE determination of this nature needs to be measured with high precision in order to minimise the uncertainty in the KIEs obtained. Benzophenone (**213**) was used as an internal standard (IS) in the IMDA reaction of triene (**156**), and was chosen because it did not overlap with the ^{1}H NMR, ^{2}H NMR, or ^{13}C NMR signals of the triene or its IMDA adducts, (**156 *cis* P**) and (**156 *trans* P**). A quantitative, normal phase analytical HPLC method was developed, and response ratios at numerous wavelengths across a range of concentrations were determined. The quantitative analytical HPLC method was first calibrated against quantitative ^{1}H NMR spectral data, and then against high precision gravimetric analysis data. The method developed was sensitive, reproducible and reliable. It was hoped that the triene could be separated from its geometrical isomers by HPLC, and a considerable period of time was spent surveying different columns and solvent systems for this purpose, using samples of the triene obtained from small scale isotopic fractionation experiments, which were enriched in the geometrical isomers. The prospect of purifying the triene recovered from a large scale isotopic fractionation event by HPLC was attractive, but the triene co-eluted with its geometrical isomers with every combination of column and solvent system surveyed.

The kinetics of the IMDA reaction of triene (**156**) had been studied previously. Using the kinetics data obtained in benzene in sealed tubes at 130 °C as a starting point, test reactions were carried out to track the consumption of the triene in chlorobenzene at 130 °C. These reactions were run in the presence of benzophenone (**213**) as an IS, and were monitored by HPLC. It was found that the rates of reaction were identical, within experimental error, in the two solvents at 130 °C. This allowed the time taken by the reaction to reach different degrees of completion to be calculated with relative confidence.

The isotopic fractionation event was carried out with 10.1938 g of triene (**156**), of >99.95% purity by ^{1}H NMR spectroscopic analysis, in the presence of 1.9358 g benzophenone (**213**), in 5.5 L of chlorobenzene. The calculated concentration of the reaction mixture was 8.8 mM in triene. A solution of 220 mg (1.0 mmol.) of BHT, a radical inhibitor, in 5.4 L of chlorobenzene in a 10 L round bottom flask was agitated with an overhead stirrer, and heated to reflux (130 °C) with a heating mantle. A solution of the triene (**156**) and benzophenone (**213**) in chlorobenzene (100 mL) was mixed thoroughly and added to the hot chlorobenzene in the RBF. The IMDA reaction was stopped 400 minutes later by the immersion of a coiled glass tube containing a stream of cooling water. The internal temperature of the reaction flask was monitored through the cooling phase, and took about 5 min to drop to 50 °C, a temperature at which the IMDA reaction was known to take place at a negligible rate.

Samples were analysed by HPLC, and the degree of completion, F, was found to be 0.9614 ± 0.001. The chlorobenzene was removed under reduced pressure on a rotary evaporator and the recovered triene (**156**) was purified by two iterations of column chromatography. A sample of the triene (**156**) weighing 382 mg was recovered, which is 97% of the amount calculated, from HPLC analysis, to be present at the end of the isotopic fractionation event. Samples of the triene (**156**) from before and after the isotopic fractionation event were analysed by 800 MHz ^{1}H NMR spectroscopy and 123 MHz ^{2}H NMR spectroscopy. The amount of triene (**156**) budgeted for the final ^{2}H NMR spectroscopic analysis was 430 mg, as it was known that this quanitity dissolves in a small amount of $CHCl_3$, yielding 700 μL of a 3 M solution. The entire 380 mg sample of triene (**156**) recovered from the isotopic fractionation reaction was used for the ^{2}H NMR spectroscopic analysis, giving a sample concentration of 2.6 M.

The isotopic fractionation reaction consumed a little more of the triene (**156**) than was expected, but the result is excellent when the uncertainties in the relevant calculations are considered. ^{2}H T_1 relaxation experiments were carried out, allowing the efficient acquisition of quantitative ^{2}H NMR data. The 123 MHz ^{2}H NMR data acquisition over 9 hr was uneventful with the 3 M natural abundance sample of the triene (**156**), representative of the triene (**156**) before the isotopic fractionation event. The state of the sample after ^{2}H NMR data acquisition was confirmed by ^{1}H NMR spectroscopic analysis. As the sample of the triene (**156**) recovered from the isotopic fractionation experiment was smaller than anticipated, and dissolved in $CHCl_3$ to give a 2.6 M solution rather than a 3 M solution, the data acquisition period was extended in this case. It was anticipated that the sample might eventually begin to decompose, so the ^{2}H NMR spectroscopic data were acquired in blocks, and the sample was checked after the acquisition of each block by ^{1}H NMR spectroscopic analysis. Oligomerisation was observed beyond 12 hr, so only 12 hr of ^{2}H NMR spectroscopic data could be used in the KIE determination. It is unfortunate that the isotopically enriched sample began to oligomerise during the ^{2}H NMR data acquisition, otherwise the complementary $^{12}C/^{13}C$ KIE data could also have been obtained (**Figure 3.25**).

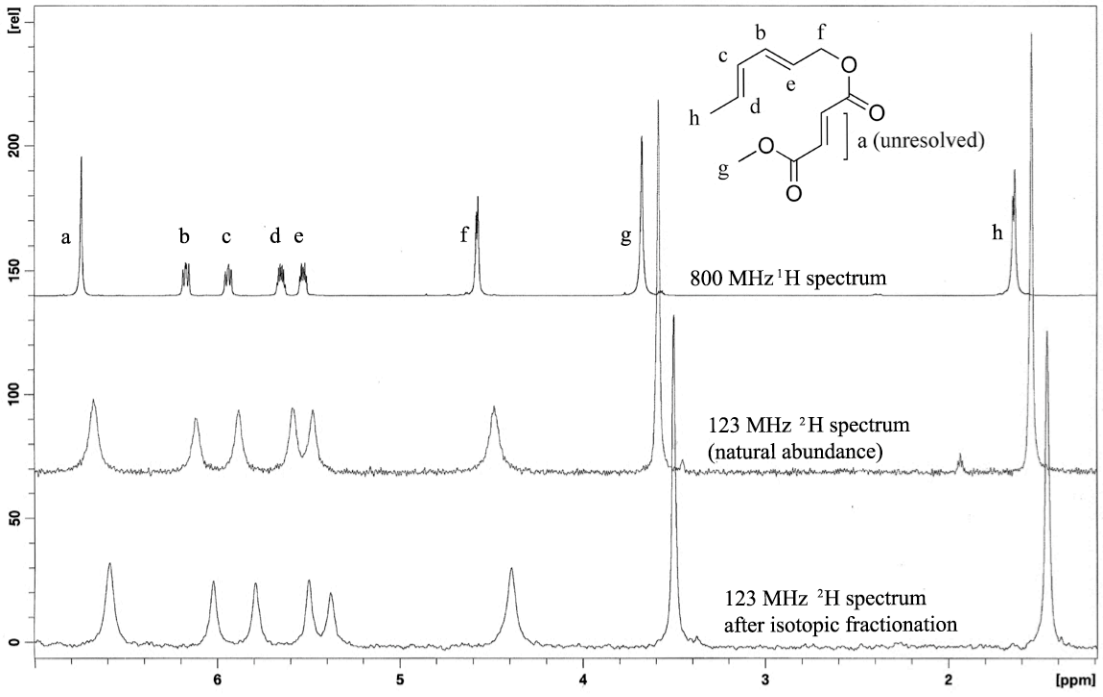


Figure 3.25 *NMR spectra of triene (**156**) run unlocked in $CHCl_3$ at 4 °C. Top: 800 MHz ^1H NMR spectrum of 3.0 M solution of triene (**156**) in $CHCl_3$, before isotopic fractionation event. Middle: Natural abundance 123 MHz ^2H NMR spectrum of 3.0 M solution of triene (**156**) in $CHCl_3$, representative of the triene before the isotopic fractionation event. Bottom: 123 MHz ^2H NMR spectrum of 2.6 M solution of triene (**156**) in $CHCl_3$, recovered from isotopic fractionation reaction taken to 96.14% ± 0.01% conversion.*

The ^2H NMR resonances are significantly broader than the corresponding ^1H NMR resonances and some of the signals of triene (**156**) overlap slightly in the ^2H NMR spectrum (**Figure 3.25**). Small differences between the ^2H NMR spectra of triene (**156**) from before and after the isotopic fractionation event are easily discernible. The resonances in the ^2H NMR spectra obtained from both samples of the triene (**156**) were fitted with a computer algorithm which gave the value of each integral and an estimate of the uncertainty in each integral value, based on an assumed Lorentzian lineshape.[211] The KIE at the methyl group of the methyl ester was assumed to be 1.000, allowing this position to be used as an internal reference for the calculation of the KIEs at the other positions in the triene (**156**) (**Figure 3.26**). The KIEs calculated will have a small systematic bias due to the fact that the KIE at this position is probably not exactly equal to 1.000.

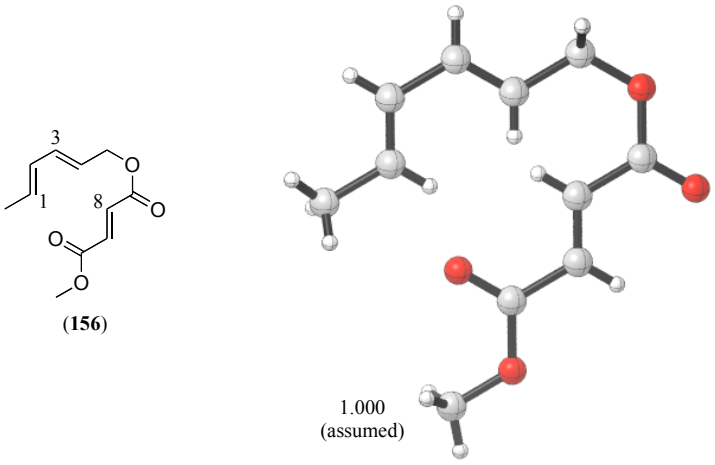


Figure 3.26 *Position chosen in triene (**156**) as an internal reference for the calculation of ^2H kinetic isotope effectss.*

The KIEs were calculated using the formula given below, where the degree of completion of the isotopic fractionation experiment, F, = 0.9614, and the degree of isotopic enrichment, (R/R_0), is calculated from the integrals taken from the ^2H NMR spectra of the triene (**156**) from before and after the isotopic fractionation experiment.

$$KIE_{calc} = \frac{\ln(1-F)}{\ln[(1-F)R/R_0]}$$

The uncertainties in the KIEs are calculated from the degree of completion of the isotopic fractionation reaction, F, the uncertainty in the degree of completion of the isotopic fractionation reaction, ΔF, the degree of isotopic enrichment at each position, (R/R_0), and the uncertainty in the degree of isotopic enrichment at each position, $\Delta(R/R_0)$.

$$\Delta KIE = \left[\frac{-\ln(R/R_0)}{(1-F)\ln^2[(1-F)R/R_0]}\Delta F\right] + \left[\frac{-\ln(1-F)}{(R/R_0)\ln^2[(1-F)R/R_0]}\Delta(R/R_0)\right]$$

The experimental KIEs and associated uncertainties obtained is this manner are shown in (**Figure 3.27**). As the signals for the methine hydrogens in the dienophile of triene (**156**) were unresolved in the ^1H and ^2H NMR spectra, an averaged value for the two sites was expected. The KIEs at these sites clearly do not match up with the KIEs in the 1,3-diene unit of triene (**156**); the KIEs at the positions in the 1,3-diene unit of the molecule are significantly stronger than those at the positions in the dienophile unit of the molecule. To help interpret the experimental data, KIEs for the IMDA reaction of

triene (**156**) were calculated by Prof. M. N. Paddon-Row. The calculated KIEs and the interpretation of the experimental data will be discussed in the following section of this thesis.

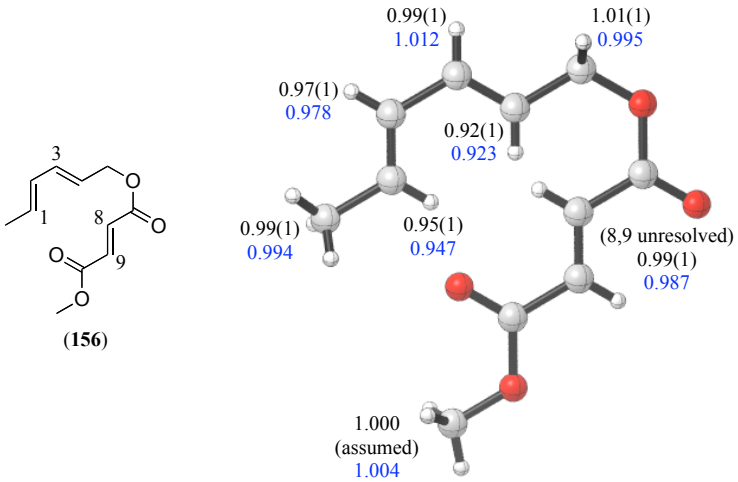


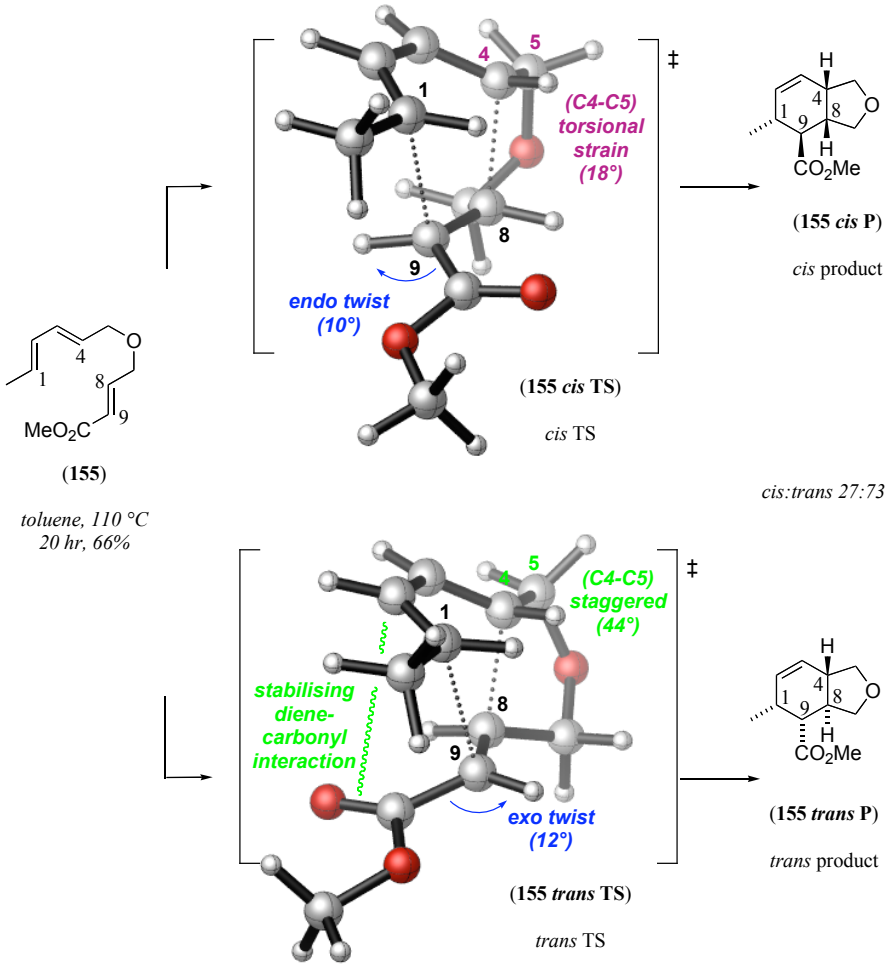
Figure 3.27 *Black: Experimental deuterium kinetic isotope effects for the intramolecular Diels-Alder reaction of triene (**156**), obtained from a natural abundance isotopic fractionation experiment run in chlorobenzene at 405 K. Blue: B3LYP/6-31+G(d) calculated deuterium kinetic isotope effects for the intramolecular Diels-Alder reaction of triene (**156**) in chlorobenzene at 405 K, obtained by averaging individual kinetic isotope effect data for cis and trans reaction channels.*

Numerous studies comparing experimental and calculated KIEs for intermolecular DA reactions have been reported,[161,191,193,212] but KIE determinations for IMDA reactions have not been reported in the past. B3LYP/6-31+G(d) calculations performed by Prof. M. N. Paddon-Row have produced calculated KIE data which compare very well with the experimental data available for the IMDA reaction of triene (**156**). The calculated and experimental KIE data reflect subtle properties of the transition structures and transition states involved in the IMDA reaction of triene (**156**). In the the IMDA reactions of this triene, larger KIEs are observed at the C1 and C4 methine groups than at the C8 and C9 methine groups due to steric compression of the C1 and C4 methine groups, relative to the ground state, in the *cis* and *trans* IMDA transition states. In addition, the KIE at the C4 methine is larger in the *trans* reaction pathway than in the *cis* reaction pathway due to an electrostatic interaction with the tether carbonyl group in the *trans* transition state, and perhaps also the greater asynchronicity of the *trans* transition state. The KIE at the C1 methine group is larger in the *cis* reaction pathway than in the *trans* reaction pathway due to an electrostatic interaction with the terminal carbonyl group in the *cis* transition state (**Appendix Scheme 6.3**).[178] The good match

between the calculated and experimental data indicates that the transition structures located by Prof. M. N. Paddon-Row accurately reproduce the features of the transition states of the IMDA reaction of this triene, including steric compression, electrostatic effects, and their remarkable asynchronicities. It is likely that the DFT modelling performs equally well for the IMDA reactions of related trienes (**Appendix Schemes 6.2** to **6.5**).[178]

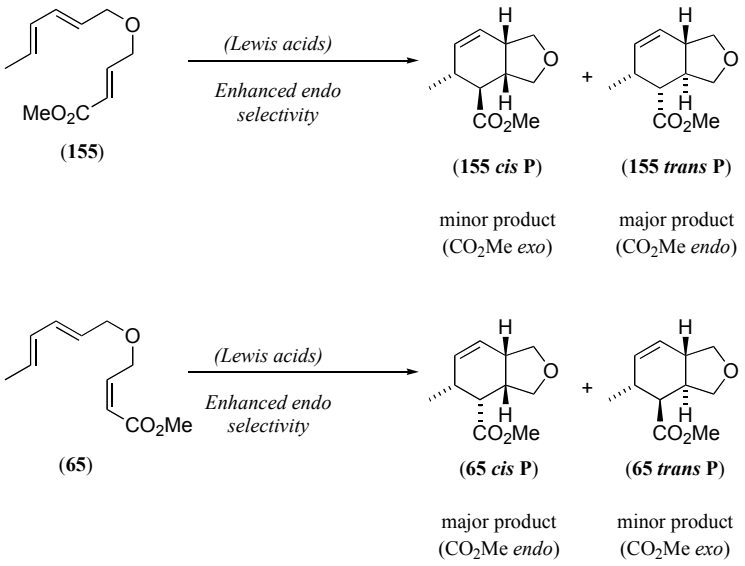
3.3 Concluding Remarks

The ether tethered trienes (**155**) and (**65**) have been synthesised, and their thermal and Lewis acid promoted IMDA reactions have been investigated. When heated to 110 °C in toluene, triene (**155**) gave a 27:73 mixture of the *cis* and *trans* IMDA adducts, respectively, and triene (**65**) gave a 51:49 mixture of the *cis* and *trans* IMDA adducts, respectively. The stereoselectivities of the heat promoted IMDA reactions of these trienes have been rationalised by inspection of the corresponding IMDA transition structures located by Prof. M. N. Paddon-Row.[178] Significant features of the IMDA transition structures include torsional strain, attractive 1,3-diene-carbonyl interactions and steric clashes. These trienes are closely related to two sets of trienes which were the subjects of previous studies. The stereoselectivities of the IMDA reactions of the ether tethered trienes, (**155**) and (**65**), are very similar to those of the corresponding trimethylene tethered trienes (**160**) and (**161**), studied by the Roush group. The effect of replacing a methylene group in trienes (**160**) and (**161**) with an ether oxygen in (**155**) and (**65**) is small. The effect of replacing the tether carbonyl group in the ester tethered trienes, (**156**) and (**156**), studied by Paddon-Row and the Sherburn group, with a methylene group in trienes (**155**) and (**65**) is more significant (**Scheme 3.51**).



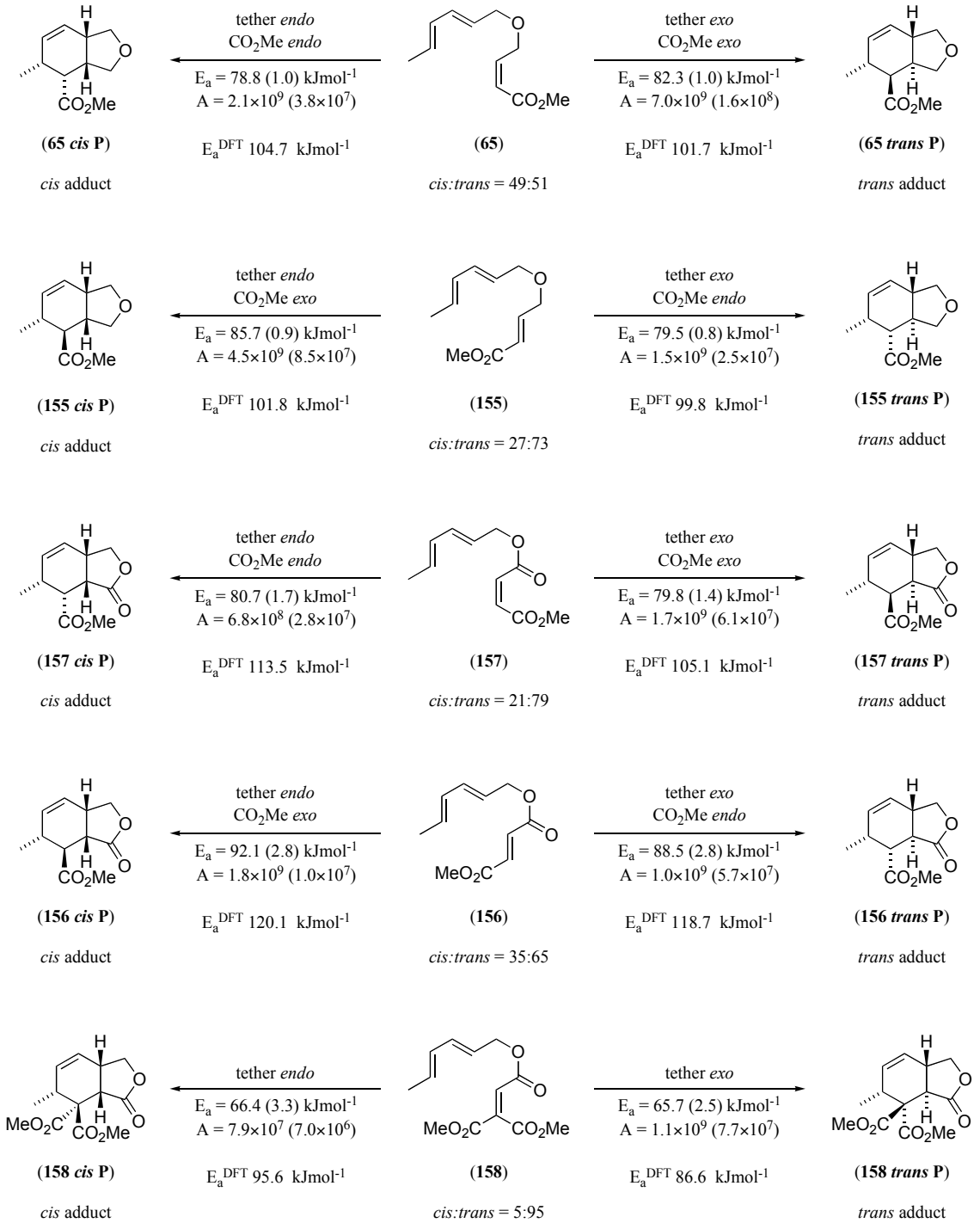
Scheme 3.51 *Heat promoted intramolecular Diels-Alder reactions of triene (155).*

The Lewis acid promoted IMDA reactions of trienes (**155**) and (**65**) have also been examined experimentally. Lewis acid promotion of the IMDA reactions of triene (**155**), with either diethylaluminium chloride (**171**), a sterically unencumbered Lewis acid, or ATPH (**49**), a sterically demanding Lewis acid, gave high levels of *trans*, or *endo*, stereoselectivity. The diethylaluminium chloride (**171**) and ATPH (**49**) promoted IMDA reactions of the (1*E*,3*E*,8*Z*)-triene (**65**) proceeded with enhanced *cis*, or *endo*, stereoselectivity relative to its heat promoted reactions, but were considerably less stereoselective than those of the (1*E*,3*E*,8*E*)-triene (**155**). ATPH (**49**) was developed as a Lewis acid promoter for *exo* selective DA and IMDA reactions,[72] but enhanced *endo* selectivity in ATPH promoted IMDA reactions has recently been reported by others in the Sherburn group.[157] The stereoselectivities of the ATPH promoted IMDA reactions of trienes (**155**) and (**65**) indicate that the ability of ATPH to promote *exo* selective IMDA reactions is substrate specific (**Scheme 3.52**).



Scheme 3.52 *Lewis acid promoted intramolecular Diels-Alder reactions of trienes (**155**) and (**65**).*

The IMDA reaction of triene (**65**) was the subject of a kinetic study, and its Arrhenius and thermodynamic activation parameters have been calculated and compared to those of the IMDA reactions of similar trienes (**155**), (**156**), (**157**) and (**158**), and with activation barriers calculated at the B3LYP/6-31+G(d) level of theory. Some aspects of IMDA stereoselectivity were rationalised through analysis of the thermodynamic activation parameters obtained from the rate data. The calculated activation barriers for trienes (**155**), (**65**), (**156**), (**157**) and (**158**) were consistently higher than the experimentally derived barriers, by approximately 20 to 30 $kJmol^{-1}$. The reasons for the differences between theory and experiment are unclear at present, and warrant further computational study (**Scheme 3.53**).



Scheme 3.53 *Experimental and calculated activation parameters for intramolecular Diels-Alder reactions of trienes (**155**), (**65**), (**156**), (**157**) and (**158**).*

A ^{2}H KIE study of the IMDA reaction of triene (**156**) was carried out. The method chosen for the KIE determination was adapted from that reported by the Singleton group for the simultaneous determination of multiple KIEs using an isotopic fractionation event and ^{2}H NMR analysis.[94] Initially, this proved problematic as isotopic fractionation events concentrated unreactive geometrical isomers of the triene

(**156**) in the recovered starting material, which interfered with the ^{2}H NMR spectroscopic analysis. These problems were circumvented by the preparation of a 10 g sample of triene (**156**), recrystallised to >99.95% purity. The availability of high purity material allowed an isotopic fractionation event to be carried out, producing a sample of isotopically enriched triene (**156**) containing less than 1% isomeric impurities. The isotopically enriched sample was analysed by quantitative ^{2}H NMR spectroscopy and KIE data matching calculated data were obtained. This is the first time the Singleton method for KIE determinations[94] has been applied to an IMDA reaction, and the first time KIE data have been obtained for an IMDA reaction. Significant limitations on the applicability of the Singleton method for KIE determinations to DA reactions were uncovered in the course of this work (**Figure 3.28**).

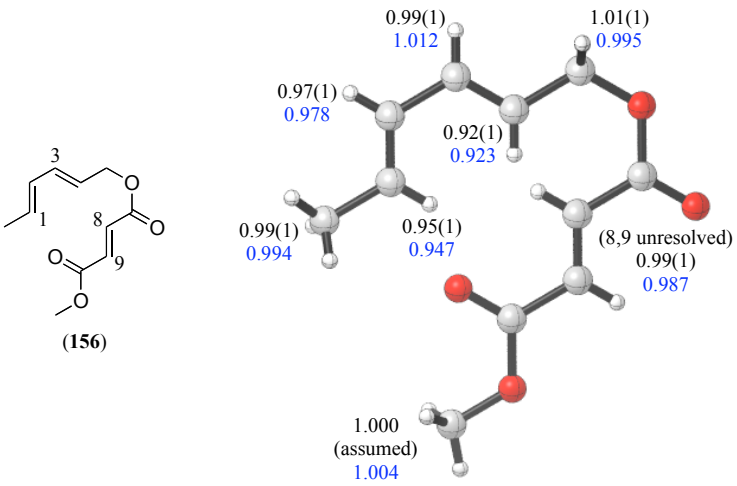


Figure 3.28 *Black: Experimental deuterium kinetic isotope effects for the intramolecular Diels-Alder reaction of triene (**156**), obtained from a natural abundance isotopic fractionation experiment run in chlorobenzene 405 K. Blue: B3LYP/6-31+G(d) calculated deuterium kinetic isotope effects for the intramolecular Diels-Alder reaction of triene (**156**) in chlorobenzene at 405 K, obtained by averaging individual kinetic isotope effect data from cis and trans reaction channels.*

A significant objective of this work was the validation of computationally generated transition structures, which can be very difficult by other means. Comparison of the experimental KIEs obtained for the IMDA reaction of triene (**156**) in chlorobenzene at 405 K with KIEs calculated by Prof. M. N. Paddon-Row using the corresponding computational conditions (405 K, SCRF for chlorobenzene) at the B3LYP/6-31+G(d) level of theory showed good agreement between the two data sets. It is thought that the transition structures located through the computational modelling accurately depict the geometries and significant features of the IMDA transition states involved in the IMDA

reaction of triene (**156**). It is also likely that the transition structures located at the same level of theory for related reactions, such as the IMDA reactions of trienes (**155**), (**65**), (**157**) and (**158**) are similarly accurate.

4 A New Domino Diels-Alder Reaction

4.1 Introduction

Synthetic organic chemistry is a vital and dynamic discipline, but practical syntheses of complex natural products are rare. Almost any endeavour in organic synthesis must address issues of chemical reactivity, chemoselectivity, regioselectivity, stereoselectivity and chemical efficiency.

The length of a synthetic sequence, often measured in the number of individual chemical transformations, or steps carried out, has a large bearing on the overall efficiency of the process (**Figure 4.1**). It can be seen that even sequences of relatively high yielding processes can result in the loss of the majority of the synthetic material in under ten steps. When sequences of less efficient processes are carried out, the loss of synthetic material can be drastic.[213]

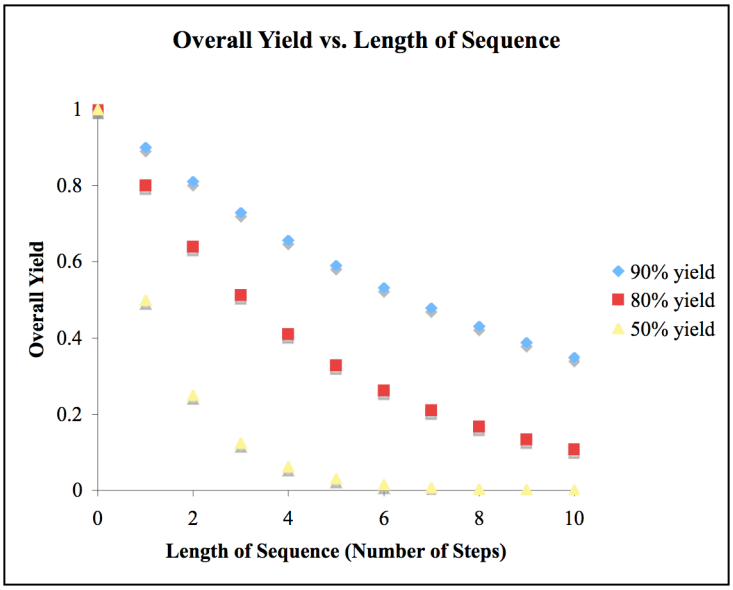
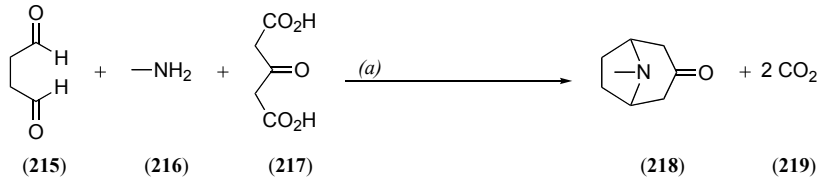


Figure 4.1 *Overall yields of sequences of chemical transformations with 90%, 80% and 50% yields per synthetic step.*

In addition to the considerations described above, increased efficiency in chemical syntheses reduces the economic, environmental, and labour costs associated with the production of a target compound.[214] The ideal chemical synthesis, as described by

Wender, is one which uses simple, inexpensive and readily available starting materials, and produces complex, valuable and otherwise inaccessible products in a single, high yielding synthetic transformation.[215] In practice, the ideas expressed by Wender have served as a guide and an inspiration to generations of synthetic chemists. The synthesis of tropinone (**218**), described by Robinson in 1917, is a remarkable example of an efficient, one step process (**Scheme 4.1**).[216] It is noteworthy that this synthetic work preceded the relevant biosynthetic considerations.[3]

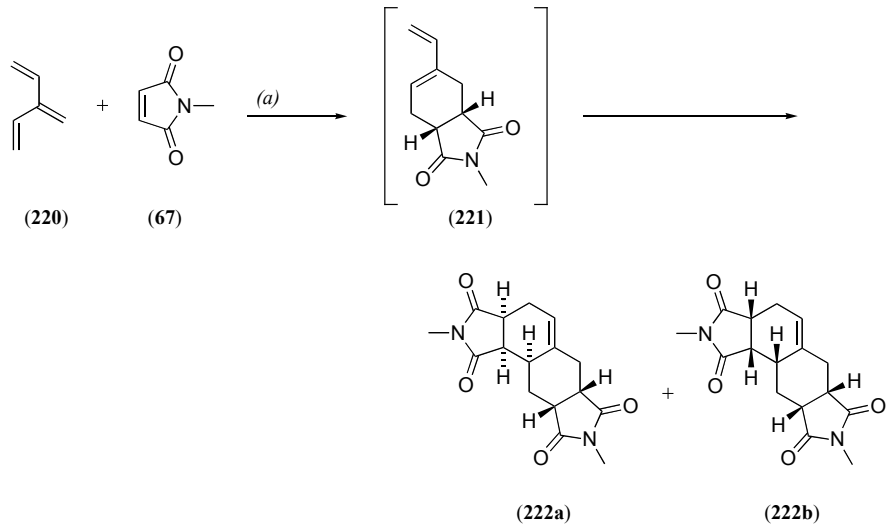


Scheme 4.1 *Robinson's one step synthesis of tropinone. Conditions: (a) 1. $CaCO_3$, H_2O, 3 d, 2. HCl, 42%.*

Robinson's approach to tropinone is impressive because two carbon-carbon bonds, two carbon-nitrogen bonds, and a bicyclic ring system are formed in a single chemical step. Chemical reactions in which multiple bond-forming events occur in sequence, without the need for additional reagents or catalysts, have been termed domino reactions. Domino reactions are often remarkably efficient processes, rapidly generating structurally complex products from relatively simple starting materials.[214,217]

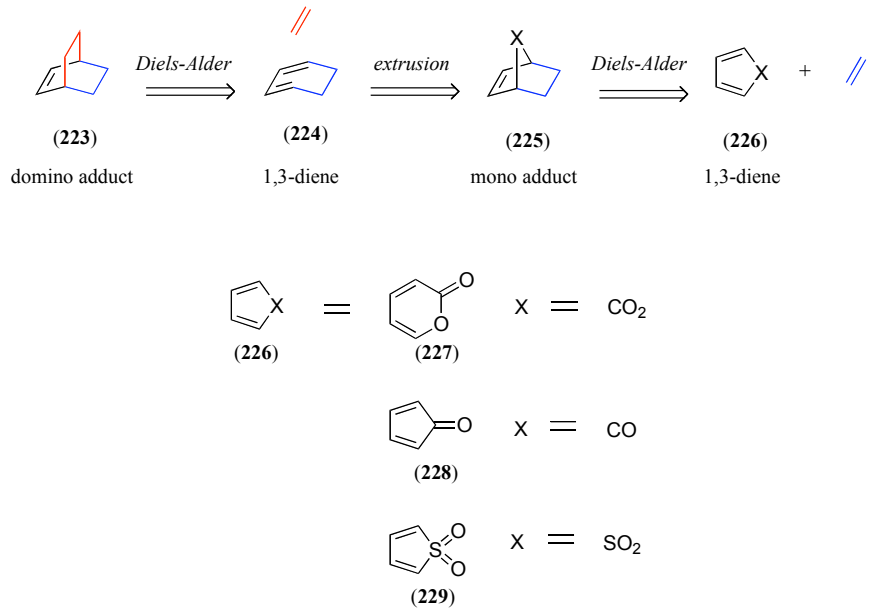
The incorporation of DA reactions into domino sequences holds special promise for the efficient, stereocontrolled synthesis of complex molecules, because the DA reaction is itself a remarkably powerful and selective synthetic transformation.[2,8,21,22,218]

Many types of domino DA reactions have been devised, including diene transmissive (DT) DA reactions of dendralenes. These reactions have been the basis of some conceptually novel and efficient synthetic approaches to complex target molecules including oxygenated nor-steroid and triterpenoid frameworks,[219] the tricyclic core of vinigrol,[220] and an advanced intermediate in the total synthesis of triptolide, constituting a formal total synthesis of that compound.[221] In the DTDA reactions of [3]dendralenes, an initial DA event involving a 1,3-diene in the dendralene generates a new1,3-diene, which then reacts with a second dienophile. The DTDA reaction of [3]dendralene (**220**) with *N*-methyl maleimide (**67**) proceeds smoothly at 25 °C, giving a 90:10 mixture of the diastereomeric *bis*-adducts (**222a**) and (**222b**) in 66% yield (**Scheme 4.2**).[222]



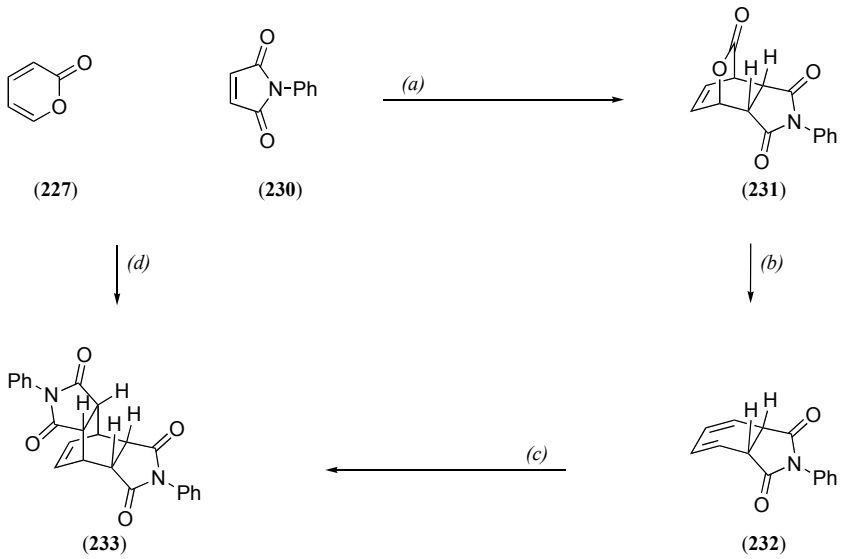
Scheme 4.2 *Diene transmissive Diels-Alder reaction of [3]-dendralene (**220**) with N-methyl maleimide (**67**). Conditions: (a) N-methyl maleimide (**67**) (5 molar equiv.), $CHCl_3$, 25 °C, 18 hr, 66%, (**222a**):(**222b**) = 90:10.*

The DTDA reactions of dendralenes are a special type of domino DA reaction,[223] and other types of domino DA reactions are known. A relatively common type uses 1,3-dienes whose termini are linked by the atoms of a small molecule. After these 1,3-dienes undergo an initial DA reaction, their bicyclic monoadducts can extrude the small molecule, generating a second 1,3-diene which can then take part in a second DA reaction. This gives bicyclo[2.2.2]oct-2-ene domino DA adducts (**Scheme 4.3**).



Scheme 4.3 *Retrosynthetic analysis of bicyclo[2.2.2]oct-2-enes (**223**); domino Diels-Alder approaches.*

The domino DA reactions of 2-pyrones produce bicyclo[2.2.2]oct-2-ene domino DA adducts as described above. 2-Pyrones possess an aromatic resonance form and partial aromatic character, which confers upon them greater stability than many cyclic 1,3-dienes. The parent compound, 2-pyrone (**227**), is estimated to have an aromatic stabilisation energy of between 30 and 60 kJmol^{-1}, which is less than half that of benzene (150 kJmol^{-1}),[224] but still, this weak aromaticity makes many 2-pyrones sluggish participants in DA reactions. The parent compound is prone to rapid polymerisation under thermal reaction conditions, and its DA reactions generally proceed with little regioselectivity.[225] The DA chemistry of 2-pyrones was last reviewed in 1999.[225,226] Relatively few examples of the DA chemistry of the parent compound are known, but he DA/retro DA/DA chemistry of simple 2-pyrones with N-phenyl maleimide (**230**) has been studied in considerable detail (**Scheme 4.4**).[226-228]



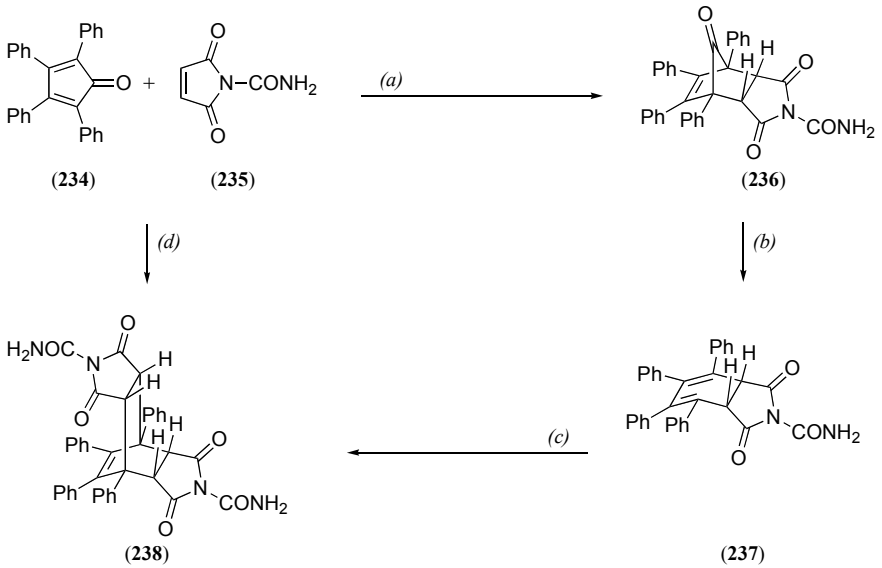
Scheme 4.4 *Domino Diels-Alder sequence with 2-pyrone (**227**) and N-phenyl maleimide (**230**). Conditions: (a) N-phenyl maleimide (**230**) (1.0 mol. equiv.), toluene, reflux, 1 hr, 80%, endo:exo = 100:0; (b) decalin, reflux, 15 min, quant.; (c) N-phenyl maleimide (**230**) (1.5 mol. equiv.), benzene, reflux, 5 hr, quant., endo:exo = 100:0; (d) N-phenyl maleimide (**230**) (3.0 mol. equiv.), decalin, reflux, 90 mins, 95%, endo,endo: endo,exo: exo.exo = 100:0:0.*

The DA reaction of the parent compound (**227**), with one molar equivalent of N-phenyl maleimide (**230**) in toluene at 110 °C for 1 hour, generates the *endo* adduct (**231**) exclusively in 80% yield. This compound (**231**) undergoes a retro DA reaction in 10 minutes at 187 °C in decalin, expelling CO_2 and producing N-phenyl-1,2-dihydrophthalimide (**232**), containing a new 1,3-diene, in quantitative yield. When treated with an additional 1.5 molar equivalents of N-phenylmaleimide in benzene at reflux for 5 hour, the N-phenyl-1,2-dihydrophthalimide (**232**) produced in the retro DA reaction participates in a second *endo* selective DA reaction, giving the bicyclic *bis*-adduct (**233**) in quantitative yield. Alternatively, these reactions can be carried out in a domino sequence, in which 2-pyrone (**227**) is treated with 3 molar equivalents of N-phenyl maleimide (**230**) at 187 °C in decalin over 90 minutes. The sequence involves an *endo* selective DA reaction with (**230**), loss of CO_2 from a bicyclic intermediate (**231**) in a retro DA step, and a second *endo* selective DA reaction with (**230**), giving the *bis*-adduct (**233**) in 95% yield.[228] During the domino sequence, a bicyclic ring system and four carbon-carbon σ-bonds are formed at the expense of two carbon-carbon π-bonds, one carbon-carbon σ-bond and one carbon-oxygen σ-bond. It is noteworthy that a temperature of nearly 200 °C was required for the retro DA reaction in the second step

of the three step synthetic sequence, and for the domino reaction of N-phenyl maleimide (**230**) with 2-pyrone (**227**).[228]

Cyclopentadienones, sometimes called cyclones, can participate in domino DA reactions. They contain a carbonyl group and are less electron rich than many cyclic 1,3-dienes. Unlike 2-pyrones, which possess an aromatic resonance form, cyclopentadienones possess an antiaromatic resonance form, have partial antiaromatic character, and are often too unstable to be useful synthetic intermediates.[224,229] Some heavily substituted cyclopentadienones are significantly more stable than the parent system and can take part in DA reactions, producing bicyclic adducts with a bridging carbonyl group. These adducts can extrude carbon monoxide by a cheleotropic mechanism, regenerating a 1,3-diene, which can then participate in a second DA reaction. [230,231]

Tetraphenyl cyclopentadienone (**234**), also called tetracyclone, reacts with N-carbamyl maleimide (**235**) in benzene at reflux over three hours, giving the bridged *endo* adduct (**236**) in approximately 70% yield. When heated to reflux in toluene for ten hours, the DA adduct (**236**) loses carbon monoxide, generating N-carbamyl tetraphenyl-1,2-dihydrophthalimide (**237**) in 83% yield. When (**237**) is treated with one molar equivalent of the maleimide (**235**) in toluene at reflux for three hours, a second *endo* selective DA reaction takes place, giving the symmetrical double DA adduct (**238**) in 85% yield. Alternatively, tetracyclone (**234**) reacts with two molar equivalents of the maleimide (**235**) in toluene at reflux over three hours, in a domino sequence involving an *endo* selective DA reaction with the maleimide, cheleotropic extrusion of carbon monoxide, and a second *endo* selective DA reaction with the maleimide, giving the double DA adduct (**238**) in 83% yield. In this domino sequence, four carbon-carbon σ-bonds and a bicyclic ring system are formed at the expense of two carbon-carbon π-bonds and two carbon-carbon σ-bonds (**Scheme 4.5**).[231]

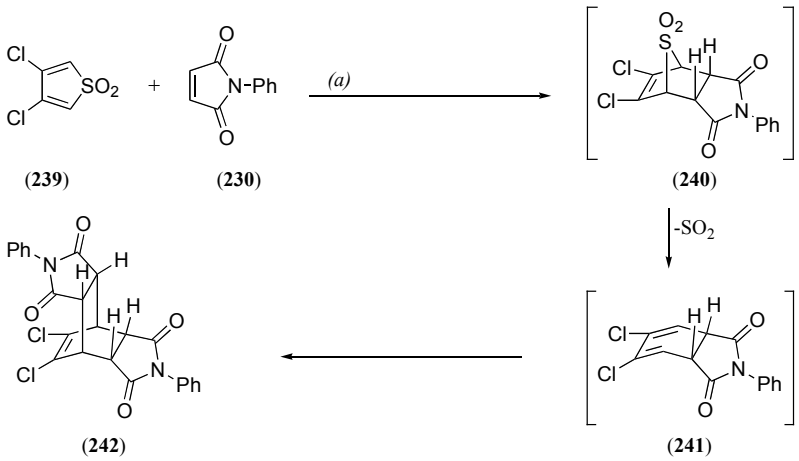


Scheme 4.5 *Domino Diels-Alder sequence with tetraphenylcyclopentadienone (**234**) and N-carbamyl maleimide (**235**). Conditions: (a) N-carbamyl maleimide (**235**) (1.0 mol. equiv.), benzene, reflux, 3 hr, 70%, endo:exo = 100:0; (b) toluene, reflux, 10 hr, 83%; (c) N-carbamyl maleimide (**235**) (1.0 mol. equiv.), toluene, reflux, 3 hr, 85%., endo:exo = 100:0; (d) N-carbamyl maleimide (**235**) (2.0 mol. equiv.), toluene, reflux, 3 hr, 83%, endo,endo: endo,exo: exo.exo = 100:0:0.*

1,1-Thiophene dioxides can also participate in domino DA reactions. The parent compound (**229**) was isolated for the first time in 1997, allowing the study of its DA and dimerisation chemistry. 1,1-Thiophene dioxides are not aromatic, and must generally carry three substituents at positions on the heterocyclic ring to be stable, isolable compounds.[232] The DA chemistry of the parent, 1,1-thiophene dioxide (**229**), is drastically limited by its tendency to dimerise by DA pathways, as the dimerisation reaction has a free energy of activation ($\Delta G^{\ddagger}$) of just 80 kJmol^{-1} at 310 K.[233,234] The Nakayama group examined the DA reactions of the parent compound (**229**) with a range of 1,3-dienes and dienophiles and found that only the fastest DA reaction, that of 1,1-thiophene dioxide as the dienophile with cyclopentadiene (**23**) as the 1,3-diene, could compete with the DA dimerisation pathway. In the presence of otherwise reactive 1,3-dienes, or dienophiles such as *p*-benzoquinone (**165**), dimethyl acetylenedicarboxylate (DMAD) (**194**) and even 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (PTAD) (**196**), 1,1-thiophene dioxide (**229**) gave none of the expected DA adducts. Instead, dimers and trimers derived from the heterocycle (**229**) through DA pathways were obtained.[233,235] The low reactivity of 1,1-thiophene dioxides with familiar 1,3-dienes and dienophiles appears to be a general phenomenon, and while these compounds can take part in DA

reactions, depending on the reaction conditions, they are not particularly well suited to either role.[232,234,235]

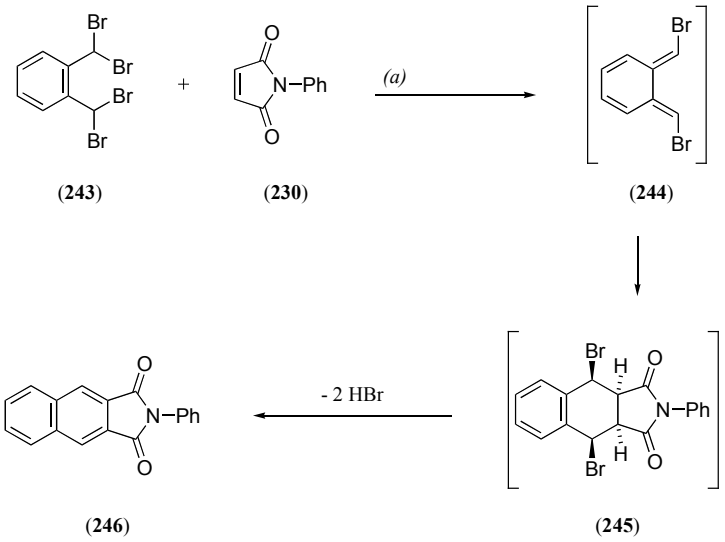
3,4-Dichloro-1,1-thiophene dioxide (**239**), however, has been shown to participate in domino DA sequences with two molar equivalents of N-substituted maleimides or maleic anhydride (**54**) at 138 °C in xylenes (**Scheme 4.6**). An initial DA reaction with one equivalent of the dienophile, in this case N-phenyl maleimide (**230**), generates a bicyclic intermediate (**240**) which extrudes sulfur dioxide under the reaction conditions, generating a second 1,3-diene (**241**). The new 1,3-diene (**241**) then reacts with a second equivalent of N-phenyl maleimide (**230**), giving the domino DA/cheleotropic extrusion/DA product (**242**) in 87% overall yield from the 1,1-thiophene dioxide (**239**). During this domino sequence, four carbon-carbon σ-bonds and a bicyclic ring system are formed, at the expense of two carbon-carbon π-bonds and two carbon-sulfur σ-bonds. The stereochemistry of the DA adducts (**240**) and (**242**) was not specified in the original publication, but *endo* stereochemistry, as is generally observed in the DA reactions of N-substituted maleimides,[228,231] is depicted in (**Scheme 4.6**).[236]



Scheme 4.6 *Domino Diels-Alder sequence with 3,4-dichloro-1,1-thiophene dioxide (**239**) and N-phenyl maleimide (**230**). Conditions: (a) N-phenyl maleimide (**230**) 2.0 molar equiv., xylene, reflux, 20 hr, 81%.*

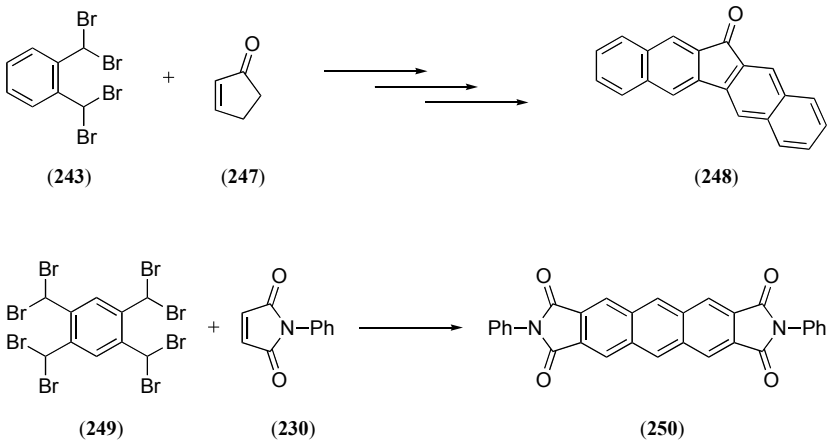
o-Quinodimethanes are versatile and reactive compounds which have found application in many areas of chemistry, including steroid synthesis, materials science and physical chemistry, and some substituted *o*-quinodimethanes are able to participate in domino DA sequences.[237] *o*-Quinodimethanes are typically made *in situ* by the thermolysis of benzocyclobutenes; through the loss of a small molecule from benzo-fused heterocyclic

compounds; or through 1,4 elimination reactions of appropriately substituted *o*-xylenes.[237,238] *o*-Quinodimethanes generally participate in DA reactions through the exocyclic 1,3-diene; these reactions are very rapid and exothermic as they proceed with concomitant aromatisation of the quinonoid carbocycle. The parent compound has been observed directly, but only at -196 °C, and it dimerises through a DA mechanism, giving a spirocyclic adduct at -150 °C. [237,238] The DA reactions of a range of *o*-quinodimethanes with dienophiles including acrylonitrile (**36**), 2-(5*H*)-furanone (**114**) and N-methyl maleimide (**67**) have been the subject of a combined experimental and density functional theory study.[239] A 1,4 elimination/DA/aromatisation sequence involving a dibromo-*o*-quinodimethane (**244**) was initiated by the reaction of tetrabromo-*o*-xylene (**243**) with sodium iodide in dimethyl formamide at 60 to 70 °C (**Scheme 4.7**).



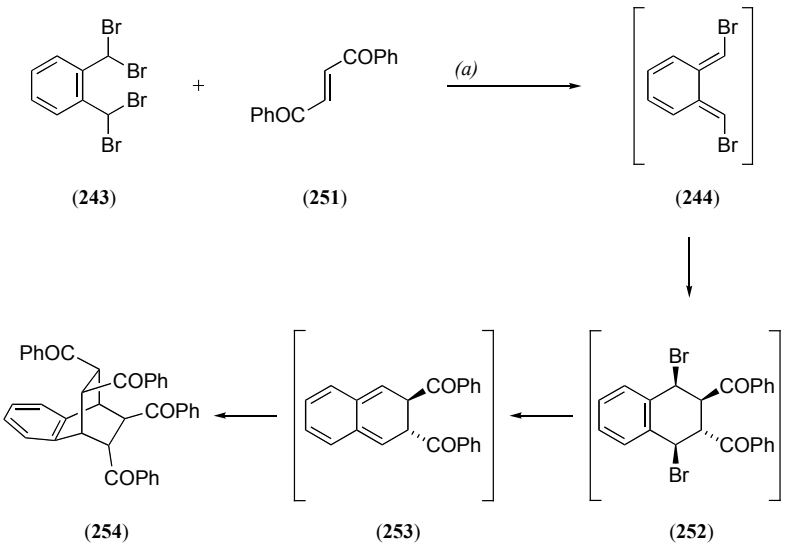
Scheme 4.7 *Domino Diels-Alder sequence with tetrabromo-o-xylene (**243**) and N-phenyl maleimide (**230**). Conditions: (a) N-phenyl maleimide (**230**) (2.3 molar equiv.), NaI (6.7 molar equiv.), DMF, 60-70 °C, 24 hr, 65%.*

The dibromo-*o*-quinodimethane (**244**) produced in this manner was trapped with N-phenyl maleimide (**230**) through a DA reaction, and the compound formed in the DA reaction (**245**) then aromatised with the loss of two molar equivalents of hydrogen bromide, giving N-phenyl-2,3-naphthalimide (**246**) in 65% yield.[240] Similar chemistry has been used to produce polycyclic aromatic systems such as (**248**) and (**250**) from tetrabromo-*o*-xylene (**243**) and octabromodurene (**249**), respectively (**Scheme 4.8**).[241]



Scheme 4.8 *Syntheses of linear aromatic compounds through Diels-Alder reactions of o-quinodimethanes with α,β-unsaturated carbonyl compounds.*

A more recent publication from the Cava group details a domino sequence, this time carried out with sodium iodide in acetone at 57 °C (**Scheme 4.9**). In this case, tetrabromo-*o*-xylene (**243**) reacts with sodium iodide, generating a dibromo-*o*-quinodimethane (**244**), which participates in a DA reaction with (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**251**), producing intermediate (**252**). In principle, this intermediate (**252**) can aromatise through the elimination of two molar equivalents of hydrogen bromide, analogous to the reaction with N-phenyl maleimide (**230**) (**Scheme 4.7**), however it undergoes 1,4 elimination, generating a second *o*-quinodimethane intermediate (**253**). Finally, this *o*-quinodimethane (**253**) participates in a second DA reaction, giving the observed product (**254**) in 49% yield.[242] Overall, this domino sequence involves two 1,4 elimination events and two DA reactions, and forms four carbon-carbon σ-bonds and a bicyclic ring system at the expense of four carbon-bromine σ-bonds.



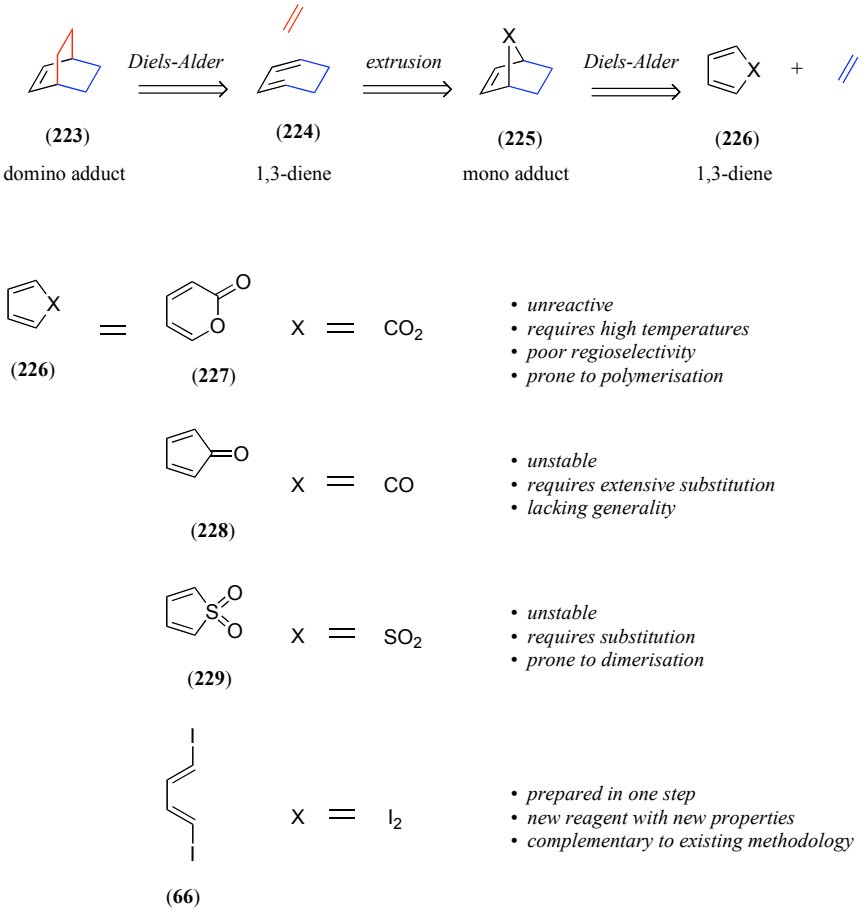
Scheme 4.9 *Domino Diels-Alder sequence involving o-quinodimethane intermediates* ***(244)*** *and* ***(253)****. Conditions: (a) Tetrabromo-o-xylene* ***(243)*** *(1.0 molar equiv.), (E)-1,4-diphenylbut-2-ene-1,4-dione* ***(251)*** *(1.3 molar equiv.), NaI (6.8 molar equiv.), acetone, reflux, 72 hr, 49%.*

4.1.1 Scope for the development of new reagents

Domino processes are inherently powerful and efficient strategies for the assembly of complex molecules, and domino processes which incorporate DA reactions have great potential because the DA reaction is a particularly versatile and stereoselective carbon-carbon bond forming reaction. The Sherburn group is interested in developing new strategies for domino DA sequences, which can complement existing protocols for carrying out these reactions, but the development of efficient new domino DA processes is contingent on the availability of suitable reagents. Such reagents must have the functionality required for multiple carbon-carbon bond forming events, but ideally their chemical reactivity will be tempered so that it can be systematically exploited.

A brief overview of existing reagents shows that there is room for innovation in this field. The scope and utility of the DA reactions of 2-pyrones is limited by their low reactivity and poor regioselectivity as 1,3-dienes. In addition, these reagents are prone to polymerisation, and forcing conditions are often required for their bicyclic DA adducts to lose carbon dioxide, generating a second 1,3-diene for a subsequent DA reaction. Cyclopentadienones are unstable species which, it appears, can only be stabilised by extensive substitution of the cyclopentadienone core. Unfortunately, this means that any domino DA processes based on these compounds will lack generality. As is the case with cyclopentadienones, the DA chemistry of 1,1-thiophene dioxides is

drastically limited by their instability and tendency to dimerise. These factors combine to make them a poor choice for the development of domino DA processes (**Scheme 4.10**).

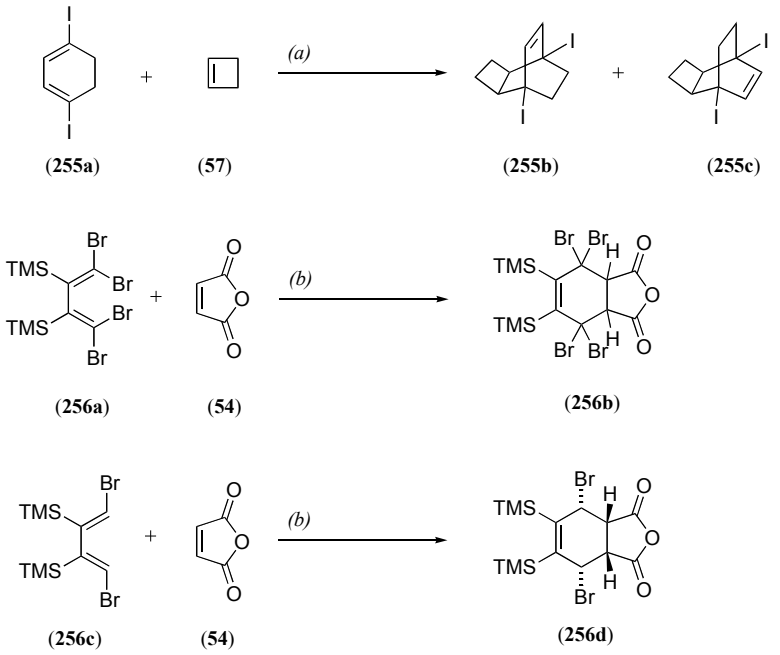


Scheme 4.10 *Scope for the development of new reagents for domino Diels-Alder reactions.*

Using optimised conditions, multigram batches of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) can be made in one step in from cheap and readily available starting materials. This easy accessibility made (**66**) an ideal reagent for the synthesis of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene as described in (**Chapter 2**) of this thesis, and a candidate for carrying out domino DA reactions. It was hoped that the DA chemistry of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) would parallel the domino DA chemistry of halogenated *o*-quinodimethanes.

The DA chemistry of 1,4-dihalo-1,3-dienes has been studied in the past. Diene (**255a**) participates in a DA reaction with cyclobutene (**57**) at 100 °C for 30 days, giving a 20:1 mixture of the two DA adducts (**255b**) and (**255c**) in 85% yield.[243] Dienes (**256a**) and (**256c**) are unstable at room temperature, but undergo DA reactons with electron poor

dienophiles including maleic anhydride (**54**), *N*-phenyl maleimide (**230**), dimethyl acetylene dicarboxylate (**194**) and *p*-benzoquinone (**165**) in toluene at 110 °C, giving DA adducts in yields of 55 to 82%. The adducts obtained from these dienes did not aromatise under the conditions used for the DA reactions (**Scheme 4.11**).[244]



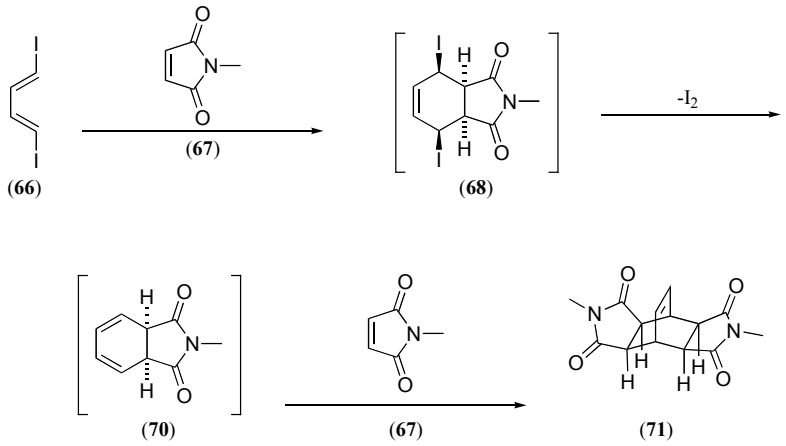
Scheme 4.11 *Diels-Alder reactions of 1,4-dihalo-1,3-butadienes. Conditions: (a) 100 °C, 30 days;*[243] *(b) Conditions not reported.*[244]

In addition, as previously developed domino DA strategies generally relied on reaction conditions involving elevated temperatures, methods which used mild reaction conditions and low reaction temperatures were deemed attractive. In the event, the DA chemistry of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) was very much like that of halogenated *o*-quinodimethanes and mild high pressure reaction conditions were developed for the domino DA reactions of this 1,3-diene.

4.1.2 Summary and research objectives

The research described in this chapter had several significant objectives, the first of which was to investigate the DA reactions of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**). When it became clear that the DA reactions of this compound with maleimide dienophiles, (**67**) and (**230**), were indeed domino processes, the investigation and optimisation of the domino DA processes became a priority. Objectives included determining the stereochemistry of the domino products, establishing the scope and

mechanism of the domino DA reactions, and investigating alternative sets of reaction conditions for the domino DA reactions. Finally, attempts were made to alter the outcomes of the domino DA sequences and to broaden the range of dienophiles which could be used in the domino DA reactions (**Scheme 4.12**).



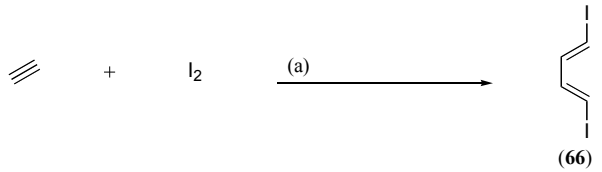
Scheme 4.12 *Domino Diels-Alder reaction of (1E,3E)-1,4-diiodo-1,3-butadiene (**66**) with N-methyl maleimide (**67**).*

4.2 Results and Discussion

(1*E*,3*E*)-1,4-Diiodo-1,3-butadiene (**66**) was originally synthesised for use in the preparation of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**), which found application in the determination of the *endo:exo* ratios of the DA reactions of 1,3-butadiene (**1**) with a range of simple dienophiles, as described in (**Chapter 2**) of this thesis. The one step synthesis of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) was carefully optimised due to the expense of the platinum catalyst and the instability of the 1,3-diene (**66**), particularly toward light, heat, and in the presence of air, which precluded the use of many standard purification procedures. The conditions used were adapted from the procedure published by the Beletskaya group,[99] which called for a saturated solution of acetylene in methanol to be treated with sodium iodide, molecular iodine and sodium hexachloroplatinate hexahydrate (**96**), and stirred for 6 hr at RT. The published workup involved precipitation of the product (**66**) with the addition of water, filtration and subsequent washing with aqueous sodium iodide and water. Finally, the product (**66**) was dried under vacuum. This procedure produced 60 mg batches of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) using a catalyst loading of 25 molar percent, which corresponds to a turn over number (TON) of just four.[99] This is a domino reaction,

involving the formation of one carbon-carbon σ-bond, and two carbon-iodine σ-bonds in a single synthetic step. Unfortunately, the published procedure is very inefficient, requiring one mole of an expensive catalyst per four moles of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) produced.

Under optimised conditions (**Scheme 4.13**), a solution of acetylene, sodium iodide, molecular iodine and potassium hexachloroplatinate (**95**) in methanol was stirred under an atmosphere of acetylene at room temperature for four days. An aqueous workup was developed. Aqueous sodium metabisulfite was used to destroy the excess molecular iodine, and the resulting mixture was partitioned between diethyl ether and water, washed with water, and dried over magnesium sulfate. The reaction and workup were carried out in darkness and the (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) obtained was stored as a solid in darkness under nitrogen with BHT at -20 °C. These conditions reliably produced 4 g batches of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) containing very small quantities of (*E*)-1,2-diiodoethylene (**98**). A catalyst loading of 0.25 molar percent, representing a turnover number (TON) of approximately 400, was used. Lower catalyst loadings gave batches of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) containing larger quantities of (*E*)-1,2-diiodoethylene (**98**), produced through a background reaction involving the direct addition of molecular iodine to acetylene.



Scheme 4.13 *Optimised platinum catalysed stereoselective synthesis of (1E,3E)-1,4-diiodo-1,3-butadiene (**66**). Conditions: (a) Acetylene, I_2, NaI, K_2PtCl_6 (**95**) (0.25 mol. %), MeOH, RT, 4 d, 76% (based on I_2).*

The analytical data for (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) matched those previously reported by the Beletskaya group[99] and the structure of the compound was proved unambiguously by single crystal X-ray diffraction (**Figure 4.2**).

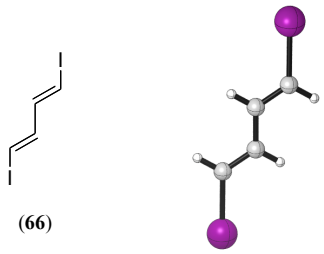


Figure 4.2 *X-ray crystal structure of (1E,3E)-1,4-diiodo-1,3-butadiene (**66**).*

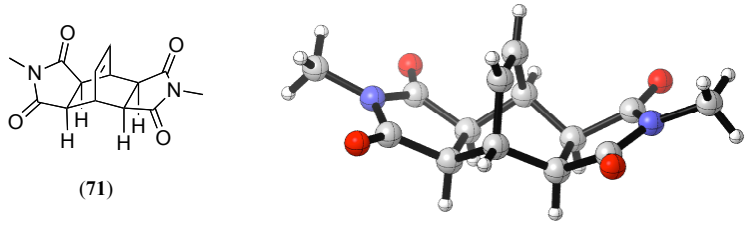
With an efficient and convenient method for the synthesis of isomerically pure (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) developed, and gram quantities of this material in hand, its DA reactions were explored.

4.2.1 Domino Diels-Alder reaction of (1E,3E)-1,4-diiodo-1,3-butadiene with N-methyl maleimide

A test reaction with (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) and 1.0 molar equivalent of *N*-methyl maleimide (**67**) in $CDCl_3$ at room temperature was carried out, and the progress of the DA reaction was monitored by ^{1}H NMR spectroscopy and TLC at regular intervals. No DA adducts were detected by ^{1}H NMR or TLC analysis after three days. Test reactions with 1.0 molar equivalent of *N*-methyl maleimide (**67**) in $CDCl_3$ were conducted at temperatures of 40 °C and 60 °C for 24 hr, and were monitored by ^{1}H NMR spectroscopy at regular intervals. ^{1}H NMR spectroscopic analysis indicated that under these conditions the (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) gradually isomerised to compounds thought to be (1*E*,3*Z*)-1,4-diiodo-1,3-butadiene and (1*Z*,3*Z*)-1,4-diiodo-1,3-butadiene. No DA adducts were detected.

As the 1,3-diene (**66**) is unstable at elevated temperatures, its DA reactions at elevated pressures were investigated. A test reaction was run with 2.0 molar equivalents of *N*-methyl maleimide (**67**) in CH_2Cl_2 at 14.7 kbar and room temperature for 2.5 hr. ^{1}H NMR spectroscopic analysis revealed that no reaction had taken place. Another reaction was run with 5.0 molar equivalents of *N*-methyl maleimide (**67**) in CH_2Cl_2 at 19 kbar and room temperature for 66 hr. The crude reaction mixture contained a considerable quantity of iodine and a product (**71**) was detected by ^{1}H NMR spectroscopic analysis of the mixture. The product (**71**) was reasonably polar and was isolated in pure form by column chromatography eluting with 2% methanol in CH_2Cl_2.

Crystals of the adduct (**71**) were grown from chloroform/acetone, and its structure was determined by X-ray crystallography (**Figure 4.3**).



(71)

(71 X-ray)

Figure 4.3 *X-ray crystal structure of adduct (71).*

Thus, it was clear the adduct (**71**) did not contain iodine, was derived from two molecules of *N*-methyl maleimide (**67**) and one molecule of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**), and had been produced in 88% yield. The adduct (**71**) was characterised using modern spectroscopic techniques including ^{1}H and ^{13}C NMR spectroscopy, high and low resolution mass spectrometry, and IR spectroscopy. All data gathered supported the structure obtained through single crystal X-ray analysis.

The ^{1}H NMR spectrum of the adduct (**71**) in d_6-DMSO was obtained. The resonances of small amounts of water and d_5-DMSO in the d_6-DMSO can be seen in the ^{1}H NMR spectrum at δ = 3.32 and 2.50 ppm, respectively. The ^{1}H NMR spectrum of (**71**) in d_6-DMSO contains four signals in a ratio 1:1:2:3; the paucity of ^{1}H NMR signals is a consequence of the compound containing two planes of symmetry. The ^{1}H NMR signals of (**71**) were assigned letters of the alphabet according to chemical shift. H_a is a doublet of doublets (J = 3.3 and 2.4 Hz) at δ = 6.02 ppm, corresponding to the two alkenic protons. H_b is a multiplet at δ = 3.38-3.30 ppm, corresponding to the two bridgehead protons. H_c is a broad singlet at δ = 3.17 ppm, corresponding to the four α-protons of the imide groups, and H_d is a sharp singlet at δ = 2.72 ppm, corresponding to the six protons of the two N-methyl groups in the succinimide units (**Figure 4.4**).

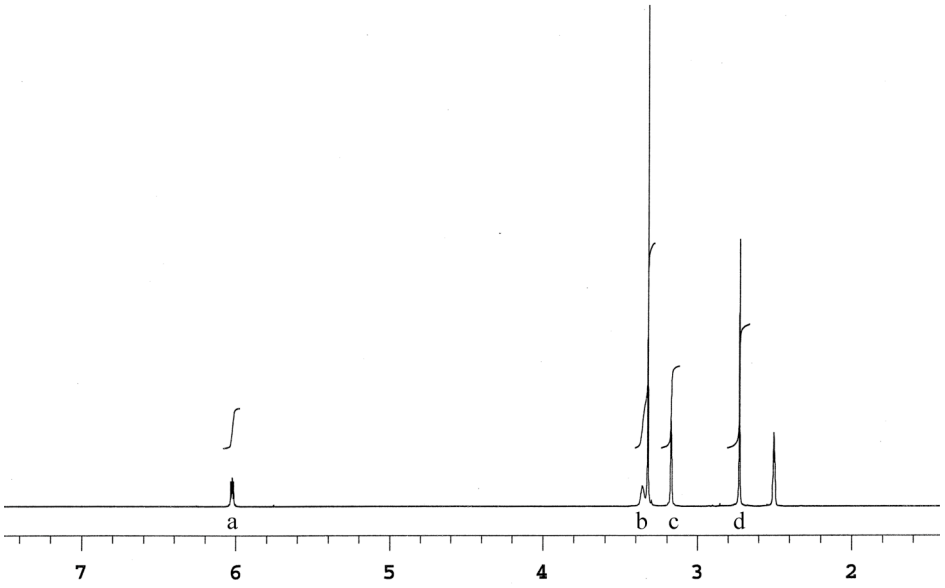


Figure 4.4 *^{1}H NMR spectrum of adduct (**71**).*

High resolution electrospray ionisation mass spectral analysis indicated that the molecular weight of the adduct (**71**) was 274.0955 Da, giving an empirical formula of $C_{14}H_{14}N_2O_4$ (274.0954 Da; 0.5 ppm), matching that obtained through single crystal X-ray diffraction.

The low resolution electron ionisation mass spectrum of (**71**) (**Figure 4.5**) contains a molecular ion at *m/z* = 274.1, a significant fragment ion at *m/z* = 163.1, corresponding to the loss of *N*-methyl maleimide (**67**), (111.03 Da), through a *retro*-DA mechanism, and the base peak at *m/z* = 78, indicative of aromatisation to benzene. Some low intensity fragment ions and the fragment at *m/z* = 78 are derived from processes reminiscent of the Norrish type 1 reaction, involving cleavage of carbon-carbon and carbon-nitrogen σ-bonds adjacent to carbonyl groups.

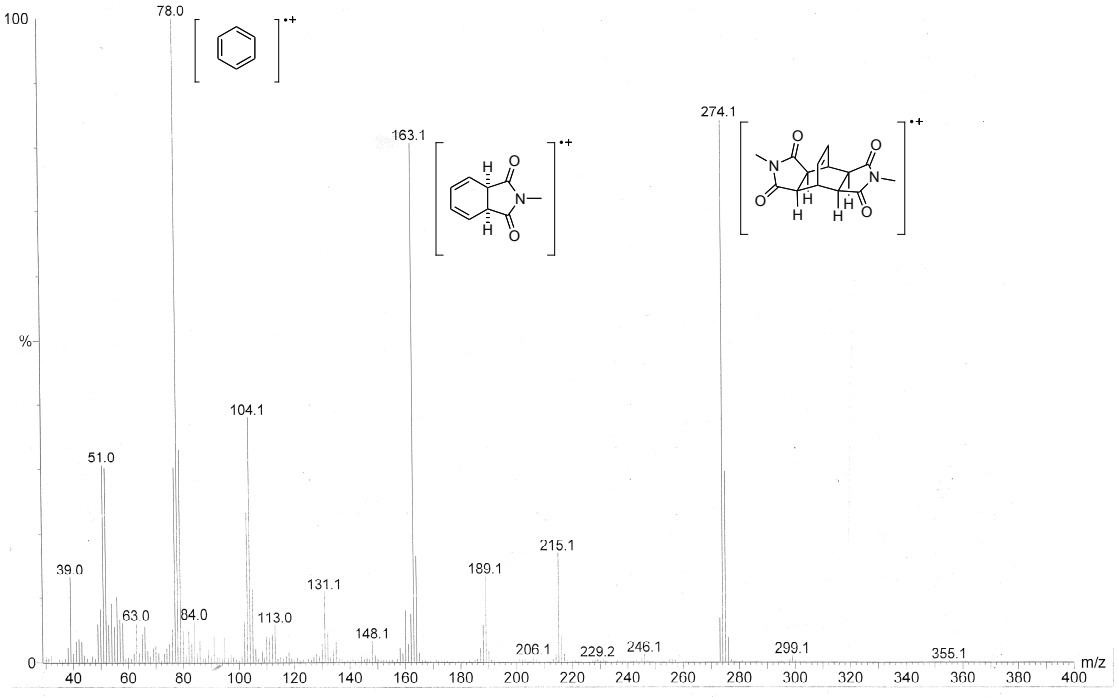
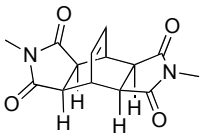


Figure 4.5 *Low resolution mass spectrum of (71).*

The IR spectrum of (**71**) within a KBr disk contains absorption bands with frequencies and intensities characteristic of the functional groups and types of chemical bonds present in the molecule (**Figure 4.6**). Significant bands include those associated with carbon-hydrogen σ-bonds at both olefinic and saturated positions; carbon-carbon and carbon-oxygen π-bonds, an isolated alkene and the imide carbonyl groups, respectively; and the carbon-nitrogen σ-bonds around the imide nitrogens.

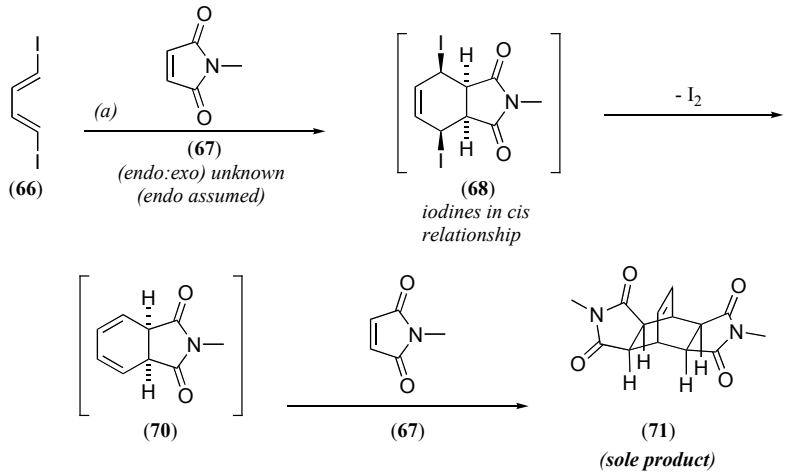


(**71**)

Frequency	Intensity	Bond	Vibrational Mode
3062	weak	C=**C-H**	asymmetric stretch
2974 2961 2950	weak weak weak	aliphatic **C-H**	asymmetric and symmetric stretches
1930	weak	**C=C**	asymmetric stretch
1766 1703	medium strong	imide **C=O**	symmetric and asymmetric stretch (C=C symmetric stretch appears as a shoulder ~1650)
1434	medium	C=**C-H**	in plane bend
1382	medium	**C-H**	methyl group symmetric bend
1319	medium	**C-C**	symmetric stretch
1285	medium	**C-N**	symmetric stretch
970	medium	C-**C-H**	in plane and out of plane bend

Figure 4.6 *Assignments of the IR absorption bands of adduct (**71**).*

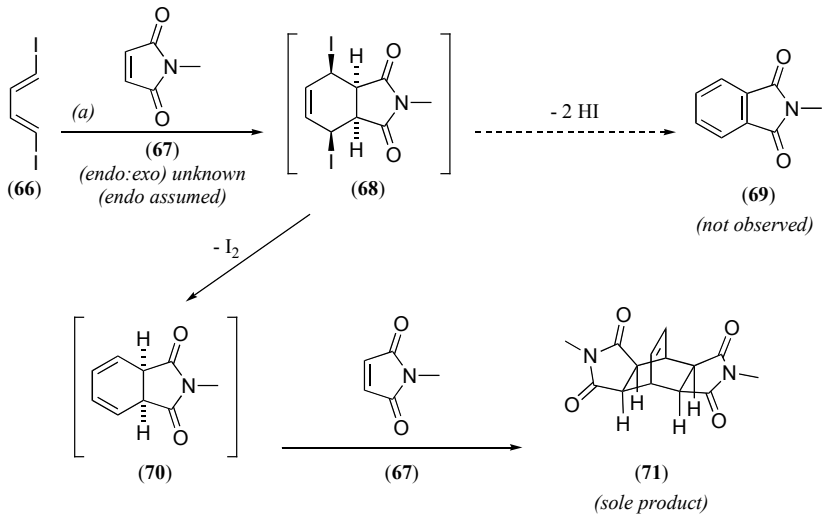
Adduct (**71**) is formed directly through a domino sequence involving short lived intermediates which have not been detected. A proposed mechanism follows (**Scheme 4.14**). At 19 kbar, (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) and *N*-methyl maleimide (**67**) participate in a DA reaction, which is presumably *endo* selective,[127,222,223,228,231] giving a diiodocyclohexene intermediate (**68**). This intermediate (**68**) eliminates molecular iodine, generating a 1,3-cyclohexadiene intermediate (**70**), which participates in a second *endo* selective DA reaction with *N*-methyl maleimide (**67**), giving the adduct (**71**) isolated from the domino sequence. Isomers of adduct (**71**), if present in the reaction mixture, were present at concentrations below the threshold of detection by ^{1}H NMR.



Scheme 4.14 *Domino Diels-Alder sequence producing adduct (**71**) from (1E,3E)-1,4-diiodo-1,3-butadiene (**66**) and N-methyl maleimide (**67**). Conditions: (a) (1E,3E)-1,4-Diiodo-1,3-butadiene (**66**), N-methyl maleimide (**67**) (5 molar equiv.), CH_2Cl_2, 19 kbar, RT, 66 hr, 85%.*

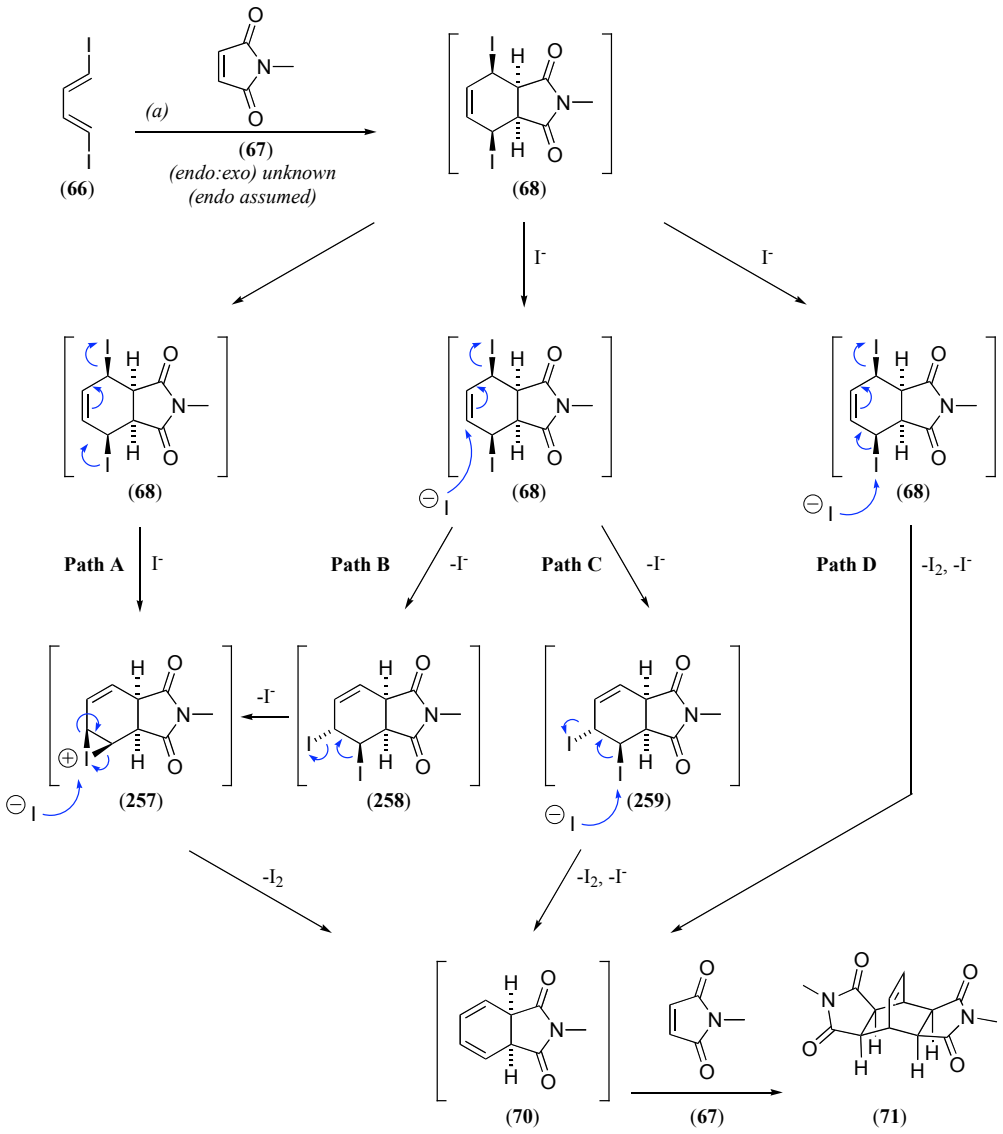
Alternative sets of reaction conditions were explored in order to investigate the mechanism of the domino DA reaction. The reaction was carried out at 19 kbar for four days with a 1:3 molar ratio of the reactants, (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) and *N*-methyl maleimide (**67**), and the domino DA adduct (**71**) was obtained in 84% yield with respect to the limiting reagent, in this case (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**). Intermediates (**68**) and (**70**) were not observed under these conditions. The reaction was also carried out at 19 kbar for four days with a 1:1 molar ratio of the reactants, (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) and *N*-methyl maleimide (**67**). Once again, intermediates (**68**) and (**70**) were not observed, and this time the domino DA adduct (**71**) was obtained in 91% yield with respect to the limiting reagent, in this case *N*-methyl maleimide (**67**).

In principle, the diiodicyclohexene intermediate (**68**) can aromatise through the elimination of two equivalents of hydrogen iodide, giving *N*-methyl phthalimide (**69**), but in no case has this behaviour been observed. An attempt to promote the aromatisation by conducting the reaction in the presence of three molar equivalents of silver (I) oxide was unsuccessful. This transformation could be a useful benzannulation of electron poor alkenes, but the reaction nevertheless produced the domino DA adduct (**71**) in a yield similar to that observed in the absence of silver (I) oxide (**Scheme 4.15**).



Scheme 4.15 *Reaction sequence producing N-methyl phthalimide (**257**) through elimination of two molar equivalents of hydrogen iodide from intermediate (**68**). Conditions: (a) (1E,3E)-1,4-Diiodo-1,3-butadiene (**66**), N-methyl maleimide (**67**) (5 molar equiv.), Ag_2O (**258**) (3 molar equiv.) CH_2Cl_2, 19 kbar, RT, 66 hr, (**71**) 88%; (**257**) not observed.*

Instead of eliminating hydrogen iodide, diiodicyclohexene (**68**) eliminates molecular iodine, producing the cyclohexadiene (**70**). The elimination of molecular iodine from the diiodocyclohexene (**78**) can occur through four distinct mechanistic scenarios involving the iodide anion (**Scheme 4.16**).



Scheme 4.16 *Domino Diels-Alder sequence producing adduct (**71**) from (1E,3E)-1,4-diiodo-1,3-butadiene (**66**) and N-methyl maleimide (**67**). Conditions: (a) (1E,3E)-1,4-Diiodo-1,3-butadiene (**66**), N-methyl maleimide (**67**) (5 molar equiv.), CH_2Cl_2, 19 kbar, RT, 66 hr, (**71**) 85%.*

Molecular bromine adds in a 1,4 sense to 1,3-butadiene (**1**),[245] and the addition of iodine electrophiles to 1,3-butadiene (**1**) is known to involve cyclic, three membered iodonium species.[246] The iodonium species can be quenched by reaction with a nucleophile directly, giving a 1,2 addition product (S_N2 opening of the iodonium species) or indirectly, giving a 1,4 addition product (S_N2' opening of the iodonium species).[247] By the principle of microscopic reversibility, the mechanism of elimination of molecular iodine from the diiodocyclohexene (**68**), could involve a similar iodonium intermediate, as shown in **Path A** of (**Scheme 4.16**). DFT calculations performed by Prof. M. N.

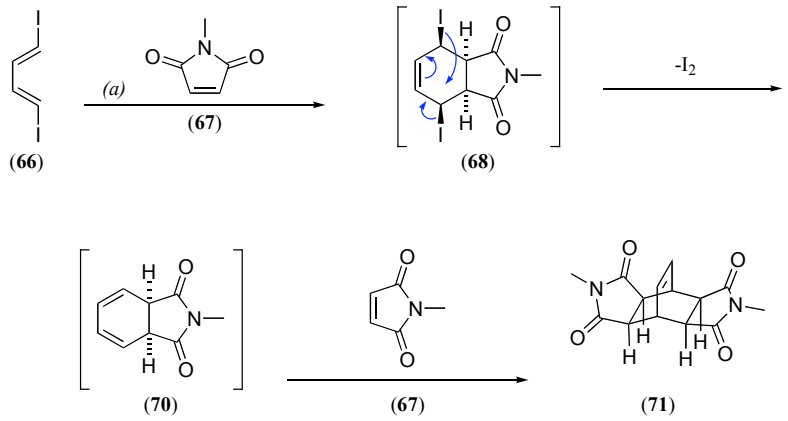
Paddon-Row suggest the spontaneous loss of molecular iodine, as depicted in **Path A** of (**Scheme 4.16**) has a barrier of well over 150 kJmol^{-1}.[178]

The mechanism represented by **Path A** is not the only possibility for the formal elimination of molecular iodine from intermediate (**68**). Molecular iodine is known to exist in equilibrium with acyclic alkenes and vicinal diiodides, but the equilibrium lies in favour of free molecular iodine and the acyclic alkene. This is the basis of a useful protocol for the equilibration of acyclic *Z*-alkenes and mixtures of stereoisomeric acyclic alkenes to the thermodynamically more stable acyclic *E*-alkenes.[248] Allylic transposition of one of the two iodide groups in intermediate (**68**) through a nucleophilic substitution (S_N2') reaction with iodide generates a vicinal diiodide, which can lose molecular iodine through the intermediacy of an iodonium species **Path B**, or through direct reaction with the iodide anion **Path C** of (**Scheme 4.16**).

In addition, a one step mechanism [240,241] could account for the iodide catalysed loss of molecular iodine from the diiodocyclohexene (**68**), with formation of the cyclohexadiene intermediate (**70**), as depicted in **Path D** of (**Scheme 4.16**). DFT calculations performed by Prof. M. N. Paddon-Row indicate that the iodide promoted loss of molecular iodine, which actually gives triiodide, has a barrier of around 50 kJmol^{-1}. Overall, the iodide promoted loss of molecular iodine appears to be a feasible pathway, but the mechanistic details of this process are yet to be elucidated.[178]

To examine the role of iodide in the elimination, a reaction was carried out with (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) and 5.0 molar equivalents of *N*-ethyl maleimide (**260**) in hexane, under conditions designed to be free of iodide. The (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) used in this reaction was taken up in hexane and washed carefully to remove as much ionic material as possible, before being dried over magnesium sulfate and placed in a high pressure reaction vessel. The iodide free conditions gave the corresponding DA adduct (**261**) in comparable yield to the original reaction conditions. It must be noted that (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) is prone to decomposition under the action of light, air or heat. While all care was taken to exclude the iodide ion, it is not out of the question that the decomposition of a small amount of this compound (**66**) seeded the otherwise iodide free reaction mixture with a catalytic quantity of the iodide anion. *N*-ethyl maleimide was used in this reaction because the solubility of *N*-methyl maleimide (**67**) in hexane is rather low.

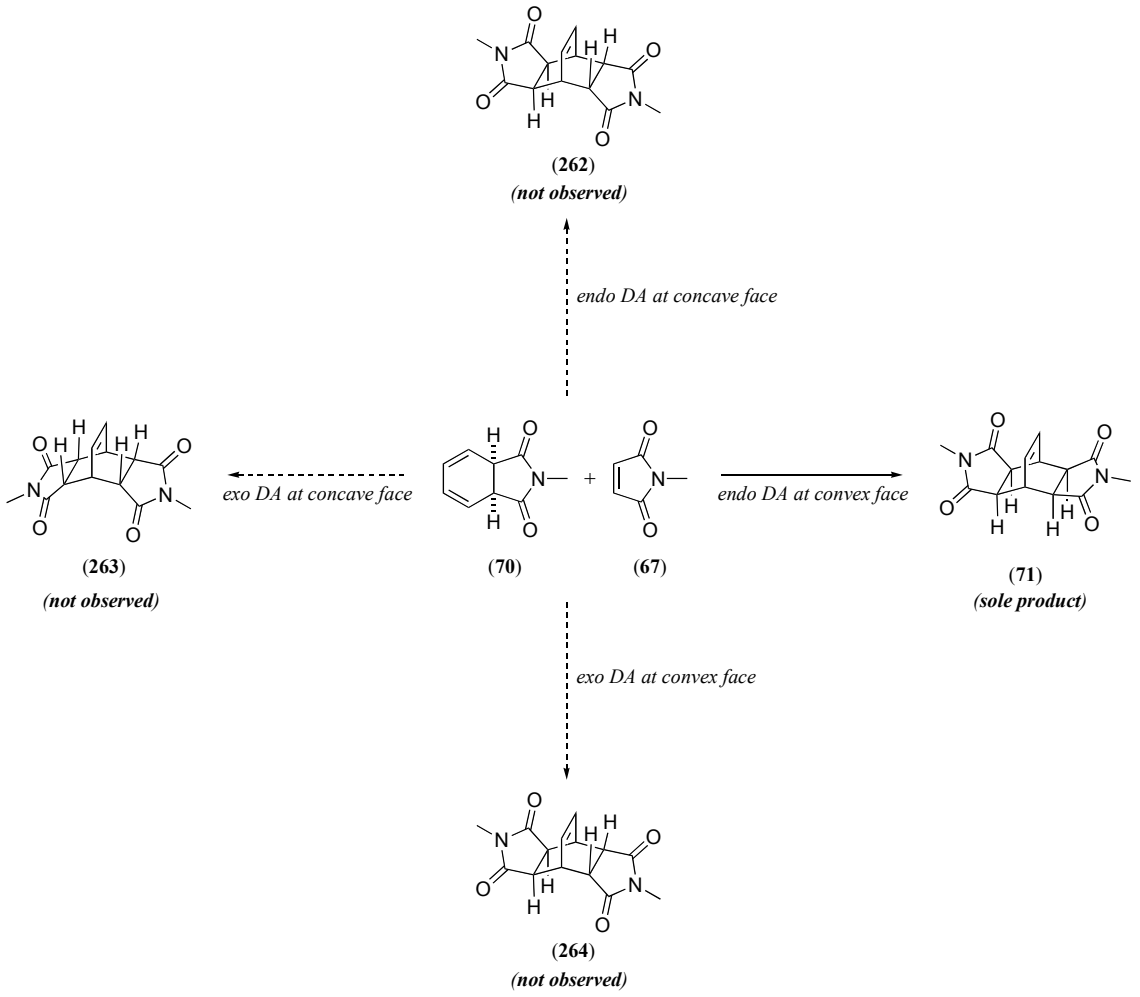
A fifth mechanistic possibility is the concerted loss of molecular iodine directly from intermediate (**68**) through a thermal [4+2] cycloreversion (**Scheme 4.17**). Similar processes, involving the loss of molecular hydrogen in the aromatisation of six membered carbocycles are well known.[249,250] This mechanism is the only candidate which does not require catalysis by the iodide anion, and does not involve charged intermediates, and therefore could account for the successful outcome of the reaction between (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**1**) and N-ethyl maleimide (**260**) in hexane, which was carried out in conditions chosen to exclude the iodide anion. DFT calculations performed by Prof. M. N. Paddon-Row, however, indicate that this reaction also has a barrier of well over 150 kJmol^{-1}. At present, it seems most likely that iodide is involved in the loss of molecular iodine from intermediate (**68**), and that the iodide free reaction gave a spurious result.



Scheme 4.17 *Possible mechanism for conversion of (1E,3E)-1,4-diiodo-1,3-butadiene (**66**) and N-methyl maleimide (**67**) into adduct (**71**). Conditions: (a) (**67**) 5 molar equiv., CH_2Cl_2, RT, 19 kbar, 66 hr, 85%.*

Molecular iodine is always observed in the crude reaction mixtures of successful domino reactions, although at elevated pressure the elimination of a small molecule might be expected to be rate limiting. The putative intermediates, (**68**) and (**70**), have not been detected in the domino DA reaction mixtures, including reactions run with a 1:1 ratio of the reactants (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) and *N*-methyl maleimide (**67**). This indicates that the rate limiting step of the domino sequence is probably the initial DA reaction between (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) and *N*-methyl maleimide (**67**).

As expected, the isomers of the adduct (**71**); (**262**), (**263**) and (**264**), formed through *exo* DA reactions involving intermediate (**70**) or reaction at the concave face of intermediate (**70**), have not been observed in the crude mixtures produced by the reaction, during purification of the domino DA adduct, or in samples of the domino adduct (**Scheme 4.18**). It appears that the second DA reaction in the domino sequence proceeds with complete facial selectivity and *endo* stereoselectivity, within the limits of detection. The DA reactions of maleimide dienophiles with many 1,3-dienes, including cyclopentadiene and 1,3-butadiene, are similarly *endo* selective.[127,228,231]



Scheme 4.18 *The final Diels-Alder reaction of the domino process is strongly endo selective and takes place exclusively at the convex face of intermediate (**70**). Only one (**71**) of the four possible isomeric adducts (**71**), (**262**), (**263**) and (**264**) is observed.*

4.2.2 Scope of the domino Diels-Alder reaction

Domino DA reactions were also carried out using microwave heating, as it was hoped that (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) would react with *N*-methyl maleimide (**67**)

before it had time to decompose. Reactions using 1.0 molar equivalent of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**), 5.0 molar equivalents of *N*-methyl maleimide (**67**), and a trace of BHT in toluene under microwave irradiation were conducted. The microwave reactions were run for 30 minutes at 100 °C, 120 °C and 150 °C and the crude mixtures were analysed by ^{1}H NMR spectroscopy. The 1,3-diene (**66**) decomposed rapidly under microwave heating and the reaction mixtures contained many compounds, but some ^{1}H NMR signals, including a new alkenic signal at δ = 6.02 ppm, and a singlet at δ = 2.72 ppm, corresponding to the alkenic protons and methyl groups of the N-methyl succinimide units of the domino DA adduct (**71**) could be identified in the ^{1}H NMR spectra of the crude reaction mixtures. Unfortunately, only traces of the domino DA adduct (**71**) were produced; the microwave reactions carried out at all three temperatures gave only a few milligrams of the domino DA adduct (**71**). The isolated yields of the domino DA adduct (**71**) from each of the three microwave reactions were less than 10%.

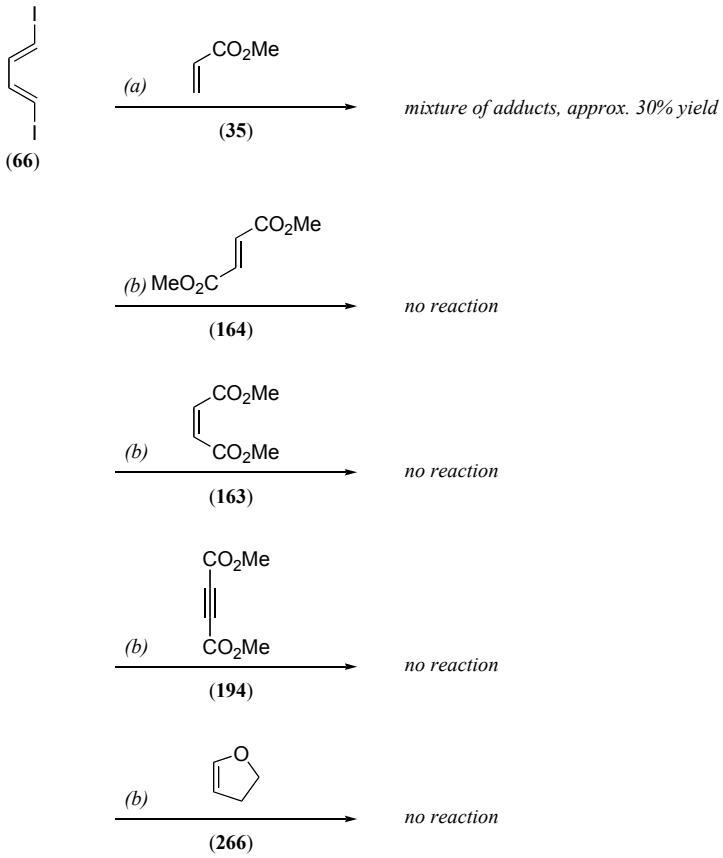
Successful domino DA reactions at 19 kbar have been carried out using *N*-methyl maleimide (**67**), *N*-ethyl maleimide (**260**) and *N*-phenyl maleimide (**230**). Maleimides are very reactive dienophiles, and the scope of the high pressure domino DA reactions was explored using a range of less reactive dienophiles, including dimethyl fumarate (**164**), dimethyl acetylenedicarboxylate (**194**), methyl acrylate (**35**) and dimethyl maleate (**163**).[251] The relative reactivities of *N*-methyl maleimide, *N*-phenyl maleimide, dimethyl fumarate, dimethyl acetylenedicarboxylate, methyl acrylate and dimethyl maleate with cyclopentadiene (**23**) and dimethyl fumarate, dimethyl acetylenedicarboxylate, methyl acrylate and dimethyl maleate with 9,10-dimethylanthracene (**265**) are given in (**Table 4.1**).

Entry	Dienophile	Cyclopentadiene	9,10-Dimethylanthracene
1	*N*-phenyl maleimide (**230**)	11200	-
2	*N*-methyl maleimide (**67**)	6290	-
3	dimethyl fumarate (**164**)	118	105
4	dimethyl acetylenedicarboxylate (**194**)	49.8	68.3
5	methyl acrylate (**35**)	1.88	35.0
6	dimethyl maleate (**163**)	1.00	1.00

Table 4.1 *Relative reactivities of selected dienophiles with cyclopentadiene (**23**) and 9,10-dimethylanthracene (**265**).*[252].

The iodide substituents in the 1,3-diene (**66**) are sterically demanding, inductively electron withdrawing, and mesomerically electron donating. The set of test dienophiles also included 2,3-dihydrofuran (**266**), which it was thought might participate in an inverse electron demand DA reaction with (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**).

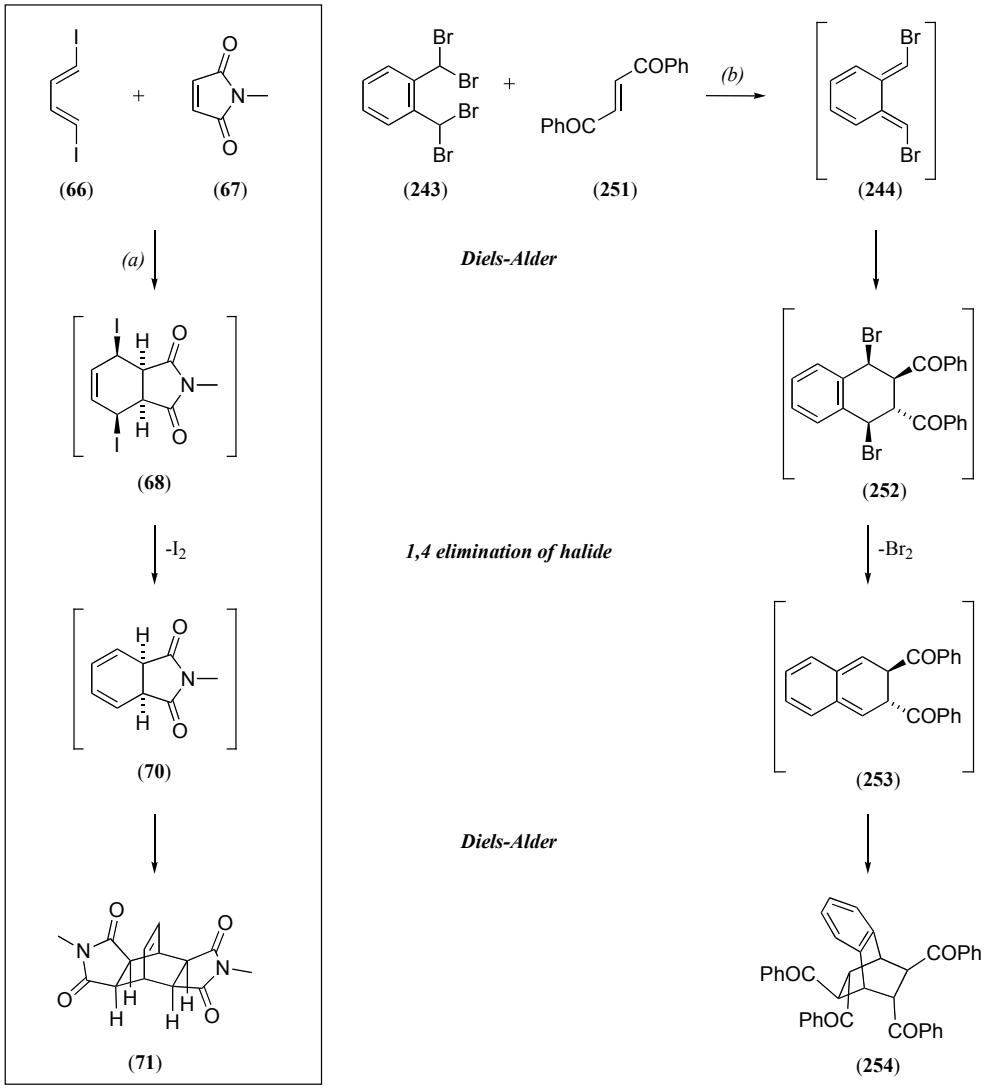
Reaction of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) with 5.0 molar equivalents of methyl acrylate (**35**) at 19 kbar for 72 hr gave what was thought to be a mixture of two isomeric domino DA adducts in a combined yield of approximately 30%, according to analysis of the crude by ^{1}H NMR spectroscopy. The reactants were returned when (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) and five molar equivalents of dimethyl fumarate (**164**), dimethyl acetylenedicarboxylate (**194**) or dimethyl maleate (**163**) were left to react at 19 kbar for 24 hours. The DA reaction of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) with five molar equivalents of 2,3-dihydrofuran (**266**) did not take place in 24 hours at 19 kbar (**Scheme 4.19**).



Scheme 4.19 *Attempted Diels-Alder reactions of (1E,3E)-1,4-diiodo-1,3-butadiene (**66**) with methyl acrylate (**35**), dimethyl fumarate (**164**), dimethyl maleate (**163**), dimethyl acetylenedicarboxylate (**194**) and 2,3-dihydrofuran (**266**). Conditions: (a) (1E,3E)-1,4-Diiodo-1,3-butadiene (**66**), methyl acrylate (**35**) (5 molar equiv.), CH_2Cl_2, 19 kbar, RT, 72 hr, mixture of adducts, approximately 30% yield. (b) (1E,3E)-1,4-Diiodo-1,3-butadiene (**66**), dienophile (**164**), (**194**), (**163**) or (**266**) (5 molar equiv.), CH_2Cl_2, 19 kbar, RT, 24 hr, no reaction.*

It is thought that the DA reactions of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) are sensitive to the steric requirements of the dienophile, due to the steric bulk of the alkenyl iodide functional groups in the 1,3-diene. This may explain the unexpected reactivity pattern seen with dimethyl fumarate (**164**), dimethyl acetylenedicarboxylate (**194**), methyl acrylate (**35**) and dimethyl maleate (**163**), where it appears methyl acrylate is the most reactive dienophile. A trend can be seen in the data in (**Table 4.1**), in which the reactivity of methyl acrylate (**35**) increases relative to the reactivities of the symmetrical dienophiles (**164**), (**194**), and (**163**) upon moving from cyclopentadiene (**23**), a cyclic 1,3-diene without substituents at the one and four positions, to 9,10-dimethylanthracene (**265**), a cyclic 1,3-diene with substituents at the one and four positions.[252]

Reactions similar to those discussed in this chapter have been described in the past. The Cava group has found that tetrabromo-*o*-xylene (**243**) reacts with sodium iodide, generating a dibromo-*o*-quinodimethane (**244**), which can participate in a DA reaction, producing an adduct carrying bromide substituents in a 1,4 relationship (**252**). In the presence of sodium iodide, this intermediate (**252**) can formally eliminate molecular bromine, generating a second 1,3-diene (**253**), which participates in a second DA reaction. The parallel to the chemistry described in this chapter is clear from inspection of (**Scheme 4.20**). Both reactions have an initial DA reaction, a formal elimination of a halide which generates a new 1,3-diene, and a final DA reaction giving a bicyclic adduct.



Scheme 4.20 *Comparison of domino Diels-Alder sequences. Conditions: (a) (1E,3E)-1,4-Diiodo-1,3-butadiene (**66**), N-methyl maleimide (**67**) (5.0 molar equiv.), CH_2Cl_2, 19 kbar, RT, 66 hr, 85%. (b) Tetrabromide (**243**) (1.0 molar equiv.), dione (**251**) (1.3 molar equiv.), NaI (6.8 molar equiv.), acetone, reflux, 72 hr, 49%.*

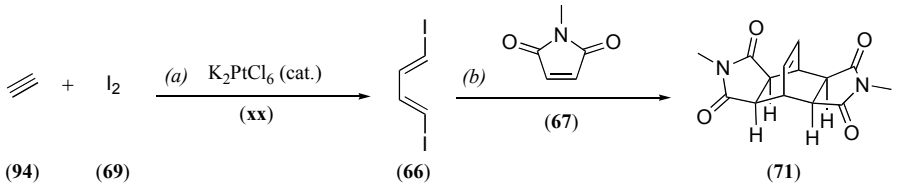
The approach developed by the Cava group, however, relies on the intermediacy of *o*-quinodimethanes, and for this reason lacks generality. It can only be used to generate benzo-fused tricyclic ring systems. It is clear from the work described in this chapter that the domino DA reactions of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) with sufficiently reactive dienophiles produce bicyclic domino DA adducts in yields of around 85%. These domino adducts contain the constituent atoms of the two dienophiles, and four methine units which have their origin in the 1,3-diene (**66**). The endocyclic alkene is an obvious site for chemical elaboration, and could provide easy access to a range of functionalised derivatives.

The use of Lewis acid promoters or catalysts was not investigated in this study, but is likely to dramatically extend the range of dienophiles which take part in the domino reactions. In addition, it is easy to imagine that (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) could be replaced as a reactant with a range of substituted 1,4-dihalo-1,3-butadienes, leading to more complex domino DA adducts, and perhaps new patterns of domino reactivity. The bicyclic adducts made in this way could have many applications including, but not limited to, the total synthesis of complex natural products.

4.3 Concluding Remarks

Under high pressure conditions, (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) participates in domino DA reactions with sufficiently reactive dienophiles, such as maleimides (**67**), (**230**) and (**260**), giving the bicyclic adducts (**71**), (**267**) and (**261**), respectively, in isolated yields around 85%. The structures of the *N*-methyl maleimide (**67**) and *N*-phenyl maleimide (**230**) domino DA adducts were secured by X-ray crystallography. In the course of the domino DA reaction, four new carbon-carbon bonds and a bicyclic ring system are generated from simple starting materials. Some variation in yields is observed between runs as the reaction mixtures are not agitated in the high pressure apparatus. The mechanism of these transformations was investigated and it appears that the initial DA reaction produces an intermediate (**68**) that loses molecular iodine, generating a new 1,3-diene (**70**) which participates in a second DA event with a second equivalent of the maleimide. It is likely that the first cycloaddition is rate limiting, as neither of the postulated intermediates, (**68**) and (**70**), have been observed in the mixtures produced by the reaction, including reactions run with a twofold excess of the iodide (**66**).

Using the reactions described in this chapter of the thesis, a bicyclic carbon skeleton is formed in two steps from acetylene and iodine, using a platinum catalyst and a maleimide dienophile (**Scheme 4.21**). This remarkable increase in molecular complexity is the result of the use of sequential domino reactions, and gives some indication of the power and potential of domino chemistry.



Scheme 4.21 *Two step reaction sequence producing domino Diels-Alder adduct (**71**). Conditions: (a) Acetylene, I_2, NaI, K_2PtCl_6 (**95**) (0.25 mol. %), MeOH, RT, 3 d, 76% (based on I_2); (b) (1E,3E)-1,4-Diiodo-1,3-butadiene (**66**), N-methyl maleimide (**67**) (5.0 molar equiv.), CH_2Cl_2, RT, 19 kbar, 24 hr, 85%.*

Attempts were made to broaden the scope of the reaction using alternative conditions and dienophiles. It was thought that conducting the reaction in the presence of a base and halide scavenger might promote aromatisation of the initial DA adduct (**68**), generating the corresponding phthalimide (**257**), but the yield of the domino adduct was not diminished when the reaction was carried out in the presence of three molar equivalents of silver (I) oxide. The 1,3-diene largely decomposed when the reactions were carried out in toluene under microwave irradiation at 100, 120 and 150 °C for 30 minutes. Reactions with dienophiles including methyl acrylate (**35**), dimethyl fumarate (**164**), dimethyl acetylenedicarboxylate (**194**), dimethyl maleate (**163**), and 2,3-dihydrofuran (**270**) were examined, and preliminary results suggest Lewis acid promotion might be useful in pushing their domino DA reactions with (1*E*,3*E*)-1,4-diiodo-1,3-butadiene to completion, significantly broadening the scope of this chemistry.

5 Experimental

5.1 General Methods

Reactions were conducted under a positive pressure of dry argon or nitrogen in flame-dried glassware. Benzene, diethyl ether, tetrahydrofuran and toluene were dried over sodium and distilled from benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Methanol, ethanol, dimethylformamide, dimethylsulphoxide, chlorobenzene and 1,2-dichlorobenzene were purified by the methods of Armarego and Chai[253] Commercially available chemicals were purified by standard procedures or used as purchased. Sodium sulphate and magnesium sulphate were dried at 160 °C for 24 hr prior to use.

Analytical thin layer chromatography (TLC) was performed with Merck (A. T. 5554) silica gel F_{254} (0.2 mm) precoated on aluminium sheets. Compounds were first visualised under UV light (254 nm), then dipped in basic potassium permanganate or acidic vanillin solutions and developed by heating to approximately 200 °C.[254] Flash chromatography employed Merck Kieselgel 60 (230-400 mesh) silica gel or SDS silica 60 AAC 40-63 μm Chromagel silica gel.

Analytical high performance liquid chromatography (HPLC) was performed using a Shimadzu Prominence LC-20AD chromatograph pump and SIL-20A autosampler, on an Alltima Silica 5 μm column (250 mm, 4.6 mm ID) or an Altima C18 5 μm column (250 mm, 4.6 mm ID) for reverse phase, monitored by a Shimadzu RID-10A refractive index detector and a SPD-M20A diode array detector. Preparative HPLC was performed using a Shimadzu LC-8A chromatograph pump monitored by a Shimadzu RID-10A refractive index detector and a SPD-M20A diode array detector. Separation by preparative HPLC employed an Altima silica 5 μm column (250 mm, 22 mm ID) for normal phase and an Altima C18 5 μm column (250 mm, 22 mm ID) for reverse phase. Analytical chiral HLPC was carried out using a Shimadzu Prominence LC-20AD chromatograph pump and SIL-20A autosampler, on a Daicel Chiralcel ODH column (200 mm, 4.6 mm ID), monitored by a Shimadzu RID-10A refractive index detector and a SPD-M20A diode array detector. Gas chromatography was carried out on an Agilent

gas chromatograph with a split/splitless (split ratio 33:1) capillary inlet, and FID or MS detection. Separation was achieved with a JW DB5 MS column (30m, 0.25 mm ID, 0.25 μm film thickness).

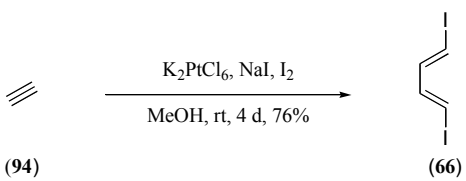
Nuclear magnetic resonance (NMR) spectra were recorded at 298 K using Varian INOVA 300 MHz, Mercury 300 MHz, MR-400 400 MHz and INOVA 500 MHz spectrometers, or Bruker Avance 600 MHz and 800 MHz spectrometers. Residual solvent signals were used as internal references for ^{1}H, ^{2}H and ^{13}C NMR spectra obtained in commonly used organic solvents.[255,256] Assignment of proton signals was assisted by COSY 1D-nOe and NOESY experiments when necessary. Signals were described in terms of chemical shifts, intensity, multiplicity and coupling constants. The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad. The assignment of carbon signals was assisted by DEPT, APT, HSQC and HMQC experiments when necessary.

Infra-red (IR) spectra were recorded on a Perkin-Elmer Spectum One spectrometer as neat films on NaCl or KBr plates or as KBr disks for solids. Mass spectra (MS) were recorded by the Mass Spectrometry Facility of the Research School of Chemistry, Australian National University, Canberra on a VG Autospec M series sector (EBE) mass spectrometer for EI, VG Quattro II triple quadrupole MS for LR ESI and Bruker Apex3 4.7 T FTICR-MS for HR ESI. Micro analyses were performed at the Microanalytical Laboratory, Research School of Chemistry, Australian National University, Canberra. Melting points were measured on a Reichert hot stage melting point apparatus and are uncorrected.

5.2 Experimental for Chapter 2

5.2.1 Synthesis of (1E,3E)-1,4-dideutero-1,3-butadiene (64)

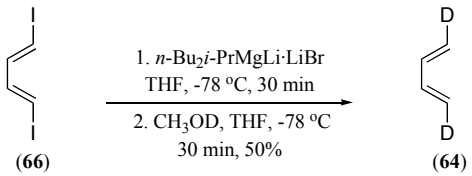
*5.2.1.1 (1E,3E)-1,4-Diiodo-1,3-butadiene (**66**)*



Scheme 5.1 *Synthesis of (1E,3E)-1,4-diiodo-1,3-butadiene (**66**).*

This compound was prepared according to the modified procedure of the Beletskaya group.[99] A stream of acetylene was bubbled through a solution of sodium iodide (3.0g, 20.0 mmol) in methanol (25 mL) for 10 mins. K_2PtCl_6 (**95**) (25 mg, 0.051 mmol) and iodine (6.0 g, 23.2 mmol) were added and the mixture was stirred at room temperature under an atmosphere of acetylene (2.5 L, 102 mmol) in darkness for 4 days. The progress of the reaction was judged by the consumption of acetylene. The reaction mixture was diluted with water (50 mL), treated with excess saturated aqueous $Na_2S_2O_5$, and the resulting suspension was stirred vigorously for 5 mins. It was then partitioned between water (700 mL) and diethyl ether (200 mL) and BHT (2 mg) was added. The aqueous layer was discarded, and the organic layer was washed three times with water (100 mL) and once with brine (100 mL), dried over $MgSO_4$ and concentrated under vacuum, giving the title compound (**66**) as a pale yellow solid (5.66 g, 18.5 mmol, 76% based on I_2), contaminated with approximately 2% (103 mg, 0.37 mmol) (*E*)-1,2-diiodoethylene (**98**). Mp 54 °C (dec.). NMR, MS and IR spectral data all matched the literature values. In addition, a single crystal X-ray structure was obtained.

*5.2.1.2 (1E,3E)-1,4-Dideutero-1,3-butadiene (**64**)*



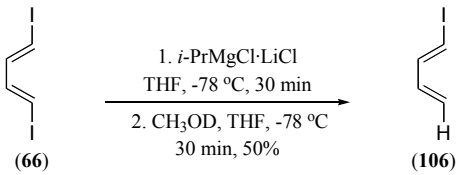
(**66**) (**64**)

Scheme 5.2 *Synthesis of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**).*

This compound was prepared according to the modified procedure of Kitigawa and coworkers.[110] A two neck round bottom flask was attached to a nitrogen line fitted with a needle valve and charged with a solution of isopropylmagnesium bromide in THF (19.7 mL, 1.14 M, 22.5 mmol) and an additional 25 mL THF. The contents of the flask were cooled to 0 °C and treated with a solution of *n*-BuLi in hexanes (28.1 mL, 1.6 M, 45.0 mmol). After stirring at 0 °C for 30 mins, the resulting solution was cooled to -78 °C and a solution of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) (5.66 g, 18.5 mmol) in THF (5 mL) was added rapidly, and in a single portion. After stirring at -78 °C for 30 mins, CH_3OD (2.64 g, 3.26 mL, 80 mmol) was added, the needle valve was closed and the reaction mixture was stirred at -78 °C for a further 30 mins. One of the necks of the flask was then fitted with an air condenser connected in sequence to a column packed

with cooled, oven dried silica, a liquid nitrogen trap containing 2 mL benzene or CH_2Cl_2, and a bubbler, and the flask was removed from the cooling bath and allowed to warm to room temperature. The contents of the flask were then gently heated to reflux, and once the reaction mixture was at reflux, the needle valve was opened, allowing a slow stream of nitrogen to pass through the headspace of the flask and vent at the bubbler. (1*E*,3*E*)-1,4-Dideutero-1,3-butadiene (**64**) (530 mg, 9.5 mmol, 50%) accumulated in the trap and was handled in benzene or CH_2Cl_2 solution. ^{1}H NMR (800 MHz, $CDCl_3$) δ 6.58 -6.52 (m, 2H), 5.44-5.38 (m, 1.94 H) and 5.33-5.29 (m, 0.104 H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 137.8 (1:1:1 triplet, J = 2.0 Hz) and 117.2 (1:1:1 triplet, J = 24.5 Hz) ppm; MS (70 eV, EI): *m/z* (%): 56 (100) $[M]^+$, 40 (70).

*5.2.1.3 (E)-1-Iodo-1,3-butadiene (**106**)*

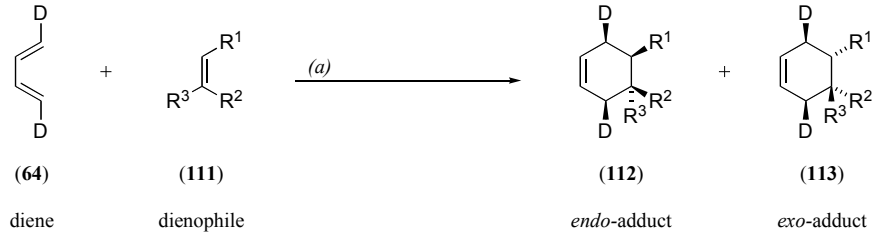


Scheme 5.3 *Synthesis of (E)-1-iodo-1,3-butadiene (**106**).*

This compound[109] was prepared according to the modified procedure of Krasovskiy and coworkers.[108] A solution of (1*E*,3*E*)-1,4-diiodo-1,3-butadiene (**66**) (300 mg, 0.98 mmol) in THF (10 mL) in a two neck round bottom flask was cooled to -78 °C and treated with a solution of isopropylmagnesium chloride lithium chloride complex (**105**) in THF (1.07 mL, 1.00 M, 1.07 mmol). After stirring at -78 °C for 30 mins, CH_3OH (0.66 g, 0.82 mL, 20 mmol) was added, and the contents of the flask were allowed to warm to RT over 15 min . The mixture was transferred to a separating funnel, diluted with pentane and washed five times with water and once with brine. The organic layer was then dried over $MgSO_4$ and the solvent was carefully removed under vacuum at 0 °C. Flash column chromatography, eluting with *n*-pentane gave the title compound (**106**) as a light sensitive, colourless oil (125 mg, 0.69 mmol, 70%): R_f 0.8 *n*-pentane; ^{1}H NMR (300 MHz, C_6D_6) δ 6.78 (1H, dd, J = 14.4, 10.5 Hz), δ 5.85 (1H, d, J = 14.4 Hz), δ 5.78 (1H, ddd, J = 16.8, 10.5, 9.3 Hz), δ 4.78 (1H, d, J = 16.8 Hz), δ 4.72 (1H, d, J = 9.3 Hz) ppm; ^{13}C NMR (75 MHz, C_6D_6) δ 145.9, 136.9, 117.8, and 80.6 ppm; IR (thin film) ν = 3052, 2958, 2926, 1623, 1281, 1205 cm^{-1}; MS (70 eV, EI): *m/z* (%): 180 (100) $[M]^+$, 127 (20), 53 (75); HRMS calc for C_4H_5I $[M]^+$: 179.9436; found: 179.9436.

5.2.2 Diels-Alder reactions of (1E,3E)-1,4-dideutero-1,3-butadiene (64)

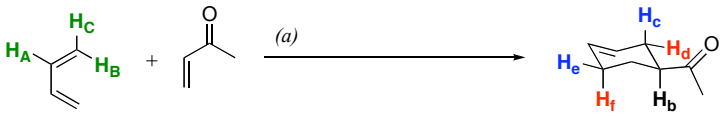
*5.2.2.1 General procedure for Diels-Alder reactions of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**)*



Scheme 5.4 *Diels-Alder reactions of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**). Typical conditions: (a) 1.0 M in 1,3-diene (**64**) and dienophile (**111**), BHT (2 mol %), benzene, 145 °C, sealed tube, 21-120 hr.*

Hydroquinone (2 mg, 0.02 mmol), the dienophile (1.0 mmol) and a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in benzene (1.0 mL, 1.0 M, 1.0 mmol) were sealed into a glass ampoule and heated to 145° C for the stated time. The ampoule was cooled and opened and the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography to give a mixture of DA adducts (**112**) and (**113**). The *endo:exo* ratio was obtained from ^{1}H NMR integral data taken from the quantitative ^{1}H NMR spectra of the adduct mixture and the sample of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) used in the DA reaction, as described in the following section. The DA reaction of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) and methyl vinyl ketone (**33**) is used as an example.

5.2.2.2 *Calculation of endo:exo selectivity for the Diels-Alder reactions of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**)*



(**64**) (**33**) (**117**)

Resonance	Integral	Resonance	Integral
H_A	1.00	H_b	1.00
H_B	0.96	H_c	0.41
H_C	0.12	H_d	0.67
		H_e	0.41
		H_f	0.66

Scheme 5.5 *Diels-Alder reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with methyl vinyl ketone (**33**). Conditions: (a) 1.0 M in 1,3-diene and dienophile, BHT (2 mol %), benzene, 145 °C, sealed tube, 24 hr, 64%.*

In calculating the *endo:exo* ratio for the DA reaction of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) with methyl vinyl ketone (**33**), it is convenient to normalise the ^{1}H NMR integrals of the ^{2}H enriched sites in the adduct mixture by comparison with the ^{1}H NMR integrals of sites containing ^{2}H at natural abundance; approximately 0.015%. This gives the ^{1}H content of ^{2}H enriched sites as a simple fraction of the natural content. It is also convenient to express the *endo*:*exo* ratio in terms which sum to unity:

$$(n,x) = (endo,\ exo)$$
$$(n + x) = 1$$

The data obtained from the two ^{2}H labelled allylic positions were combined, allowing redundant integral data to be used in the calculations:

$$H_{d,f} = (H_d + H_f)/2 = 0.665$$
$$H_{c,e}(H_c + H_e)/2 = 0.41$$

The integrals of the adduct mixture at positions carrying deuterium (lower case subscripts) were expressed in terms of the integrals in the (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) used in the DA reaction (upper case subscripts) and the *endo:exo* ratio.

$$H_{d,f} = nH_B + xH_C$$
$$H_{c,e} = xH_B + nH_C$$

The proportion of the product mixture produced through *endo* reaction pathways could then be expressed in terms of the ^{1}H NMR integrals at positions *d* and *f* of the mixture of DA adducts, and the ^{1}H NMR integrals of the (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) used in the DA reaction.

$$H_{d,f} = nH_B + xH_C$$
$$H_{d,f} = nH_B + (1-n)H_C$$
$$H_{d,f} = nH_B + (H_C - nH_C)$$
$$H_{d,f} = H_C + n(H_B - H_C)$$
$$(H_{d,f} - H_C) = n(H_B - H_C)$$
$$n = (H_{d,f} - H_C)/(H_B - H_C)$$

Integral values were substituted into the rearranged equation and it was solved for *n*, giving the proportion of the product mixture formed through *endo* DA reaction pathways:

$$n = (H_{d,f} - H_C)/(H_B - H_C)$$
$$n = (0.665 - 0.12)/(0.96 - 0.12)$$
$$n = (0.545)/(0.84)$$
$$n = 0.65 \ \ (x = 0.35)$$

Complementary integral data from positions *c* and *e* were then used to calculate the proportion of the product mixture formed through *exo* reaction pathways:

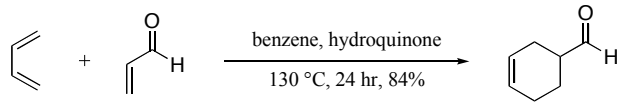
$$H_{c,e} = xH_B + nH_C$$
$$H_{c,e} = xH_B + (1-x)H_C$$
$$H_{c,e} = xH_B + (H_C - xH_C)$$
$$H_{c,e} = H_C + x(H_B - H_C)$$
$$(H_{c,e} - H_C) = x(H_B - H_C)$$
$$x = (H_{c,e} - H_C)/(H_B - H_C)$$

Integral values were substituted into the rearranged equation and it was solved for *x*, the proportion of the products produced through *exo* reaction pathways:

$$x = (H_{c,e} - H_C)/(H_B - H_C)$$
$$x = (0.41 - 0.12)/(0.96 - 0.12)$$
$$x = (-0.29/-0.84)$$
$$x = 0.35 \ (n = 0.65)$$

The figures obtained from the two calculations correspond to within 1%. The calculated *endo:exo* ratio of the DA reaction of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) with methyl vinyl ketone (**33**) is 65:35. The *endo:exo* ratios of the DA reactions of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene with other dienophiles, (**32**), (**34**), (**35**), (**36**), (**60**), (**61**), (**67**), (**114**) and (**115**), were obtained in a similar manner.

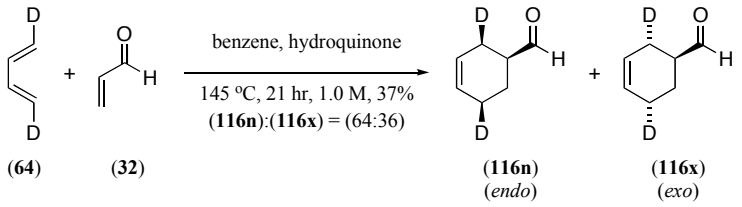
*5.2.2.3 ±Cyclohex-3-enecarbaldehyde (**116**)*



(**1**) (**32**) (**116**)

Scheme 5.6 *Diels-Alder reaction of 1,3-butadiene (**1**) with acrolein (**32**).*

This compound was prepared according to the modified procedure of Diels and Alder.[1] A solution of acrolein (**32**) (280 mg, 5.0 mmol) and hydroquinone (3 mg, 0.027 mmol) in benzene (10 mL) was stirred under an atmosphere of 1,3-butadiene (**1**) in a screw cap tube fitted with a rubber septum for 10 mins at RT. Excess 1,3-butadiene (**1**) dissolved into the solution. The tube was then sealed and placed in a preheated oil bath with stirring at 130 °C for 24 h. The tube was then removed from the oil bath, cooled and opened, and its contents were concentrated under vacuum. The crude material was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (40:1) to give the title compound (**116**) as a colourless oil (462 mg, 4.20 mmol, 84%): R_f 0.2 40-60 petrol:ethyl acetate (40:1); ^{1}H NMR (800 MHz, C_6D_6/DMSO-d_6 49:1) δ 9.29 (s, 1H), 5.51-5.46 (m, 2H), 1.99-1.95 (m, 1H), 1.95-1.91 (m, 1H), 1.87-1.82 (m, 1H), 1.82-1.76 (m, 1H), 1.72-1.66 (m, 1H), 1.56-1.51 (m, 1H) and 1.34-1.28 (m, 1H) ppm; ^{13}C NMR (200 MHz, C_6D_6/DMSO-d_6 49:1) δ 202.7, 127.1, 125.1, 45.9, 24.4, 23.8 and 22.1 ppm; IR (thin film) ν = 3026, 2921, 2840, 2710, 1726, 1652, 1438 cm^{-1}; MS (70 eV, EI): *m/z* (%): 110 (70) $[M]^+$, 92 (26), 81 (79), 79 (100), 57 (36); HRMS calc for $C_7H_{10}O$ $[M]^+$: 110.0732; found: 110.0732.

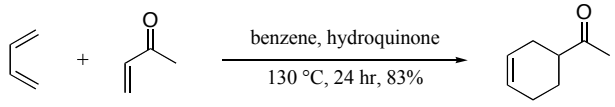


(**64**) (**32**) (**116n**) (*endo*) (**116x**) (*exo*)

Scheme 5.7 *Diels-Alder reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with acrolein (**32**).*

Hydroquinone (2 mg, 0.02 mmol), acrolein (**32**) (56 mg, 1.0 mmol) and a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in benzene (1.0 mL, 1.0 M, 1.0 mmol) were sealed into a glass ampoule and heated to 145° C for 21 h. The ampoule was cooled and opened and the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (40:1) to give a mixture of the Diels-Alder adducts (**116n**) and (**116x**) (*endo:exo* 64:36) as a colourless oil (50 mg, 0.37 mmol, 37%): R_f 0.2 40-60 petrol:ethyl acetate (40:1); ^{1}H NMR (800 MHz, C_6D_6/DMSO-d_6 49:1) δ 9.29 (s, 0.99 H), 5.51-5.46 (m, 2.01 H), 1.99-1.95 (m, 0.39 H), 1.95-1.91 (m, 0.97 H), 1.87-1.82 (m, 0.68 H), 1.82-1.76 (m, 0.37 H), 1.72-1.66 (m, 0.64 H), 1.56-1.51 (m, 0.97 H) and 1.34-1.28 (m, 1.00 H) ppm; IR (thin film) ν = 3026, 2924, 2867, 2161 (C-D), 1726, 1647, 1452 cm^{-1}; MS (70 eV, EI): *m/z* (%): 112 (71) $[M]^+$, 83 (100), 80 (84), 56 (56); HRMS calc for $C_7H_8D_2O$ $[M]^+$: 112.0857; found: 112.0854.

*5.2.2.4 ±1-(Cyclohex-3-enyl)ethanone (**117**)*

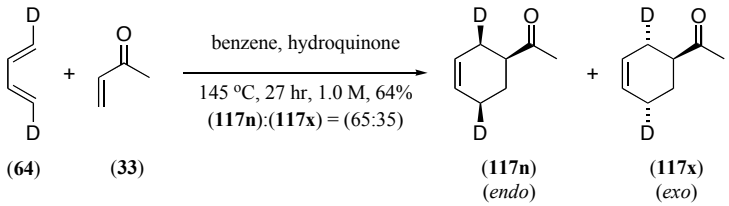


(**1**) (**33**) (**117**)

Scheme 5.8 *Diels-Alder reaction of 1,3-butadiene (**1**) with methyl vinyl ketone (**33**).*

This compound was prepared according to the modified procedure of Petrov.[119] A solution of methyl vinyl ketone (**33**) (350 mg, 5.0 mmol) and hydroquinone (3 mg, 0.027 mmol) in benzene (10 mL) was stirred under an atmosphere of 1,3-butadiene (**1**) in a screw cap tube fitted with a rubber septum for 10 mins at RT. Excess 1,3-butadiene (**1**) dissolved into the solution. The tube was then sealed and placed in a preheated oil bath with stirring at 130 °C for 24 h. The tube was then removed from the oil bath, cooled and opened, and its contents were concentrated under vacuum. The crude

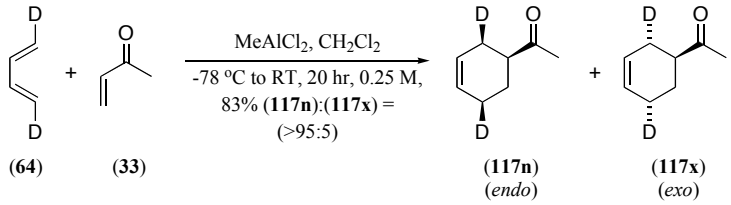
material was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (40:1) to give the title compound (**117**) as a colourless oil (513 mg, 4.13 mmol, 83%): R_f 0.2 40-60 petrol:ethyl acetate (40:1); ^{1}H NMR (800 MHz, C_6D_6/DMSO-d_6 24:1) δ 5.57-5.52 (m, 2H), 2.18-2.11 (m, 1H), 2.10-2.03 (m, 1H), 1.92-1.87 (m, 1H), 1.87-1.82 (m, 1H), 1.82-1.75 (m, 1H), 1.72 (3H, s), 1.69-1.64 (m, 1H) and 1.42-1.35 (m, 1H) ppm; ^{13}C NMR (200 MHz, C_6D_6/DMSO-d_6 24:1) δ 209.0, 126.7, 125.7, 47.0, 27.4, 27.0, 24.9 and 24.7 ppm; IR (thin film) ν = 3026, 2921, 2840, 1710, 1653, 1436 cm^{-1}; MS (70 eV, EI): *m/z* (%): 124 (76) $[M]^+$, 109 (22), 81 (98), 79 (43), 43 (100); HRMS calc for $C_8H_{12}O$ $[M]^+$: 124.0888; found: 124.0888.



(**64**) (**33**) (**117n**) (*endo*) (**117x**) (*exo*)

Scheme 5.9 *Diels-Alder reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with methyl vinyl ketone (**33**).*

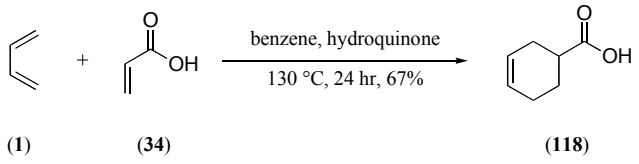
Hydroquinone (2 mg, 0.02 mmol), methyl vinyl ketone (**33**) (70 mg, 1.0 mmol) and a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in benzene (1.0 mL, 1.0 M, 1.0 mmol) were sealed into a glass ampoule and heated to 145° C for 27 h. The ampoule was cooled and opened and the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (40:1) to give a mixture of the Diels-Alder adducts (**117n**) and (**117x**) (*endo:exo* 65:35) as a colourless oil (81 mg, 0.64 mmol, 64%): R_f 0.2 40-60 petrol:ethyl acetate (40:1); ^{1}H NMR (800 MHz, C_6D_6/DMSO-d_6 24:1) δ 5.57-5.52 (m, 2.00 H), 2.18-2.11 (m, 1.00 H), 2.10-2.03 (m, 0.48 H), 1.92-1.87 (m, 0.67 H), 1.87-1.82 (m, 0.47 H), 1.82-1.75 (m, 0.66 H), 1.72 (3.01 H, s), 1.69-1.64 (m, 0.99 H) and 1.42-1.35 (m, 1.00 H) ppm; IR (thin film) ν = 3025, 2924, 2866, 2161 (C-D), 2134 (C-D), 1709, 1647, 1425 cm^{-1}; MS (70 eV, EI): *m/z* (%): 126 (76) $[M]^+$, 111 (16), 81 (84), 82 (40), 43 (100); HRMS calc for $C_8H_{10}D_2O$ $[M]^+$: 126.1014; found: 126.1012.



Scheme 5.10 *Methylaluminium dichloride (**133**) promoted Diels-Alder reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with methyl vinyl ketone (**33**).*

Methyl vinyl ketone (**33**) (70 mg, 1.0 mmol) was added to a round bottom flask containing a solution of methylaluminium dichloride in hexanes (0.9 mL, 1.0 M, 0.9 mmol) at -78 °C. The resulting mixture was stirred at -78 °C for 30 mins and a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in CH_2Cl_2 (3.1 mL, 0.33 M, 1.1 mmol) was added. After warming to RT and stirring at this temperature for 20 hr, the contents of the flask were poured into water and the aqueous phase was extracted four times with CH_2Cl_2. The CH_2Cl_2 extracts were pooled, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (40:1) to give a mixture of the Diels-Alder adducts (**117n**) and (**117x**) (*endo:exo* >95:5) as a colourless oil (105 mg, 0.83 mmol, 83%): R_f 0.2 40-60 petrol:ethyl acetate (40:1); ^{1}H NMR (800 MHz, C_6D_6/DMSO-d_6 24:1) δ 5.57-5.52 (m, 2.00 H), 2.18-2.11 (m, 1.00 H), 2.10-2.03 (m, 0.14 H), 1.92-1.87 (m, 0.99 H), 1.87-1.82 (m, 0.15 H), 1.82-1.75 (m, 0.99 H), 1.72 (3.01 H, s), 1.69-1.64 (m, 1.01 H) and 1.42-1.35 (m, 1.00 H) ppm; IR (thin film) ν = 3025, 2924, 2866, 2161 (C-D), 2134 (C-D), 1709, 1647, 1425 cm^{-1}; MS (70 eV, EI): *m/z* (%): 126 (76) $[M]^+$, 111 (16), 81 (84), 82 (40), 43 (100); HRMS calc for $C_8H_{10}D_2O$ $[M]^+$: 126.1014; found: 126.1012.

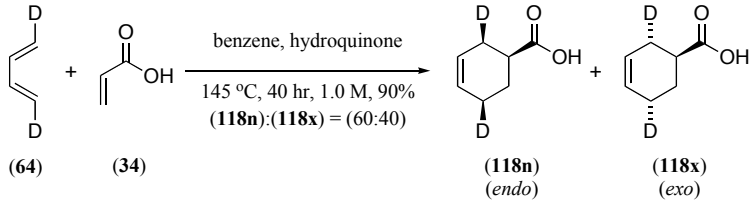
*5.2.2.5 ±Cyclohex-3-enecarboxylic acid (**118**)*



Scheme 5.11 *Diels-Alder reaction of butadiene (**1**) with acrylic acid (**34**).*

This compound was prepared according to the modified procedure of Petrov and Sopov.[120] A solution of freshly distilled acrylic acid (**34**) (1.48 g, 20.5 mmol) and hydroquinone (4 mg, 0.036 mmol) in benzene (10 mL) was stirred under an atmosphere

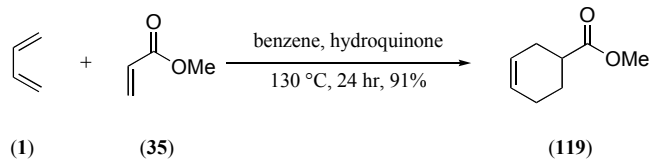
of 1,3-butadiene (**1**) in a screw cap tube fitted with a rubber septum for 10 mins at RT. Excess 1,3-butadiene (**1**) dissolved into the solution. The tube was then sealed and placed in a preheated oil bath with stirring at 130 °C for 24 hr. The tube was then removed from the oil bath, cooled and opened, and its contents were concentrated under vacuum. The crude material was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (4:1) to give the title compound (**118**) as a colourless oil (1.75 g, 13.9 mmol, 67%): R_f 0.2 40-60 petrol:ethyl acetate (4:1); ^{1}H NMR (800 MHz, C_6D_6/DMSO-d_6 49:1) δ 5.61-5.53 (m, 2H), 2.59-2.54 (m, 1H), 2.48-2.41 (m, 1H), 2.31-2.26 (m, 1H), 2.07-2.02 (m, 1H), 1.97-1.90 (m, 1H), and 1.89-1.75 (m, 2H) ppm; ^{13}C NMR (200 MHz, C_6D_6/DMSO-d_6 49:1) δ 177.7, 126.8, 125.9, 35.6, 28.0, 25.6, and 24.8 ppm; IR (thin film) ν = 3027, 2922, 2660, 1706, 1638, 1420 cm^{-1}; MS (70 eV, EI): *m/z* (%): 126 (4) $[M]^+$, 108 (44), 81 (79), 80 (100), 55 (87); HRMS calc for $C_7H_{10}O_2$ $[M]^+$: 126.0681; found: 126.0681.



Scheme 5.12 *Diels-Alder reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with acrylic acid (**34**).*

Hydroquinone (2 mg, 0.02 mmol), freshly distilled acrylic acid (**34**) (65 mg, 0.9 mmol) and a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene in benzene (1.0 mL, 1.0 M, 1.0 mmol) were sealed into a glass ampoule and heated to 145° C for 40 h. The ampoule was cooled and opened and the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (4:1) to give a mixture of the Diels-Alder adducts (**118n**) and (**118x**) (*endo:exo* 60:40) as a colourless oil (104 mg, 0.81 mmol, 90%): R_f 0.2 40-60 petrol:ethyl acetate (4:1); ^{1}H NMR (800 MHz, C_6D_6/DMSO-d_6 49:1) δ 5.61-5.53 (m, 1.99 H), 2.59-2.54 (m, 0.99 H), 2.48-2.41 (m, 0.48 H), 2.31-2.26 (m, 0.58 H), 2.07-2.02 (m, 1.00 H), 1.97-1.90 (m, 0.48 H), and 1.89-1.75 (m, 1.58 H) ppm; IR (thin film) ν = 3027, 2927, 2628, 2165 (C-D), 2139 (C-D), 1705, 1651, 1421 cm^{-1}; MS (70 eV, EI): *m/z* (%): 128 (48) $[M]^+$, 110 (32), 83 (97), 82 (100), 55 (47); HRMS calc for $C_7H_{10}D_2O_2$ $[M]^+$: 128.0806; found: 128.0807.

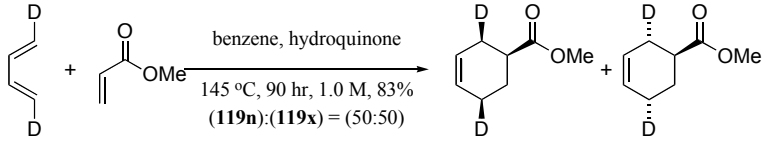
*5.2.2.6 ±Methyl cyclohex-3-enecarboxylate (**119**)*



(**1**) (**35**) (**119**)

Scheme 5.13 *Diels-Alder reaction of 1,3-butadiene (**1**) with methyl acrylate (**35**).*

This compound was prepared according to the modified procedure of Doucet and Rumpf.[121] A solution of methyl acrylate (**35**) (430 mg, 5.0 mmol) and hydroquinone (3 mg, 0.027 mmol) in benzene (10 mL) was stirred under an atmosphere of 1,3-butadiene (**1**) in a screw cap tube fitted with a rubber septum for 10 mins at RT. Excess 1,3-butadiene (**1**) dissolved into the solution. The tube was then sealed and placed in a preheated oil bath with stirring at 130 °C for 24 h. The tube was then removed from the oil bath, cooled and opened, and its contents were concentrated under vacuum. The crude material was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (40:1) to give the title compound (**119**) as a colourless oil (638 mg, 4.55 mmol, 91%): R_f 0.2 40-60 petrol:ethyl acetate (40:1); ^{1}H NMR (800 MHz, DMSO-d_6) δ 5.68-5.63 (m, 2H), 3.61 (s, 3H), 2.54 (1H, dddd, J = 10.1, 9.6, 3.1, 2.4 Hz), 2.22-2.17 (m, 1H), 2.15-2.10 (m, 1H), 2.06-2.00 (m, 2H), 1.92-1.88 (m, 1H) and 1.58-1.52 (m, 1H) ppm; ^{13}C NMR (200 MHz, DMSO-d_6) δ 175.3, 126.6, 125.1, 51.5, 38.3, 27.0, 24.7 and 23.8 ppm; IR (thin film) ν = 3027, 2951, 2930, 2843, 1737, 1653, 1436 cm^{-1}; MS (70 eV, EI): *m/z* (%): 140 (24) [M]$^+$, 108 (36), 81 (100), 80 (99), 53 (29); HRMS calc for $C_8H_{12}O_2$ [M]$^+$: 140.0835; found: 140.0837.



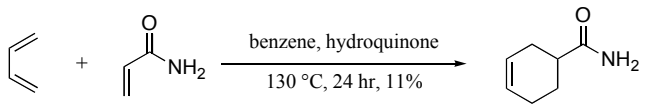
(**64**) (**35**) (**119n**) (*endo*) (**119x**) (*exo*)

Scheme 5.14 *Diels-Alder reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with methyl acrylate (**35**).*

Hydroquinone (2 mg, 0.02 mmol), methyl acrylate (**35**) (86.1 mg, 1.0 mmol) and a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in benzene (1.0 mL, 1.0 M, 1.0 mmol) were sealed into a glass ampoule and heated to 145° C for 90 h. The ampoule

was cooled and opened and the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (40:1) to give a mixture of the Diels-Alder adducts (**119n**) and (**119x**) (*endo:exo* 50:50) as a colourless oil (118 mg, 0.83 mmol, 83%): R_f 0.2 40-60 petrol:ethyl acetate (40:1); ^{1}H NMR (800 MHz, DMSO-d_6) δ 5.68-5.63 (m, 2.00 H), 3.61 (s, 3.01 H), 2.54 (0.99 H, dddd, J = 10.1, 9.6, 3.1, 2.4 Hz), 2.22-2.17 (m, 0.54 H), 2.15-2.10 (m, 0.52 H), 2.06-2.00 (m, 1.05 H), 1.92-1.88 (m, 1.01 H) and 1.58-1.52 (m, 1.00 H) ppm; IR (thin film) ν = 3027, 2951, 2930, 2869, 2165 (C-D), 2137 (C-D), 1737, 1649, 1435 cm^{-1}; MS (70 eV, EI): *m/z* (%): 142 (24) $[M]^+$, 110 (16), 83 (100), 82 (61), 55 (51); HRMS calc for $C_8H_{10}D_2O_2$ $[M]^+$: 142.0963; found: 142.0964.

*5.2.2.7 ±Cyclohex-3-ene-carboxamide (**120**)*

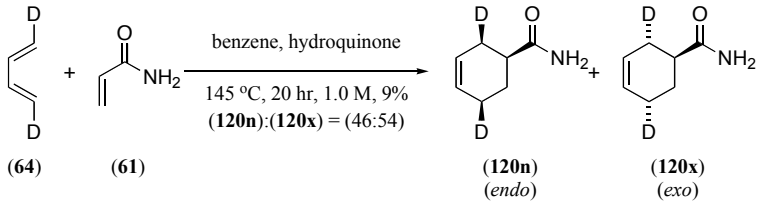


(**1**) (**61**) (**120**)

Scheme 5.15 *Diels-Alder reaction of 1,3-butadiene (**1**) with acrylamide (**61**).*

This compound was prepared according to the modified procedure of Hall.[122] Acrylamide (**61**) (125 mg, 1.00 mmol) and hydroquinone (2 mg, 0.018 mmol) were placed in a 2 mL glass ampoule and the neck of the ampoule was fitted with a rubber septum. A solution of 1,3-butadiene (**1**) (60 mg, 1.10 mmol) in benzene (1 mL) was added by syringe and the ampoule was sealed and placed in a preheated oil bath at 130 °C for 24 h. The ampoule was then removed from the oil bath, cooled and opened, and its contents were concentrated under vacuum. The residue was taken up in CH_2Cl_2 (20 mL) and washed three times with water (20 mL), washed once with brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude material was purified by flash column chromatography eluting with diethyl ether:ethyl acetate (20:1) to give the title compound (**120**) as a pale yellow solid (14 mg, 0.11 mmol, 11%): R_f 0.2 diethyl ether:ethyl acetate (20:1); mp 155 °C; ^{1}H NMR (800 MHz, acetone-d_6) δ 6.75 (s br, 1H), 6.13 (s br, 1H), 5.68-5.61 (m, 2H), 2.44-2.38 (m, 1H), 2.23-2.17 (m, 1H), 2.14-2.00 (m, 3H) 1.96-1.91 (m, 1H) and 1.63-1.56 (m, 1H) ppm; ^{13}C NMR (200 MHz, 800 MHz, acetone-d_6) δ 178.1, 127.2, 126.6, 41.1, 28.9, 26.7 and 25.5 ppm; IR (KBr disk) ν = 3352, 3177, 3029, 2923, 1661, 1625, 1423 cm^{-1}; MS (70 eV, EI): *m/z* (%): 125 (100)

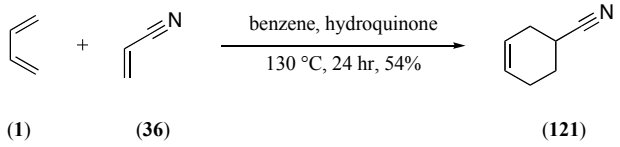
$[M]^+$, 105 (100), 108 (20), 96 (28), 81 (99) 67 (60); HRMS calc for $C_7H_{11}NO$ $[M]^+$: 125.0841; found: 125.0841.



Scheme 5.16 *Diels-Alder reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with acrylamide (**61**).*

Hydroquinone (2 mg, 0.02 mmol), acrylamide (**61**) (64 mg, 0.9 mmol) and a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in benzene (1.0 mL, 1.0 M, 1.0 mmol) were sealed into a glass ampoule and heated to 145° C for 20 h. The ampoule was cooled and opened and the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography eluting with diethyl ether:ethyl acetate (20:1) to give a mixture of the Diels-Alder adducts (**120n**) and (**120x**) (*endo:exo* 46:54) as a pale yellow solid (10 mg, 0.081 mmol, 9%): R_f 0.2 diethyl ether:ethyl acetate (20:1) ^{1}H NMR (800 MHz, acetone-d_6) δ 6.75 (s br, 1.00 H), 6.13 (s br, 1.00 H), 5.68-5.61 (m, 2.00 H), 2.44-2.38 (m, 1.00 H), 2.23-2.17 (m, 0.54 H), 2.14-2.00 (m, 1.58 H) 1.96-1.91 (m, 1.01 H) and 1.63-1.56 (m, 1.00 H) ppm; IR (KBr disk) ν = 3352, 3179, 3031, 2923, 2162 (C-D), 2137 (C-D), 1658, 1633, 147 cm^{-1}; MS (70 eV, EI): *m/z* (%): 127 (80) $[M]^+$, 111 (16), 97 (25), 83 (100) 69 (92); HRMS calc for $C_7H_9D_2NO$ $[M]^+$: 127.0966; found: 127.0965.

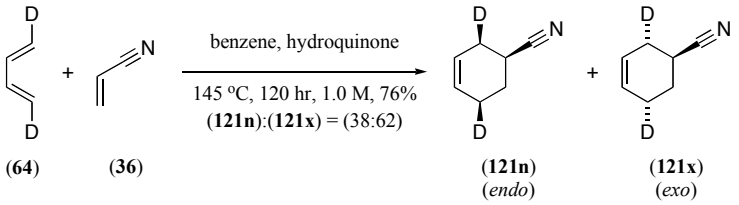
*5.2.2.8 ±Cyclohex-3-enecarbonitrile (**121**)*



Scheme 5.17 *Diels-Alder reaction of 1,3-butadiene (**1**) with acrylonitrile (**36**).*

This compound was prepared according to the modified procedure of Petrov and Sopov.[120] A solution of acrylonitrile (**36**) (265 mg, 5.0 mmol) and hydroquinone (3 mg, 0.027 mmol) in benzene (10 mL) was stirred under an atmosphere of 1,3-butadiene (**1**) in a screw cap tube fitted with a rubber septum for 10 mins at room temperature. Excess 1,3-butadiene (**1**) dissolved into the solution. The tube was then sealed and

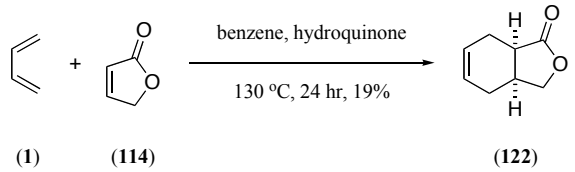
placed in a preheated oil bath with stirring at 130 °C for 24 h. The tube was then removed from the oil bath, cooled and opened, and its contents were concentrated under vacuum. The crude material was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (40:1) to give the title compound (**121**) as a colourless oil (290 mg, 2.71 mmol, 54%): R_f 0.2 40-60 petrol:ethyl acetate (40:1); ^{1}H NMR (800 MHz, $CDCl_3$) δ 5.75 (1H, dddd, *J* = 10.2, 5.7, 2.1, 2.1 Hz), 5.65-5.62 (m, 1H), 2.83-2.80 (m, 1H), 2.41-2.37 (m, 1H), 2.34-2.29 (m, 1H), 2.27-2.21 (m, 1H), 2.13-2.07 (m, 1H), 1.95 (1H, ddddd, *J* = 13.3, 5.8, 5.8, 3.1, 0.8 Hz) and 1.91-1.86 (m, 1H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 127.2, 123.4, 122.6, 28.3, 25.5, 24.4, and 23.1 ppm; IR (thin film) ν = 3032, 2931, 2845, 2239, 1653, 1438 cm^{-1}; MS (70 eV, EI): *m/z* (%): 107 (43) $[M]^+$, 92 (20), 80 (46), 67 (25), 54 (100); HRMS calc for C_7H_9N $[M]^+$: 107.0735; found: 107.0738.



Scheme 5.18 *Diels-Alder reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with acrylonitrile (**36**).*

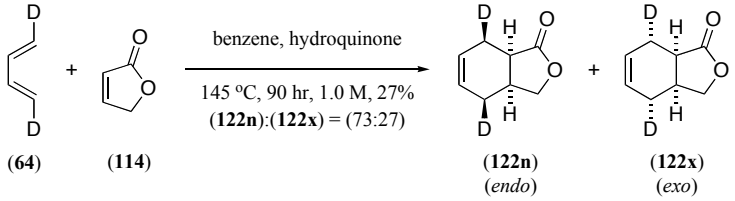
Hydroquinone (2 mg, 0.02 mmol), acrylonitrile (**36**) (53 mg, 1.0 mmol) and a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in benzene (1.0 mL, 1.0 M, 1.0 mmol) were sealed into a glass ampoule and heated to 145° C for 120 h. The ampoule was cooled and opened and the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (40:1) to give a mixture of the Diels-Alder adducts (**121n**) and (**121x**) (*endo:exo* 38:62) as a colourless oil (83 mg, 0.76 mmol, 76%): R_f 0.2 40-60 petrol:ethyl acetate (40:1); ^{1}H NMR (800 MHz, $CDCl_3$) δ 5.75 (1.00 H, dddd, *J* = 10.2, 5.7, 2.1, 2.1 Hz), 5.65-5.62 (m, 1.01 H), 2.83-2.80 (m, 0.99 H), 2.41-2.37 (m, 0.44 H), 2.34-2.29 (m, 0.65 H), 2.27-2.21 (m, 0.65 H), 2.13-2.07 (m, 0.45 H), 1.95 (1.01 H, ddddd, *J* = 13.3, 5.8, 5.8, 3.1, 0.8 Hz) and 1.91-1.86 (m, 1.00 H) ppm; IR (thin film) ν = 3032, 2931, 2872, 2238, 1653, 2164 (C-D), 2133(C-D), 1650, 1452 cm^{-1}; MS (70 eV, EI): *m/z* (%): 109 (100) $[M]^+$, 93 (26), 82 (68), 68 (32), 56 (78); HRMS calc for $C_7H_7D_2N$ $[M]^+$: 109.0861; found: 109.0864.

*5.2.2.9 ±3a,4,7,7a-Tetrahydroisobenzofuran-1(3H)-one (**122**)*



Scheme 5.19 *Diels-Alder reaction of 1,3-butadiene (**1**) with furan-2(5H)-one (**114**).*

This compound was prepared according to the modified procedure of Ortuno and Corbera.[123] A solution of furan-2(5*H*)-one (**114**) (474 mg, 5.64 mmol) and hydroquinone (3 mg, 0.027 mmol) in benzene (10 mL) was stirred under an atmosphere of 1,3-butadiene (**1**) in a screw cap tube fitted with a rubber septum for 10 mins at RT. Excess 1,3-butadiene (**1**) dissolved into the solution. The tube was then sealed and placed in a preheated oil bath with stirring at 130 °C for 24 h. The tube was then removed from the oil bath, cooled and opened, and its contents were concentrated under vacuum. The crude material was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (20:1) to give the title compound (**122**) as a colourless oil (150 mg, 1.09 mmol, 19%): R_f 0.2 40-60 petrol:ethyl acetate (20:1); ^{1}H NMR (800 MHz, $CDCl_3$) δ 5.77-5.71 (m, 2H), 4.31 (1H, dd, *J* = 8.5, 5.0 Hz), 4.02 (1H, dd, *J* = 9.2, 2.3 Hz), 2.80-2.75 (m, 1H), 2.65-2.60 (m, 1H), 2.53-2.48 (m, 1H), 2.42-2.36 (m, 1H), 2.30-2.24 (m, 1H) and 1.94-1.88 (m, 1H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 179.2, 125.3, 125.0, 72.9, 37.4, 32.2, 24.9 and 22.2 ppm; IR (thin film) ν = 3031, 2971, 2905, 2843, 1773, 1659, 1480, 1436, 1372 cm^{-1}; MS (70 eV, EI): *m/z* (%): 138 (88) $[M]^+$, 97 (69), 93 (100), 79 (89), 77 (73); HRMS calc for $C_8H_{10}O_2$ $[M]^+$: 138.0681; found: 138.0681.

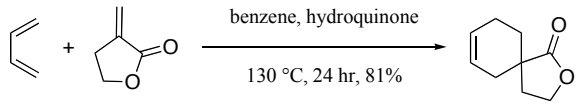


Scheme 5.20 *Diels-Alder reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with furan-2(5H)-one (**114**).*

Hydroquinone (2 mg, 0.02 mmol), furan-2(5*H*)-one (**114**) (84 mg, 1.0 mmol) and a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in benzene (1.0 mL, 1.0 M, 1.0

mmol) were sealed into a glass ampoule and heated to 145° C for 90 h. The ampoule was cooled and opened and the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (20:1) to give a mixture of the Diels-Alder adducts (**122n**) and (**122x**) (*endo:exo* 73:27) as a colourless oil (38 mg, 0.27 mmol, 27%): R_f 0.2 40-60 petrol:ethyl acetate (20:1); ^{1}H NMR (800 MHz, $CDCl_3$) δ 5.77-5.71 (m, 2.00 H), 4.31 (1.00 H, dd, *J* = 8.5, 5.0 Hz), 4.02 (1.00 H, dd, *J* = 9.2, 2.3 Hz), 2.80-2.75 (m, 1.00 H), 2.65-2.60 (m, 1.00 H), 2.53-2.48 (m, 0.36 H), 2.42-2.36 (m, 0.75 H), 2.30-2.24 (m, 0.75 H) and 1.94-1.88 (m, 0.35 H) ppm; IR (thin film) ν = 3031, 2972, 2904, 2132, 2115, 1771, 1479, 1434, 1373 cm^{-1}; MS (70 eV, EI): *m/z* (%): 140 (78) $[M]^+$, 98 (63), 94 (85), 81 (100), 78 (82); HRMS calc for $C_8H_8D_2O_2$ $[M]^+$: 140.0807; found: 140.0806.

*5.2.2.10 ±2-Oxa-spiro[4.5]dec-6-en-1-one (**123**)*

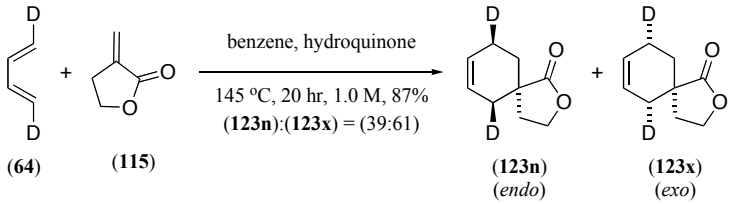


(**1**) (**115**) (**123**)

Scheme 5.21 *Diels-Alder reaction of 1,3-butadiene (**1**) with dienophile (**115**).*

This compound was prepared according to the modified procedure of Kwan and coworkers.[124] Hydroquinone (2 mg, 0.018 mmol) was placed in a 2 mL glass ampoule and the neck of the ampoule was fitted with a rubber septum. Dihydro-3-methylenefuran-2(3*H*)-one (**115**) (90 mg, 1.06 mmol) and a solution of 1,3-butadiene (**1**) (55 mg, 1.02 mmol) in benzene (1 mL) were added by syringe and the ampoule was sealed and placed in a preheated oil bath at 130 °C for 24 h. The ampoule was then removed from the oil bath, cooled and opened, and its contents were concentrated under vacuum. The crude material was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (20:1) to give the title compound (**123**) as a white solid (123 mg, 0.81 mmol, 81%): R_f 0.2 40-60 petrol:ethyl acetate (20:1); mp 60-62 °C; ^{1}H NMR (800 MHz, toluene-d_8) δ 5.59-5.45 (m, 1H), 5.41-5.37 (m, 1H), 3.59-3.51 (m, 2H), 2.41 (1H, d, *J* = 17.9 Hz), 1.81 (1H, d, *J* = 17.9 Hz), 1.70 (1H, ddd, *J* = 11.7, 11.7, 4.6 Hz), 1.64-1.58 (m, 1H), 1.50 (1H, d, *J* = 17.4 Hz), 1.37-1.32 (m, 2H) and 1.19 (1H, dd, *J* = 12.9, 4.6 Hz) ppm; ^{13}C NMR (200 MHz, toluene-d_8) δ 180.2, 126.3, 124.2, 64.2, 40.8, 32.8, 32.2, 28.3 and 22.0 ppm; IR (thin film) ν = 2986, 2936, 2842, 1772, 1439 cm^{-1};

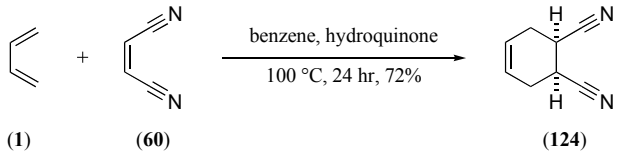
MS (70 eV, EI): *m/z* (%): 152 (42) $[M]^+$, 123 (23), 93 (35), 79 (100), 54 (34); HRMS calc for $C_9H_{12}O_2$ $[M]^+$: 152.0837; found: 152.0837.



Scheme 5.22 *Diels-Alder reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with dienophile (**115**).*

Hydroquinone (2 mg, 0.02 mmol), dihydro-3-methylenefuran-2(3*H*)-one (**115**) (98 mg, 1.0 mmol) and a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in benzene (1.0 mL, 1.0 M, 1.0 mmol) were sealed into a glass ampoule and heated to 145° C for 20 h. The ampoule was cooled and opened and the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (20:1) to give a mixture of the Diels-Alder adducts (**123n**) and (**123x**) (*endo:exo* 39:61) as a colourless oil (134 mg, 0.87 mmol, 87%): R_f 0.2 40-60 petrol:ethyl acetate (20:1); ^{1}H NMR (800 MHz, toluene-d_8) δ 5.59-5.45 (m, 0.99 H), 5.41-5.37 (m, 1.01 H), 3.59-3.51 (m, 2.00 H), 2.41 (0.64 H, d, J = 17.8 Hz), 1.81 (0.65 H, d, J = 17.9 Hz), 1.70 (1.00 H, ddd, J = 11.7, 11.7, 4.6 Hz), 1.64-1.58 (m, 0.47 H), 1.50 (0.46 H, d, J = 17.4 Hz), 1.37-1.32 (m, 2.01 H) and 1.19 (0.99 H, dd, J = 12.9, 4.9 Hz) ppm; IR (thin film) ν = 3028, 2917, 2895, 2152 (C-D), 2137 (C-D), 1770, 1645, 1486, 1445, 1372 cm^{-1}; MS (70 eV, EI): *m/z* (%): 154 (56) $[M]^+$, 126 (31) 95 (34), 81 (100), 56 (30); HRMS calc for $C_9H_{10}D_2O_2$ $[M]^+$: 154.0965; found: 154.0963.

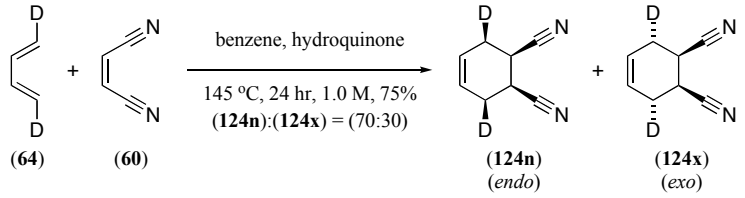
*5.2.2.11 Cyclohex-4-ene-1,2-dicarbonitrile (**124**)*



Scheme 5.23 *Diels-Alder reaction of 1,3-butadiene (**1**) with maleonitrile (**60**).*

This compound was prepared according to the modified procedure of Asastaseva and Vereshchagin.[125] Maleonitrile (**60**) (80.0 mg, 1.02 mmol) and hydroquinone (2 mg, 0.018 mmol) were placed in a 2 mL glass ampoule and the neck of the ampoule was fitted with a rubber septum. A solution of 1,3-butadiene (**1**) (60 mg, 1.10 mmol) in

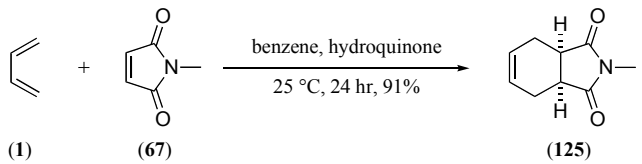
benzene (1 mL) was added by syringe and the ampoule was sealed and placed in a preheated oil bath at 100 °C for 24 h. The ampoule was then removed from the oil bath, cooled and opened, and its contents were concentrated under vacuum. The crude material was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (7:1) to give the title compound (**124**) as a colourless oil (97 mg, 0.72 mmol, 72%): R_f 0.1 40-60 petrol:ethyl acetate (7:1); ^{1}H NMR (800 MHz, C_6D_6/DMSO-d_6 49:1) δ 5.10-5.08 (m, 2H), 2.32-2.29 (m, 2H), 1.98-1.93 (m, 2H) and 1.65-1.60 (m, 2H) ppm; ^{13}C NMR (200 MHz, C_6D_6/DMSO-d_6 49:1) δ 123.5, 119.1, 27.3 and 26.3 ppm; IR (thin film) ν = 3068, 2932, 2853, 1657, 1438 cm^{-1}; MS (70 eV, EI): *m/z* (%): 132 (34) $[M]^+$, 105 (100), 79 (72), 66 (19), 54 (49); HRMS calc for $C_9H_{12}O_2$ $[M]^+$: 132.0687; found: 132.0690.



Scheme 5.24 *Diels-Alder reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with maleonitrile (**60**).*

Hydroquinone (2 mg, 0.02 mmol), maleonitrile (**60**) (78 mg, 1.0 mmol) and a solution of *(1E,3E)*-1,4-dideutero-1,3-butadiene (**64**) in benzene (1.0 mL, 1.0 M, 1.0 mmol) were sealed into a glass ampoule and heated to 100° C for 24 h. The ampoule was cooled and opened and the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (7:1) to give a mixture of the Diels-Alder adducts (**124n**) and (**124x**) (*endo:exo* 70:30) as a colourless oil (101 mg, 0.75 mmol, 75%): R_f 0.1 40-60 petrol:ethyl acetate (7:1); ^{1}H NMR (800 MHz, C_6D_6/DMSO-d_6 49:1) δ 5.10-5.08 (m, 2.00 H), 2.32-2.29 (m, 2.00 H), 1.98-1.93 (m, 0.78 H) and 1.65-1.60 (m, 1.54 H) ppm; IR (thin film) ν = 3067, 2941, 2245, 2183 (C-D), 2150 (C-D), 1650, 1512 cm^{-1}; MS (70 eV, EI): *m/z* (%): 134 (60) $[M]^+$, 107 (88), 80 (100), 67 (35), 56 (85); HRMS calc for $C_9H_{10}D_2O_2$ $[M]^+$: 134.0813; found: 134.0812.

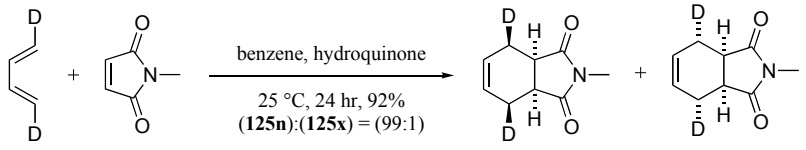
5.2.2.12 *(3aR,7aS)-3a,4,7,7a-Tetrahydro-2-methyl-2H-isoindole-1,3-dione (**125**)*



(**1**) (**67**) (**125**)

Scheme 5.25 *Diels-Alder reaction of 1,3-butadiene (**1**) with N-methyl maleimide (**67**).*

This compound was prepared according to the modified procedure of Rice.[126] *N*-methyl maleimide (**67**) (110.0 mg, 1.02 mmol) and hydroquinone (2 mg, 0.018 mmol) were placed in a 2 mL glass ampoule and the neck of the ampoule was fitted with a rubber septum. A solution of 1,3-butadiene (**1**) (60 mg, 1.10 mmol) in benzene (1 mL) was added by syringe and the ampoule was sealed and placed in a preheated oil bath at 25 °C for 24 h. The ampoule was then removed from the oil bath, cooled and opened, and its contents were concentrated under vacuum. The crude material was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (4:1) to give the title compound (**125**) as a white solid (152 mg, 0.92 mmol, 92%): R_f 0.3 40-60 petrol:ethyl acetate (4:1); mp 74-75 °C; ^{1}H NMR (800 MHz, $CDCl_3$) δ 5.82-5.80 (m, 2H), 3.04-3.02 (m, 2H), 2.87 (s, 3H), 2.54-2.50 (m, 2H) and 2.18-2.14 (m, 2H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 177.5, 130.7, 42.3, 33.3 and 24.3 ppm; IR (thin film) ν = 3442, 3041, 2952, 1764, 1693, 1442 cm^{-1}; MS (70 eV, EI): *m/z* (%): 165 (100) $[M]^+$, 136 (30), 110 (23), 80 (96), 51 (36); HRMS calc for $C_9H_{11}NO_2$ $[M]^+$: 165.0790; found: 165.0788.



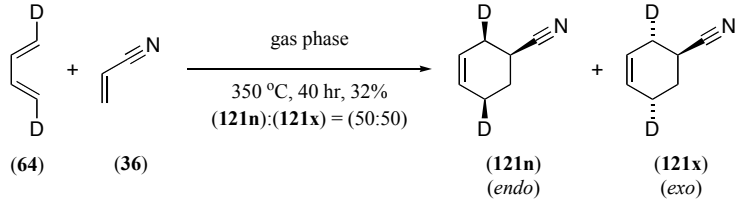
(**64**) (**67**) (**125n**) (*endo*) (**125x**) (*exo*)

Scheme 5.26 *Diels-Alder reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with N-methyl maleimide (**67**).*

Hydroquinone (2 mg, 0.02 mmol), *N*-methyl maleimide (**67**) (110 mg, 1.0 mmol) and a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in benzene (1.0 mL, 1.0 M, 1.0 mmol) were sealed into a glass ampoule and held at 25° C for 24 h. The ampoule was cooled and opened and the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography eluting with 40-60 petrol:ethyl

acetate (4:1) to give a mixture of the Diels-Alder adducts (**125n**) and (**125x**) (*endo:exo* 99:1) as a white solid (152 mg, 0.95 mmol, 95%): R_f 0.3 40-60 petrol:ethyl acetate (4:1); ^{1}H NMR (800 MHz, $CDCl_3$) δ 5.82-5.80 (m, 2.00 H), 3.04-3.02 (m, 2.00 H), 2.87 (s, 3H), 2.54-2.50 (m, 0.13 H) and 2.18-2.14 (m, 1.98 H) ppm; IR (thin film) ν = 3441, 3045, 2966, 2163 (C-D), 1750, 1699, 1442 cm^{-1}; MS (70 eV, EI): *m/z* (%): 167 (93) $[M]^+$, 138 (40), 111 (33), 82 (100), 56 (49); HRMS calc for $C_9H_9D_2NO_2$ $[M]^+$: 167.0915; found: 167.0914.

*5.2.2.13 Gas phase reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with acrylonitrile (**36**)*

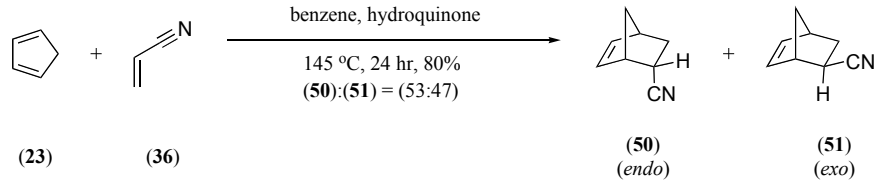


Scheme 5.27 *Diels-Alder reaction of (1E,3E)-1,4-dideutero-1,3-butadiene (**64**) with acrylonitrile (**36**).*

Acrylonitrile (**36**) (53 mg, 1.0 mmol) and a solution of (1*E*,3*E*)-1,4-dideutero-1,3-butadiene (**64**) in benzene (1.0 mL, 1.0 M, 1.0 mmol) were sealed into a 1 L glass vessel under vacuum, and heated to 350° C for 40 h. A visual check while the vessel was at 350 °C confirmed that the contents of the vessel had completely evaporated. The vessel was cooled and opened and the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (40:1) to give a mixture of the Diels-Alder adducts (**121n**) and (**121x**) (*endo:exo* 50:50) as a pale yellow oil (35 mg, 0.32 mmol, 32%): R_f 0.2 40-60 petrol:ethyl acetate (40:1); ^{1}H NMR (800 MHz, $CDCl_3$) δ 5.75 (1.00 H, dddd, *J* = 10.2, 5.7, 2.1, 2.1 Hz), 5.65-5.62 (m, 1.00 H), 2.83-2.80 (m, 1.01 H), 2.41-2.37 (m, 0.55 H), 2.34-2.29 (m, 0.56 H), 2.27-2.21 (m, 0.55 H), 2.13-2.07 (m, 0.55 H), 1.95 (1.01 H, ddddd, *J* = 13.3, 5.8, 5.8, 3.1, 0.8 Hz) and 1.91-1.86 (m, 1.00 H) ppm; IR (thin film) ν = 3032, 2931, 2872, 2238, 1653, 2164 (C-D), 2133(C-D), 1650, 1452 cm^{-1}; MS (70 eV, EI): *m/z* (%): 109 (100) $[M]^+$, 93 (26), 82 (68), 68 (32), 56 (78); HRMS calc for $C_7H_7D_2N$ $[M]^+$: 109.0861; found: 109.0864.

5.2.3 Diels-Alder reactions of cyclic dienophiles

*5.2.3.1 Diels-Alder reaction of cyclopentadiene (**23**) and acrylonitrile (**36**)*

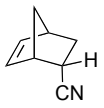


(**23**) (**36**) (**50**) (*endo*) (**51**) (*exo*)

Scheme 5.28 *Diels-Alder reaction of cyclopentadiene (**23**) with acrylonitrile (**36**).*

The reaction of cyclopentadiene (**23**) with acrylonitrile (**36**) was carried out using the modified procedure of Petrov and Sopov.[120] Hydroquinone (2 mg, 0.018 mmol) was placed in a 2 mL glass ampoule and a rubber septum was fitted to the neck of the ampoule. Benzene (1.0 mL), acrylonitrile (**36**) (56 mg, 1.06 mmol) and freshly cracked cyclopentadiene (**23**) (66 mg, 0.98 mmol) were added by syringe, and the ampoule was sealed and placed in a preheated oil bath at 145 °C for 24 h. The ampoule was then removed from the oil bath, cooled and opened, and its contents were concentrated under vacuum. The crude material was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (40:1) to give (93 mg, 0.78 mmol, 80%) of the two DA adducts (**50**) and (**51**), *endo* and *exo*, respectively, in a (53:47, *endo:exo*) ratio.

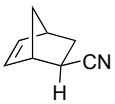
*5.2.3.2 ±Endo-bicyclo[2.2.1]hept-5-ene-2-carbonitrile (**50**)*



(**50**)
(*endo*)

Colourless oil: R_f 0.10 40-60 petrol:ethyl acetate (40:1); ^{1}H NMR (800 MHz, C_6D_6) δ 5.97-5.95 (m, 1H), 5.88-5.86 (m, 1H), 2.56-2.54 (m, 1H), 2.32-2.29 (m, 1H), 1.97 (1H, ddd, *J* = 9.8, 3.7, 3.5 Hz), 1.32 (1H, ddd, *J* = 11.8, 9.8, 3.5 Hz) 1.00 (1H, dd, *J* = 8.7, 1.6 Hz), 0.88 (1H, ddd, *J* = 11.8, 4.1, 2.4 Hz) and 0.40 (1H, d, *J* = 8.7 Hz) ppm; ^{13}C NMR (200 MHz, C_6D_6) δ 138.5, 132.9, 122.5, 48.3, 45.8, 42.5, 32.3, and 27.1 ppm; IR (thin film) ν = 3066, 2980, 2877, 2237, 1448, 1340 cm^{-1}; MS (70 eV, EI): *m/z* (%): 119 (73) $[M]^+$, 104 (77), 91 (100), 79 (91); HRMS calc for C_8H_9N $[M]^+$: 119.0735; found: 119.0735.

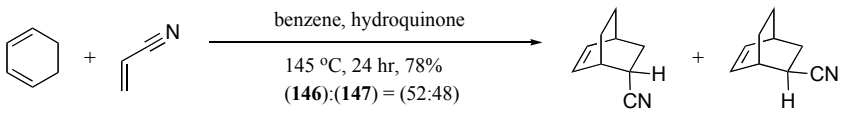
*5.2.3.3 ±Exo-bicyclo[2.2.1]hept-5-ene-2-carbonitrile (**51**)*



(**51**)
(*exo*)

Colourless oil: R_f 0.15 40-60 petrol:ethyl acetate (20:1); ^{1}H NMR (800 MHz, C_6D_6) δ 5.59 (1H, dd, *J* = 5.7, 3.2 Hz), 5.42 (1H, dd, *J* = 5.7, 3.2 Hz), 2.65-2.63 (m, 1H), 2.35-2.33 (m, 1H), 1.45 (1H, ddd, *J* = 11.4, 4.1, 4.0 Hz), 1.43 (1H, ddd, *J* = 9.1, 4.1, 2.6 Hz), 1.23 (1H, d, *J* = 9.1 Hz), 1.15-1.12 (m, 1H) and 0.84 (1H, ddd, *J* = 11.4, 8.5, 2.6 Hz) ppm; ^{13}C NMR (200 MHz, C_6D_6) δ 137.6, 134.1, 123.1, 47.5, 47.0, 41.9, 32.0 and 27.2 ppm; IR (thin film) ν = 3067, 2981, 2877, 2235, 1439, 1448, 1334 cm^{-1}; MS (70 eV, EI): *m/z* (%): 119 (4) $[M]^+$, 104 (4), 91 (5), 79 (5), 66 (100); HRMS calc for C_8H_9N $[M]^+$: 119.0735; found: 119.0736.

*5.2.3.4 Diels-Alder reaction of cyclohexadiene (**145**) with acrylonitrile (**36**)*

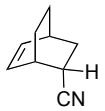


(**145**) (**36**) (**146**) (*endo*) (**147**) (*exo*)

Scheme 5.29 *Diels-Alder reaction of cyclohexadiene (**145**) with acrylonitrile (**36**).*

The reaction of cyclohexadiene (**145**) with acrylonitrile (**36**) was carried out using the modified procedure of Petrov and Sopov.[120] Hydroquinone (2 mg, 0.018 mmol) was placed in a 2 mL glass ampoule and a rubber septum was fitted to the neck of the ampoule. Benzene (1.0 mL), acrylonitrile (**36**) (53 mg, 1.00 mmol) and cyclohexadiene (**145**) (80 mg, 1.0 mmol) were added by syringe, and the ampoule was sealed and placed in a preheated oil bath at 145 °C for 24 h. The ampoule was then removed from the oil bath, cooled and opened, and its contents were concentrated under vacuum. The crude material was purified by flash column chromatography eluting with 40-60 petrol:ethyl acetate (40:1) to give (103 mg, 0.78 mmol, 78%) of the two Diels-Alder adducts (**146**) and (**147**), *endo* and *exo*, respectively, in a (52:48, *endo:exo*) ratio.

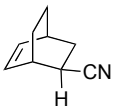
*5.2.3.5 ±Endo-bicyclo[2.2.2]oct-5-ene-2-carbonitrile (**146**)*



(**146**)
(*endo*)

White needles: R_f 0.1 40-60 petrol:ethyl acetate (40:1); mp 34-35 °C; ^{1}H NMR (800 MHz, acetone-d_6) δ 6.46 (1H, dd, *J* = 8.7, 6.2 Hz), 6.29 (1H, dd, *J* = 8.7, 6.2 Hz), 2.90 (1H, ddd, *J* = 9.8, 4.7, 2.3 Hz), 2.86-2.84 (m, 1H), 2.65-2.62 (m, 1H), 2.05-2.01 (m, 1H), 1.64-1.59 (m, 1H), 1.54-1.49 (m, 1H), 1.43-1.38 (m, 1H), 1.27 (1H, dddd, *J* = 16.2, 16.2, 3.8, 3.8 Hz) and 1.24-1.18 (m, 1H) ppm; ^{13}C NMR (200 MHz, acetone-d_6) δ 137.1, 131.9, 124.2, 33.5, 32.3, 29.5, 28.0, 24.9 and 24.2 ppm; IR (thin film) ν = 3052, 2949, 2871, 2236, 1649, 1453 cm^{-1}; MS (70 eV, EI): *m/z* (%): 133 (6) $[M]^+$, 105 (12), 80 (100), 65 (5), 51 (8); HRMS calc for C_7H_9N $[M]^+$: 133.0891; found: 133.0889.

*5.2.3.6 ±Exo-bicyclo[2.2.2]oct-5-ene-2-carbonitrile (**147**)*



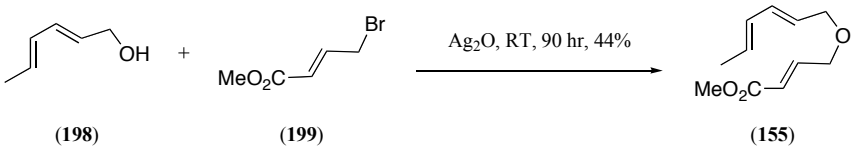
(**147**)
(*exo*)

Colourless oil: R_f 0.2 40-60 petrol:ethyl acetate (40:1); ^{1}H NMR (800 MHz, C_6D_6) δ 5.86 (1H, dd, *J* = 8.6, 6.3 Hz), δ 5.73 (1H, dd, *J* = 7.0, 6.3, 1.2 Hz), 2.20-2.18 (m, 1H), 1.98-1.95 (m, 1H), 1.95-1.90 (m, 1H), 1.74 (1H, dddd, *J* = 11.0, 5.0, 2.9, 2.6 Hz), 1.31 (1H, ddd, *J* = 12.8, 5.0, 2.3 Hz), 1.27-1.23 (m, 1H), 1.12-1.07 (m, 1H) and 0.96-0.92 (m, 2H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 134.9, 132.4, 122.6, 32.1, 30.5, 28.8, 24.9 and 21.0 ppm; IR (thin film) ν = 3050, 2945, 2872, 2233, 1616, 1454 cm^{-1}; MS (70 eV, EI): *m/z* (%): 133 (24) $[M]^+$, 105 (61), 104 (30), 80 (100), 65 (6); HRMS calc for $C_9H_{11}N$ $[M]^+$: 133.0891; found: 133.0894.

5.3 Experimental for Chapter 3

5.3.1 Synthesis of 1,3,8-nonatrienes (65) and (155)

*5.3.1.1 (2E)-Methyl 4-((2E,4E)-hexa-2,4-dienyloxy)but-2-enoate (**155**)*

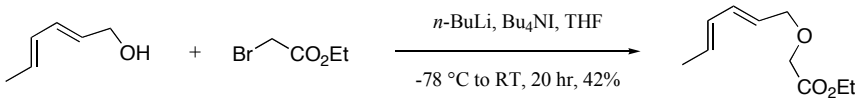


(**198**) (**199**) (**155**)

Scheme 5.30 *Synthesis of (2E)-methyl 4-((2E,4E)-hexa-2,4-dienyloxy)but-2-enoate (**155**).*

This compound was prepared by a modification of a literature procedure.[177,194] Silver (I) oxide (2.78 g, 12 mmol) was stirred under vacuum for 2 h before (*E*)-methyl 4-bromobut-2-enoate (**199**) (3.58 g, 20 mmol) and sorbyl alcohol (**198**) (6.87 g, 70 mmol) were added. The slurry was stirred under N_2 at room temperature for 90 h, diluted with CH_2Cl_2, filtered through celite and the volatile material was removed under vacuum. Flash column chromatography, eluting with 30-40 petrol/diethyl ether (4:1) gave the 1,3,8-nonatriene (**155**) as a colourless oil (1.71 g, 8.72 mmol, 44%).

*5.3.1.2 Ethyl 2-((2E,4E)-hexa-2,4-dienyloxy)acetate (**201**)*



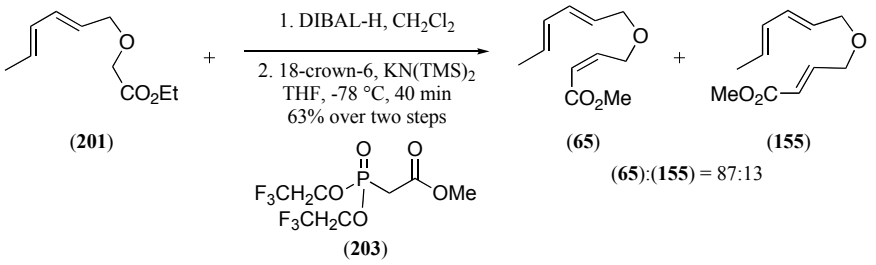
(**198**) (**200**) (**201**)

Scheme 5.31 *Synthesis of ethyl 2-((2E,4E)-hexa-2,4-dienyloxy)acetate (**201**).*

This compound was prepared by a modification of a literature procedure.[195] A 1.6 M solution of *n*-butyl lithium in hexanes (6.3 mL, 10 mmol) was added dropwise to a stirred solution of sorbyl alcohol (**198**) (0.98 g, 10 mmol) and tetrabutylammonium iodide (0.74 g, 2.0 mmol) in THF (40 mL) under N_2 at -78 °C. After 30 min, ethyl bromoacetate (**200**) (5.55 mL, 50 mmol) was added dropwise and the mixture was stirred for 4 h at -78 °C, then at room temperature for 16 h. The reaction mixture was partitioned between diethyl ether and water, the ethereal layer was washed three times with brine, dried over $MgSO_4$ and the volatile material was removed under vacuum. Flash column chromatography, eluting with 30-40 petrol/diethyl ether (9:1) gave the desired product (**200**) as a pale yellow oil (0.775 g, 4.21 mmol 42%): R_f = 0.50; 30-40

petrol/diethyl ether (9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (1H, dd, *J* = 14.1, 10.5 Hz), 6.04 (1H, ddq, *J* = 14.7, 10.5, 1.5 Hz), 5.70 (1H, dq, *J* = 14.7, 6.9 Hz), 5.59 (1H, dt, *J* = 14.7, 6.3 Hz), 4.19 (2H, q, *J* = 7.2 Hz), 4.08 (2H, d, *J* = 6.3 Hz), 4.03 (2H, s), 1.73 (3H, d, *J* = 6.9 Hz), 1.26 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 134.5, 130.8, 130.7, 125.5, 71.9, 67.0, 60.9, 18.2 and 14.3 ppm; IR (thin film) ν = 2983, 1754, 1659, 1446 cm^{-1}; MS (70 eV, EI): *m/z* (%): 184 (78) $[M]^+$, 97 (93), 88 (37), 81 (100); HRMS calc for $C_{10}H_{16}O_3$ $[M]^+$: 184.1099; found: 184.1095.

*5.3.1.3 (2Z)-Methyl 4-((2E,4E)-hexa-2,4-dienyloxy)but-2-enoate (**65**)*



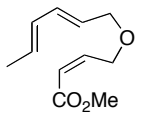
Scheme 5.32 *Synthesis of (2Z)-methyl 4-((2E,4E)-hexa-2,4-dienyloxy)but-2-enoate (**65**).*

This compound was prepared by a modification of one literature procedure,[195] and the direct application of another.[196] A 1.0 M solution of DIBALH in CH_2Cl_2 (2.2 mL, 2.2 mmol) was added dropwise to a stirred solution of ethyl 2-((2*E*,4*E*)-hexa-2,4-dienyloxy)acetate (**201**) (220 mg, 1.20 mmol) in CH_2Cl_2 (10 mL) under N_2 at -78 °C. After 90 min, methanol (100 μL, 2.42 mmol) was added and the mixture was stirred for a futher 20 min at -78 °C. The flask was removed from the cooling bath, sat. aq. $KHSO_4$ (2.5 mL), water (2.5 mL), and a crystal of BHT were added and the biphasic mixture was stirred for another 10 min. The reaction mixture was added to water and extracted with CH_2Cl_2. The extracts were combined and washed with brine until the washings were neutral, dried over $MgSO_4$ and carefully reduced in volume under gentle vacuum. The aldehyde (**202**) was used in the next step without further purification.

Following the procedure published by the Still group,[196] 18-crown-6 (1.80 g, 6.18 mmol), THF (10 mL) and bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl) phosphonate (**203**) (0.28 mL, 1.32 mmol) were mixed under N_2 at -78 °C. A 0.5 M solution of potassium bis(trimethylsilyl) amide in toluene (2.60 mL, 1.30 mmol) was added dropwise and 10 min later a solution of the crude aldehyde (**202**) in THF (10 mL) was added over 10 min. The reaction was quenched after 40 min with the addition of

sat. aq. NH_4Cl and the mixture was added to water and extracted with diethyl ether. The extracts were dried over $MgSO_4$ and the solvent was removed under vacuum. Flash column chromatography, eluting with 40-60 petrol/diethyl ether (9:1) gave the two olefination products (**65**) and (**155**) as colourless oils (0.147 g, 0.75 mmol 63%, (**65**):(**155**) = 87:13).

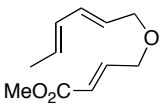
*5.3.1.4 (2Z)-Methyl 4-((2E,4E)-hexa-2,4-dienyloxy)but-2-enoate (**65**)*



(**65**)

Colourless oil; R_f = 0.46; 40-60 petrol/diethyl ether (9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (1H, dt, *J* = 11.7, 4.8 Hz), 6.22 (1H, dd, *J* = 15.0, 10.5 Hz), 6.06 (1H, ddq, *J* = 14.7, 11.1, 1.5 Hz), 5.82 (1H, dt, *J* = 11.7, 2.4 Hz), 5.80 – 5.56 (2H, m), 4.57 (2H, dd, *J* = 5.0, 2.3 Hz), 4.02 (2H, d, *J* = 6.0 Hz), 3.71 (3H, s) 1.75 (3H, d, *J* = 7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 148.9, 133.8, 130.9, 130.4, 126.3, 119.1, 71.3, 68.2, 51.5 and 18.2 ppm; IR (thin film) ν = 3021, 2952, 2851, 1721, 1655, 1438 cm^{-1}; MS (ES+): *m/z* (%): 219 (10) $[M+Na]^+$, 197(4) $[M+H]^+$; HRMS calc for $C_{10}H_{16}O_3$ $[M]^+$: 196.1099; found: 196.1102.

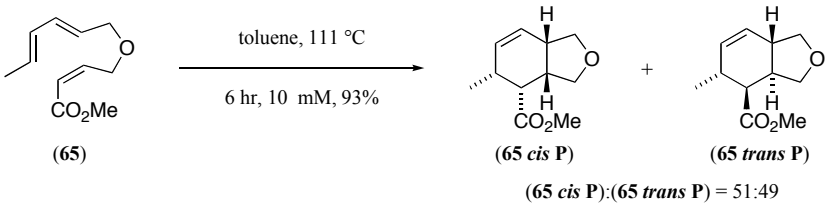
*5.3.1.5 (2E)-Methyl 4-((2E,4E)-hexa-2,4-dienyloxy)but-2-enoate (**155**)*



(**155**)

Colourless oil; R_f = 0.21; 40-60 petrol/diethyl ether (9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (1H, dtd, *J* = 15.6, 4.2, 0.9 Hz), 6.17 (1H, dd, *J* = 15.0, 10.5 Hz), 6.04 (1H, dtd, *J* = 15.6, 2.1, 0.9 Hz), 6.08 – 5.95 (1H, m), 5.68 (1H, dq, *J* = 15.0, 6.9 Hz), 5.56 (1H, dt, *J* = 15.3, 6.3 Hz), 4.08 (2H, dd, *J* = 4.2, 2.1 Hz), 3.98 (2H, d, *J* = 6.3 Hz), 3.69 (3H, s) 1.71 (3H, d, *J* = 6.6 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 144.8, 133.6, 130.7, 130.4, 125.9, 120.7, 71.1, 68.3, 51.6 and 18.1 ppm; IR (thin film) ν = 3020, 2951, 2850, 1725, 1663, 1436 cm^{-1}; MS (70 eV, EI): *m/z* (%): 196 (48) $[M]^+$, 161 (60), 136 (51), 97 (70), 55 (100); HRMS calc for $C_{10}H_{16}O_3$ $[M]^+$: 196.1099; found: 196.1098.

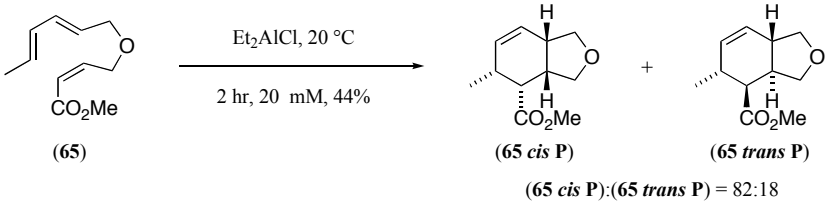
*5.3.1.6 Intramolecular Diels-Alder reactions of (2Z)-methyl 4-((2E,4E)-hexa-2,4-dienyloxy)but-2-enoate (**65**)*



Scheme 5.33 *Heat promoted intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**65**).*

A stirred solution of (2*Z*)-methyl 4-((2*E*,4*E*)-hexa-2,4-dienyloxy)but-2-enoate (**65**) (80 mg, 0.41 mmol) in toluene (40 mL) was heated to reflux (110 °C) under N_2 for 6 h. The solvent was removed under vacuum and the crude material was subjected to flash column chromatography, eluting with 30-40 petrol/diethyl ether (4:1) to give a mixture of cycloadducts (75 mg, 0.38 mmol, 93%, (**65** ***cis*** **P**):(**65** ***trans*** **P**) = 51:49. The diastereoisomeric IMDA adducts were separated by HPLC, eluting with 40-60 petrol/ethyl acetate (17:3).

*5.3.1.7 Diethylaluminium chloride (**171**) promoted intramolecular Diels-Alder reaction of (2Z)-methyl 4-((2E,4E)-hexa-2,4-dienyloxy)but-2-enoate (**65**)*



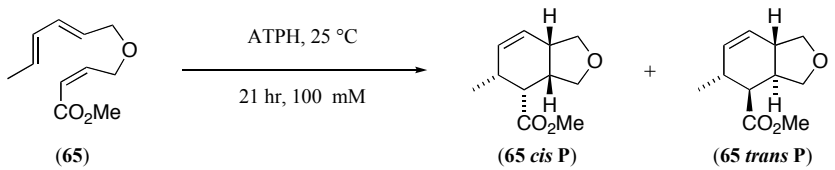
Scheme 5.34 *Diethylaluminium chloride (**171**) promoted intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**65**).*

A solution of (2*Z*)-methyl 4-((2*E*,4*E*)-hexa-2,4-dienyloxy)but-2-enoate (**65**) (24 mg, 0.122 mmol) in CH_2Cl_2 (6 mL) was treated with a 1.8 M solution of diethylaluminium chloride (**171**) in toluene (0.135 mL, 0.25 mmol) and the resulting mixture was stirred at 20 °C under N_2. After two hr the contents of the flask were partitioned between CH_2Cl_2 and dil. aq. $NaHCO_3$, the organic layer was washed three times with water and dried over $MgSO_4$, and the volatile material was removed under vacuum and the crude was subjected to flash column chromatography, eluting with 30-40 petrol/diethyl ether (4:1) to give a mixture of cycloadducts (11 mg, 0.054 mmol, 44%, (**65** ***cis*** **P**):(**65** ***trans***

P) = 82:18). The diastereoisomeric IMDA adducts were separated by HPLC, eluting with 40-60 petrol/ethyl acetate (17:3).

A variety of alternative conditions were investigated for this reaction including using from 0.95 to 2 equivalents of the Lewis acid, concentrations from 5 to 100 mM, temperatures from -25 °C to reflux in CH_2Cl_2, scales from 20 to 50 mg, and durations from 0.5 to 24 hr.

*5.3.1.8 ATPH (**49**) promoted intramolecular Diels-Alder reaction of (2Z)-methyl 4-((2E,4E)-hexa-2,4-dienyloxy)but-2-enoate (**65**)*



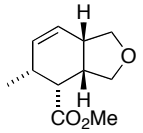
(**65**) (**65** ***cis*** **P**) (**65** ***trans*** **P**)

(**65** ***cis*** **P**):(**65** ***trans*** **P**) = 62:38

Scheme 5.35 *ATPH (**49**) promoted intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**65**).*

2,6-diphenylphenol (189 mg, 0.77 mmol) was stirred under vacuum for 1 h before being dissolved in CH_2Cl_2 (0.5 mL) under N_2. A 2 M solution of trimethylaluminium in toluene (0.128 mL, 0.26 mmol) was added and the solution was stirred at 25 °C for 45 min. A solution of (2*Z*)-methyl 4-((2*E*,4*E*)-hexa-2,4-dienyloxy)but-2-enoate (**65**) (25 mg, 0.13 mmol) in CH_2Cl_2 (0.75 mL) was slowly added. After 21 h at 25 °C, the contents of the flask were partitioned between CH_2Cl_2 and water and extracted twice with CH_2Cl_2. The extracts were combined and dried over $MgSO_4$ and the solvent was removed under vacuum. Flash column chromatography, eluting with 30-40 petrol/diethyl ether (4:1) gave a mixture of the two diastereomeric cycloadducts (18 mg, 0.95 mmol 73%, (**65** ***cis*** **P**):(**65** ***trans*** **P**) = 68:32). The IMDA adducts were separated by HPLC, eluting with 40-60 petrol/ethyl acetate (17:3).

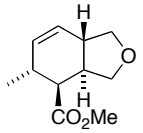
*5.3.1.9 ± (3aR,4S,5S,7aR)-Methyl 1,3,3a,4,5,7a-hexahydro-5-methylisobenzofuran-4-carboxylate (**65 cis P**)*



(**65 *cis* P**)

Colourless oil; t_R = 13.7 min, hexane-ethyl acetate (17:3); R_f = 0.51; 30-40 petrol/ethyl acetate (4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, ddd, *J* = 13.2, 4.8, 1.8 Hz), 5.57 (1H, dm, *J* = 10.2 Hz), 4.06 – 3.90 (2H, m), 3.81 (1H, dd, *J* = 8.4, 6.3 Hz), 3.70 (3H, s), 3.66 (1H, dd, *J* = 8.1, 2.1 Hz), 3.04 (1H, dd, *J* = 6.0, 4.2 Hz) 2.86 – 2.74 (2H, m), 2.74 – 2.58 (1H, m), 1.05 (3H, d, *J* = 7.5 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 132.3, 127.1, 73.2, 70.6, 51.6, 44.1, 39.4, 38.0, 30.2 and 18.1 ppm; IR (thin film) ν = 3015, 2953, 2878, 1734, 1658, 1435 cm^{-1}; MS (70 eV, EI): *m/z* (%): 196 (19) $[M]^+$, 166 (39), 136 (19), 107 (100), 91 (72); HRMS calc for $C_{10}H_{16}O_3$ $[M]^+$: 196.1099; found: 196.1099.

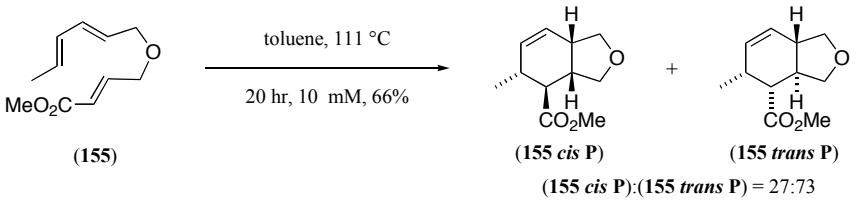
*5.3.1.10 ± (3aS,4R,5S,7aR)-Methyl 1,3,3a,4,5,7a-hexahydro-5-methylisobenzofuran-4-carboxylate (**65 trans P**)*



(**65 *trans* P**)

Colourless oil; t_R = 15.8 min, hexane-ethyl acetate (17:3); R_f = 0.51; 30-40 petrol/ethyl acetate (4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (1H, bd, *J* = 9.9 Hz), 5.62 (1H, dt, *J* = 9.9, 2.7 Hz), 4.06 (1H, t, *J* = 7.5 Hz), 3.96 (1H, t, *J* = 7.5 Hz), 3.66 (3H, s), 3.59 (1H, dd, *J* = 11.1, 7.5 Hz), 3.33 (1H, dd, *J* = 11.1, 7.2 Hz), 2.82 – 2.70 (1H, m), 2.71 (1H, d, *J* = 4.2 Hz), 2.58 – 2.43 (1H, m), 2.10 (1H, tdd, *J* = 11.4, 7.2, 4.2 Hz), 1.12 (3H, d, *J* = 7.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 133.4, 123.8, 70.7, 70.1, 51.6, 44.6, 40.9, 39.0, 33.4 and 21.8 ppm; IR (thin film) ν = 3021, 2956, 2872, 1734, 1636, 1436 cm^{-1}; MS (70 eV, EI): *m/z* (%): 196 (7) $[M]^+$, 166 (75), 119 (68), 107 (100), 91 (79); HRMS calc for $C_{10}H_{16}O_3$ $[M]^+$: 196.1099; found: 196.1099.

*5.3.1.11 Intramolecular Diels-Alder reactions of (2E)-methyl 4-((2E,4E)-hexa-2,4-dienyloxy)but-2-enoate (**155**)*



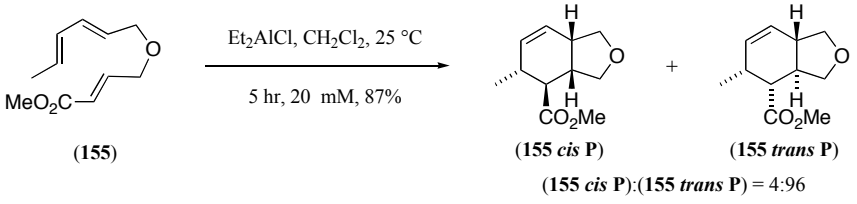
(**155**) (**155** ***cis*** **P**) (**155** ***trans*** **P**)

(**155** ***cis*** **P**):(**155** ***trans*** **P**) = 27:73

Scheme 5.36 *Heat promoted intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**155**).*

A stirred solution of (2*E*)-methyl 4-((2*E*,4*E*)-hexa-2,4-dienyloxy)but-2-enoate (**155**) (200 mg, 1.02 mmol) and a crystal of BHT in toluene (100 mL) was heated to reflux (110 °C) under N_2 for 20 h. The solvent was removed under vacuum and the crude material was subjected to flash column chromatography, eluting with 30-40 petrol/diethyl ether (4:1), affording the diastereomeric IMDA adducts (131 mg, 0.67 mmol 66%, (**155** ***cis*** **P**):(**155** ***trans*** **P**) = 27:73). The IMDA adducts were isolated in pure form by column chromatography.

*5.3.1.12 Diethylaluminium chloride (**171**) promoted intramolecular Diels-Alder reaction of (2E)-methyl 4-((2E,4E)-hexa-2,4-dienyloxy)but-2-enoate (**155**)*



(**155**) (**155** ***cis*** **P**) (**155** ***trans*** **P**)

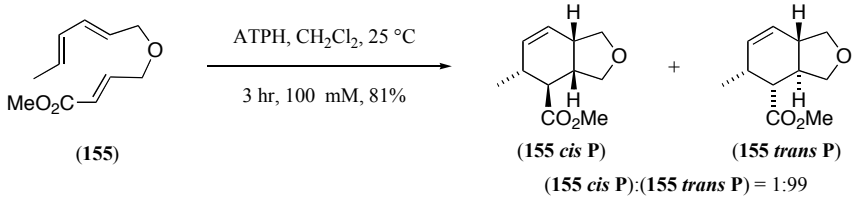
(**155** ***cis*** **P**):(**155** ***trans*** **P**) = 4:96

Scheme 5.37 *Diethylaluminium chloride (**171**) promoted intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**155**).*

A solution of (2*E*)-methyl 4-((2*E*,4*E*)-hexa-2,4-dienyloxy)but-2-enoate (**155**) (100 mg, 0.51 mmol) in CH_2Cl_2 (25 mL) was treated with a 1.8 M solution of diethylaluminium chloride (**171**) in toluene (0.57 mL, 1.02 mmol) and heated to reflux under N_2. After 5 h the contents of the flask were added to water and extracted twice with CH_2Cl_2. The extracts were combined and dried over $MgSO_4$, filtered through celite, and the volatile material was removed under vacuum, and the crude material was subjected to flash column chromatography, eluting with 30-40 petrol/diethyl ether (4:1), affording the

diastereomeric IMDA adducts (87 mg, 0.45 mmol 87%, (**155** ***cis*** **P**):(**155** ***trans*** **P**) = 4:96). The major diastereomer was isolated in pure form by column chromatography.

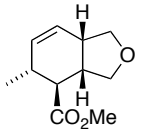
*5.3.1.13 ATPH (**49**) promoted intramolecular Diels-Alder reaction of (2E)-methyl 4-((2E,4E)-hexa-2,4-dienyloxy)but-2-enoate (**155**)*



Scheme 5.38 *ATPH (**49**) promoted intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**155**).*

2,6-diphenylphenol (189 mg, 0.77 mmol) was stirred under vacuum for 0.5 h and then dissolved in CH_2Cl_2 (0.5 mL) under N_2. A 2 M solution of trimethylaluminium in toluene (0.128 mL, 0.26 mmol) was added and the solution was stirred at 25 °C for 45 min. A solution of (2*E*)-methyl 4-((2*E*,4*E*)-hexa-2,4-dienyloxy)but-2-enoate (**155**) (25 mg, 0.13 mmol) in CH_2Cl_2 (0.75 mL) was slowly added. After 3 h at 25 °C, the contents of the flask were partitioned between CH_2Cl_2 and water, the organic layer was retained and dried over $MgSO_4$ and the volatile material was removed under vacuum. Flash column chromatography, eluting with 30-40 petrol/diethyl ether (4:1) afforded the diastereomeric IMDA adducts (22 mg, 0.11 mmol 81%, (**155** ***cis*** **P**):(**155** ***trans*** **P**) = 1:99). The major diastereomer was isolated in pure form by column chromatography.

*5.3.1.14 ± (3aR,4R,5S,7aR)-Methyl 1,3,3a,4,5,7a-hexahydro-5-methylisobenzofuran-4 carboxylate (**155 cis P**)*

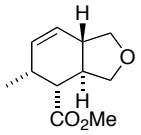


(**155** ***cis*** **P**)

Colourless oil; R_f = 0.29; 30-40 petrol/diethyl ether (4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (1H, dt, *J* = 9.9, 2.7 Hz), 5.57 (1H, dt, *J* = 9.9, 1.8 Hz), 4.01 (1H, t, *J* = 8.4 Hz), 3.89 (1H, dd, *J* = 9.0, 5.7 Hz), 3.71 (3H, s), 3.67 (1H, dd, *J* = 9.3, 2.1 Hz), 3.35 (1H, dd, *J* = 9.6, 8.1 Hz), 2.88 – 2.51 (1H, m), 2.64 – 2.48 (1H, m), 2.50 – 2.32 (1H, m), 2.09 (1H, dd, *J* = 12.0, 10.8 Hz), 1.00 (3H, d, *J* = 6.9 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$)

δ 176.0, 133.4, 124.4, 72.5, 72.4, 51.6, 49.4, 40.4, 39.3, 32.9 and 19.7 ppm; IR (thin film) ν = 3021, 2957, 2873, 1733, 1435 cm^{-1}; MS (70 eV, EI): *m/z* (%): 196 (7) $[M]^+$, 165 (26), 119 (51), 107 (100), 91 (94); HRMS calc for $C_{10}H_{16}O_3$ $[M]^+$: 196.1099; found: 196.1096.

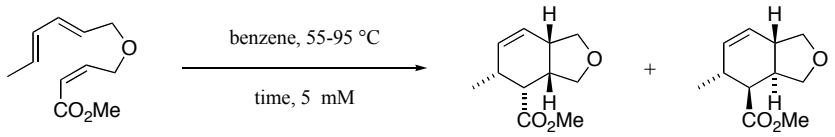
*5.3.1.15 ± (3aS,4S,5S,7aR)-Methyl 1,3,3a,4,5,7a-hexahydro-5-methylisobenzofuran-4-carboxylate (**155 trans P**)*



(**155 *trans* P**)

Colourless oil; R_f = 0.20; 30-40 petrol/diethyl ether (4:1); ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (1H, bd, *J* = 9.6 Hz), 5.61 (1H, dt, *J* = 9.9, 2.7 Hz), 4.27 (1H, t, *J* = 7.5 Hz), 4.04 (1H, t, *J* = 7.2 Hz), 3.69 (3H, s), 3.45 – 3.31 (2H, m), 2.92 – 2.76 (2H, m), 2.45 – 2.31 (1H, m), 2.13 (1H, qd, *J* = 11.1, 6.9 Hz), 0.94 (3H, d, *J* = 7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 134.1, 123.5, 70.6, 70.4, 51.6, 47.0, 44.6, 40.0, 33.4 and 17.4 ppm; IR (thin film) ν = 3022, 2950, 2853, 1737, 1635, 1436 cm^{-1}; MS (70 eV, EI): *m/z* (%): 196 (4) $[M]^+$, 165 (13), 149 (15), 119 (48), 107 (100), 91 (83); HRMS calc for $C_{10}H_{16}O_3$ $[M]^+$: 196.1099; found: 196.1096.

5.3.2 Rate study with (2Z)-methyl 4-((2E,4E)-hexa-2,4-dienyloxy)but-2-enoate (65)



(**65**) (**65 *cis* P**) (**65 *trans* P**)

(**65 *cis* P**):(**65 *trans* P**) = 51:49

Scheme 5.39 *Rate study of intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**65**).*

A solution of (2*Z*)-methyl 4-((2*E*,4*E*)-hexa-2,4-dienyloxy)but-2-enoate (**65**) (25 mg, 0.128 mmol), *t*-butyl benzene (5 mg, 0.037 mmol) and BHT (1 mg) in C_6D_6 (30 mL) was stirred under nitrogen for 30 mins. The solution was then sealed into 20 ampoules.

20 ampoules, prepared by the method described above, were placed in an ethylene glycol filled Lauda Ecoline 006 bath fitted with a Lauda E 300 thermostat and pump. The bath temperature was regulated to 55, 65, 75, 85 or 95 ±0.05 °C (328.15, 338.15,

348.15, 358.15 or 368.15 ±0.05 K). The ampoules were removed at regular intervals over two half-lives of reaction and cooled quickly by immersion in a CO_2/acetone bath. The ampoules were later brought to room temperature and opened, and the solutions they contained were filtered and transferred to NMR tubes. Quantitative 300 MHz ^{1}H NMR spectra were obtained and the consumption of the triene (**65**) and production of the cycloadducts, (**65 *cis* P**) and (**65 *trans* P**), were followed by the integrals of the resonances of the corresponding methyl groups relative to the resonance of the *t*-butyl group of the internal standard.

The following rate constants and stereoselectivities were obtained:

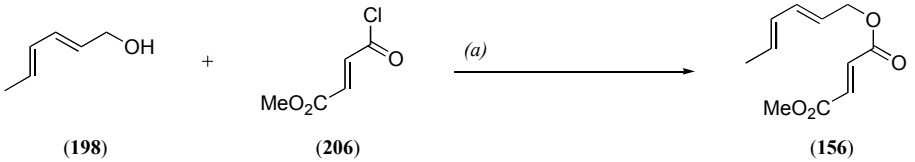
Entry	Temperature (°C), (K)		k_{ob}(sec^{-1})	(**65 *cis P***)/(**65 *trans* P**)	k(*cis*) (sec^{-1})	k(*trans*) (sec^{-1})
1	55	328.15	0.00122	0.935	0.000590	0.000631
2	65	338.15	0.00267	0.971	0.00132	0.00135
3	75	348.15	0.00565	1.020	0.00285	0.00279
4	85	358.15	0.01284	1.041	0.00654	0.00629
5	95	368.15	0.02659	1.075	0.0138	0.0128

Table 5.1 *Observed rate constants, stereoselectivities, and partitioned rate constants obtained from kinetics study with 1,3,8-nonatriene (**65**).*

The observed rate constants were partitioned using the stereoselectivity data into rate constants for the cycloadditions producing the *cis* fused and *trans* fused IMDA adducts (**65 *cis* P**) and (**65 *trans* P**). The partitioned rate constant data were used in the construction of Arrhenius plots from which the activation energies, E_a, and pre-exponential factors, A, of the cycloadditions giving the *cis* fused cycloadduct and the *trans* fused cycloadduct were calculated. The partitioned rate constant data were also used in the construction of Eyring plots, from which the enthalpies of activation $\Delta H^{\ddagger}$, entropies of activation $\Delta G^{\ddagger}$ and free energies of activation $\Delta G^{\ddagger}$ of the cycloadditions giving the *cis* fused cycloadduct (**65 *cis* P**) and the *trans* fused cycloadduct (**65 *trans* P**) were obtained.

5.3.3 Kinetic isotope effect study with (2E,4E)-hexadienyl methyl fumarate (156)

*5.3.3.1 Large scale synthesis of (2E,4E)-hexadienyl methyl fumarate (**156**)*

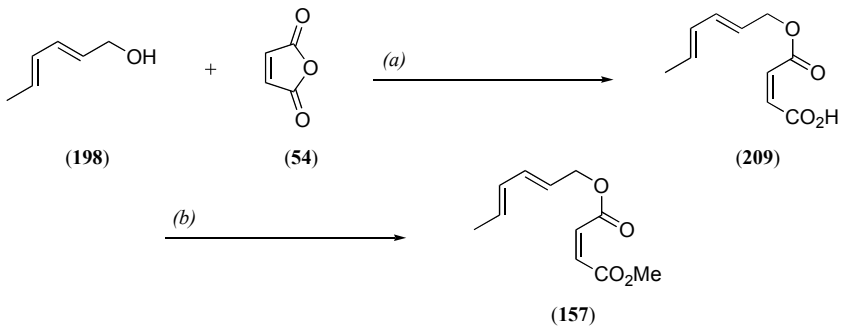


(**198**) (**206**) (**156**)

Scheme 5.40 *Efficient, large scale synthesis of 1,3,8-nonatriene (**156**) from methyl fumaroyl chloride (**206**) and sorbyl alcohol (**198**). Conditions: (a) Hunig's base (**207**), CH_2Cl_2, -78 to 0 °C, 1 hr, 87%.*

A solution of sorbyl alcohol (**198**) (8.4 g, 86 mmol) and diisopropylethylamine (**207**) (16.6 g, 129 mmol) in CH_2Cl_2 (300 mL) was cooled to -78 °C. Methyl fumaroyl chloride (**206**) (13.47g, 91 mmol) was added dropwise over 20 min and the mixture was stirred at -78 °C for a further 20 min and then allowed to warm to 0 °C over 20 min. Aqueous HCl (1.0 M, 100 mL, 100 mmol) was added and the biphasic mixture was stirred at 0 °C for 10 min before being transferred to a separating funnel. The mixture was then diluted with diethyl ether and shaken carefully, and the lower, aqueous layer was discarded. The organic layer was washed twice with aqueous HCl (1.0 M), three times with saturated aqueous Na_2CO_3, once with water, once with brine, and then dried over $MgSO_4$. Removal of the solvents under vacuum at RT gave the title compound (**156**) as a white solid (15.68 g, 75 mmol, 87%) which gave analytical data matching previously reported values.[92,257] This compound can be taken up in *n*-pentane (20 mL/g) and recrystallised by slowly cooling from RT to -50°C. The recovery after five cycles was approximately 80%. This compound can be stored as a solid at -20 °C.

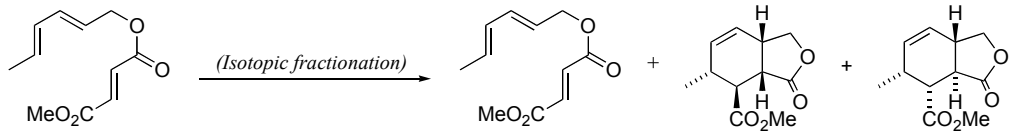
*5.3.3.2 Large scale synthesis of (2E,4E)-hexadienyl methyl maleate (**157**)*



Scheme 5.41 *Efficient synthesis of 1,3,8-nonatriene (**157**) from recrystallised sorbyl alcohol (**198**) and maleic anhydride (**54**). Conditions: (a) Hunig's base (**207**), CH_2Cl_2, 0 °C to RT, 1 hr (b) CH_3I (**210**), Hunig's base (**207**), DMF, RT, 2 hr, 86% over two steps.*

A solution of sorbyl alcohol (**198**) (9.99 g, 102 mmol) and diisopropylethylamine (**207**) (22.26g, 172 mmol) in CH_2Cl_2 (200 mL) was cooled to 0 °C. Maleic anhydride (**54**) (10.8 g 110 mmol) was added and the mixture was allowed to warm to RT over 1 hr. The reaction mixture was transferred to a separating funnel, diluted with diethyl ether, and washed four times with HCl (1.0 M) and once with a small quantity of water (10 mL). The organic layer was then dried over $MgSO_4$ and the solvents were quickly removed under vacuum at RT. The residue was taken up in DMF (40 mL) and cooled to 0 °C, and diisopropylethylamine (**207**) (14.22 g, 110 mmol) was carefully added. Methyl iodide (**210**) (28.39 g, 200 mmol) was added and the mixture was stirred at RT for 2 hr. The excess methyl iodide was removed under hard vacuum at RT. The reaction mixture was added to aqueous HCl (1.0 M, 200 mL), and the aqueous phase was washed four times with diethyl ether. The organic layers were pooled and washed four times with aqueous HCl (1.0 M) and twice with saturated aqueous $NaHCO_3$. The organic phase was then dried over $MgSO_4$ and the solvent was removed under vacuum at RT. The crude material was purified by flash column chromatography eluting with a gradient (30-40 petrol to 1% diethyl ether in 30-40 petrol) to give the title compound (**157**) as a colourless oil (18.47 g, 88 mmol, 86% over two steps) which gave analytical data matching previously reported values.[92,257] This compound can be taken up in *n*-pentane (50 mL/g) and recrystallised by slowly cooling from 0 °C to -78°C. The recovery after three cycles was approximately 80%. This compound is best stored as a dilute solution in CH_2Cl_2 at -20 °C.

*5.3.4 Natural abundance kinetic isotope effect determination with (2E,4E)-hexadienyl methyl fumarate (**156**)*



(**156**) (**156**) (**156 *cis* P**) (**156 *trans* P**)

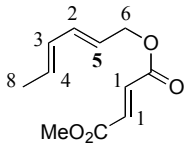
isotopically enriched

Scheme 5.42 *Large scale isotopic fractionation event with 1,3,8-nonatriene (**156**).*

A solution of BHT (220 mg 1.0 mmol) in chlorobenzene (5.4 L) was heated to reflux (130 °C) in a 10 L round bottom flask fitted with an overhead stirrer. A solution of >99.95% pure (2*E,*4*E*)-hexadienyl methyl fumarate (**156**) (10.1938, 48.5 mmol) and benzophenone (**213**) (1.9358 g, 10.6 mmol) in chlorobenzene (100 mL) was stirred under nitrogen for 30 min, before being poured into the 10 L round bottom flask. 400 minutes later, coiled glass tube containing a stream of cold water was immersed in the contents of the flask, causing the internal temperature to drop below 50 °C in approximately 5 min. The degree of completion of the reaction was then determined with high precision by a calibrated normal phase HPLC method using benzophenone as an internal standard. The degree of completion observed was 0.9614.

The solvent was removed at RT under vacuum, leaving a mixture of cycloadducts containing small quantities of benzophenone and the 1,3,8-nonatriene. The unreacted 1,3,8-nonatriene was purified by two iterations of column chromatography eluting with hexane:ethyl acetate (20:1), giving 382 mg of the triene, a recovery of 97%.

The recovered triene and a sample of the starting material for the isotopic fractionation reaction were taken up in $CHCl_3$ and transferred to NMR tubes. The quantitative 123 MHz ^2H NMR spectra of the two samples were integrated through a curve fitting programme in the Bruker software, based on a Lorentzian lineshape. This gave NMR data suitable for the calculation of the ^2H KIEs and their associated uncertainties.



(**xx**)

Entry	Frequency	R_0 integral	R_{final} integral	R/R_0	F
1	6.86	350.323	358.380	1.0230	0.9614
2	6.29	222.654	223.389	1.0033	0.9614
3	6.07	247.850	220.884	0.8912	0.9614
4	5.78	271.593	235.091	0.8656	0.9614
5	**5.64**	**269.532**	**205.275**	**0.7616**	**0.9614**
6	4.69	334.855	341.318	1.0193	0.9614
7	3.80	526.953	526.953	1.0000	0.9614
8	1.77	586.403	559.722	0.9545	0.9614

Table 5.2 *^{2}H NMR shifts and integrals for samples of 1,3,8-nonatriene (**156**), before and after a large scale isotopic fractionation event.*

Using the data from entry 5, the KIE can be calculated in the following way:[94]

$$KIE_{calc} = \frac{\ln(1-F)}{\ln[(1-F)R/R_0]}$$

$$KIE_{calc} = \frac{\ln(0.0386)}{\ln[(0.0386)0.7616]}$$

$$KIE_{calc} = 0.92$$

Using conservative estimates of the uncertainties in the degree of completion, ΔF, and the ^{2}H NMR data, $\Delta R/R_0$, the uncertainty in the observed KIE for entry 5 can be calculated in the following way:[94]

$$\Delta KIE = \left[\frac{-\ln(R/R_0)}{(1-F)\ln^2[(1-F)R/R_0]}\Delta F\right] + \left[\frac{-\ln(1-F)}{(R/R_0)\ln^2[(1-F)R/R_0]}\Delta R/R_0\right]$$

$$\Delta KIE = \left[\frac{-\ln(0.7616)}{(0.0386)\ln^2[(0.0386)0.7616]} \times 0.001\right] + \left[\frac{-\ln(0.0386)}{(0.7616)\ln^2[(0.0386)0.7616]} \times 0.02\right]$$

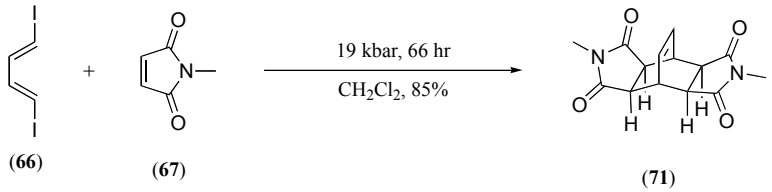
$$\Delta KIE = 0.0009 + 0.0069 \approx 0.01$$

The experimental KIEs and their uncertainties for the other positions in triene (**156**) were calculated using the above equations.

5.4 Experimental for Chapter 4

5.4.1 Domino Diels-Alder reactions of (1E,3E)-diiodo-1,3-butadiene (66)

*5.4.1.1 Bicyclo[2.2.2]oct-2-ene (**71**)*

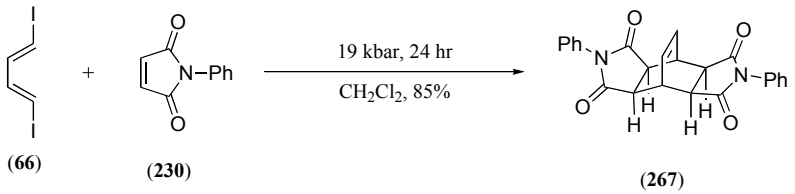


(**66**) (**67**) (**71**)

Scheme 5.43 *Synthesis of bicyclo[2.2.2]oct-2-ene (**71**).*

A plastic high pressure reaction vessel was loaded with (1*E*,3*E*)-1,4-diodo-1,3-butadiene (**66**) (300 mg, 0.98 mmol), N-methyl maleimide (**67**) (550 mg, 4.95 mmol) and CH_2Cl_2 (2.0 mL). The vessel was held at 19 kbar in a high pressure reactor at RT for 66 hr. The contents of the vessel were then transferred to a separating funnel and shaken with saturated aqueous $Na_2S_2O_5$, diluted with diethyl ether, washed twice with water and once with brine. The organic phase was dried over $MgSO_4$ and the solvent was removed under vacuum. Flash column chromatography, with gradient elution (CH_2Cl_2:MeOH, 50:1 to 20:1) gave the title compound as white plates from $CHCl_3$/acetone (228 mg, 0.83 mmol, 85%): mp >300 °C, R_f 0.1 CH_2Cl_2:MeOH (50:1); 0.5 CH_2Cl_2:MeOH (20:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.02 (2H, dd, J = 3.3, 2.4 Hz), 3.38-3.30 (m, 2H), 3.17 (s, br, 4H), 2.72 (s, 6H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.5, 130.7, 42.3, 33.3, and 24.1 ppm; IR (KBr disk) ν = 3435, 3062, 2975, 2951, 1766, 1702, 1437, 1380, 1319, 1284 cm^{-1}; MS (70 eV, EI): *m/z* (%): 274 (83) $[M]^+$, 163 (80), 104 (38), 78 (100), 51 (30); HRMS calc for $C_{14}H_{14}N_2O_4$ $[M]^+$: 274.0954; found: 274.0955.

*5.4.1.2 Bicyclo[2.2.2]oct-2-ene (**267**)*

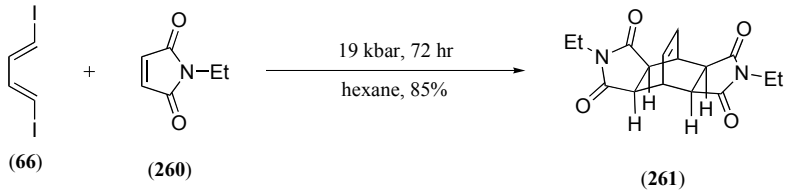


(**66**) (**230**) (**267**)

Scheme 5.44 *Synthesis of bicyclo[2.2.2]oct-2-ene (**267**).*

A plastic high pressure reaction vessel was loaded with (1*E*,3*E*)-1,4-diodo-1,3-butadiene (**66**) (300 mg, 0.98 mmol), N-phenyl maleimide (**230**) (860 mg, 4.96 mmol) and CH_2Cl_2 (2.0 mL). The vessel was held at 19 kbar in a high pressure reactor at RT for 24 hr. The contents of the vessel were then transferred to a separating funnel and shaken with saturated aqueous $Na_2S_2O_5$, diluted with diethyl ether, washed twice with water and once with brine. The organic phase was dried over $MgSO_4$ and the solvent was removed under vacuum. Flash column chromatography, eluting with CH_2Cl_2:MeOH (20:1) gave the title compound as off white needles from CH_2Cl_2 (330 mg, 0.83 mmol, 84%): mp >300 °C, R_f 0.15 CH_2Cl_2:MeOH (50:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.42 (m, 4H), 7.42-7.36 (m, 2H), 7.20-7.15 (m, 4H), 6.37 (2H, dd, *J* = 4.4, 3.2 Hz), 4.01-3.95 (m, 2H), 3.24-3.20 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 131.4, 129.3, 129.0, 126.4, 43.0 and 34.1 ppm; IR (KBr disk) ν = 3466, 3044, 2946, 1772, 1708, 1497, 1383, 1194 cm^{-1}; MS (70 eV, EI): *m/z* (%): 398 (100) $[M]^+$, 173 (62), 129 (14), 119 (58); HRMS calc for $C_{24}H_{18}N_2O_4$ $[M]^+$: 398.1267; found: 398.1267.

*5.4.1.3 Bicyclo[2.2.2]oct-2-ene (**261**)*



(**66**) (**260**) (**261**)

Scheme 5.45 *Synthesis of bicyclo[2.2.2]oct-2-ene (**261**).*

A plastic high pressure reaction vessel was loaded with (1*E*,3*E*)-1,4-diodo-1,3-butadiene (**66**) (300 mg, 0.98 mmol), N-ethyl maleimide (**260**) (620 mg, 4.95 mmol) and hexane (2.0 mL). The vessel was held at 19 kbar in a high pressure reactor at RT for 72 hr. The contents of the vessel were then transferred to a separating funnel and shaken with saturated aqueous $Na_2S_2O_5$, diluted with diethyl ether, washed twice with water and once with brine. The organic phase was dried over $MgSO_4$ and the solvent was removed under vacuum. Flash column chromatography, eluting with CH_2Cl_2:MeOH (50:1) gave the title compound as a white solid (250 mg, 0.83 mmol, 84%): mp >300 °C, R_f 0.2 CH_2Cl_2:MeOH (50:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (2H, dd, *J* = 4.8, 3.2 Hz), 3.80-3.76 (m, 2H), 3.47 (4H, q, *J* = 7.2 Hz), 2.96-2.94 (m, 4H), 2.72 (6H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 130.7, 42.3, 33.3,

and 24.1 ppm; IR (KBr disk) ν = 3435, 3062, 2975, 2951, 1766, 1702, 1437, 1380, 1319, 1284 cm^{-1}; MS (70 eV, EI): *m/z* (%): 302 (55) $[M]^+$, 177 (20), 149 (17), 78 (100); HRMS calc for $C_{16}H_{18}N_2O_4$ $[M]^+$: 302.1267; found: 302.1267.

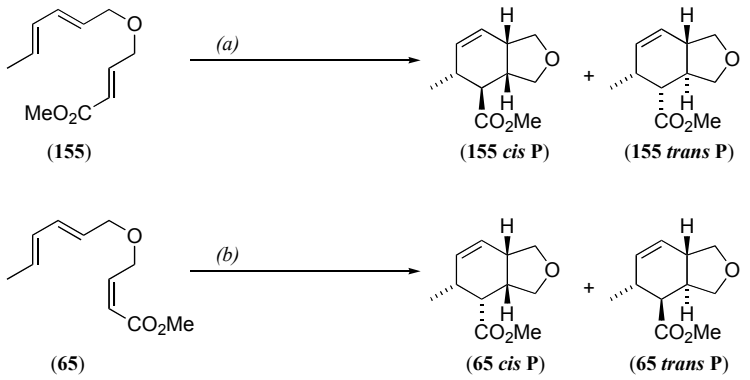
6 Appendix

6.1 Introduction

Included in this appendix are proofs of the structures of compounds (**155 *cis* P**), (**155 *trans* P**), (**155 *cis* P**) and (**155 *trans* P**) based on 800 MHz COSY, 600 MHz DQF-COSY and 800 MHz 1D nOe ^{1}H NMR spectra,[114] and B3LYP/6-31G(d) calculated ^{2}H KIEs for the heat promoted IMDA reactions of 1,3,8-nonatrienes (**278**), (**156**), (**157**) and (**158**) in chlorobenzene at 298.15 K.[178]

6.2 Stereochemistry of Intramolecular Diels-Alder Cycloadducts (155 *cis* P), (155 *trans* P), (65 *cis* P) and (65 *trans* P)

IMDA adducts (**155 *cis* P**), (**155 *trans* P**), (**155 *cis* P**) and (**155 *trans* P**) were obtained through heat or Lewis acid promoted IMDA reactions of 1,3,8-nonatrienes (**155**) and (**65**) (**Scheme 6.1**).



Scheme 6.1 *Heat promoted IMDA reactions of ether linked trienes (**155**) and (**65**). Conditions: (a) toluene, 10 mM in triene, BHT (1 mol. %) reflux, 20 hr, 66%, (**155 cis P**):(**155 trans P**) 27:73. (b) toluene, 10 mM in triene, BHT (1 mol. %), reflux, 6 hr, 93%, (**65 cis P**):(**65 trans P**) 51:49.*

6.2.1 Cycloadduct (155 cis P)

The atom connectivity of IMDA adduct (**155 *cis* P**) was confirmed from inspection of the 800 MHz ^{1}H COSY spectrum of the compound in $CDCl_3$ solution (**Figure 6.1**). The proton signals were assigned letters of the alphabet. The doublet corresponding to the methyl group at 1.0 ppm, H_l, is linked to the signals corresponding to the ring junction methine units, H_i and H_h, by three bond couplings; H_l couples to H_j, H_j couples

to H_k, H_k couples to H_i, and H_i couples to H_h. The signals corresponding to the methylene units adjacent to H_h and H_i, the alkene interposed between H_j and H_h, and the methyl ester, H_e, are well resolved and easily identified.

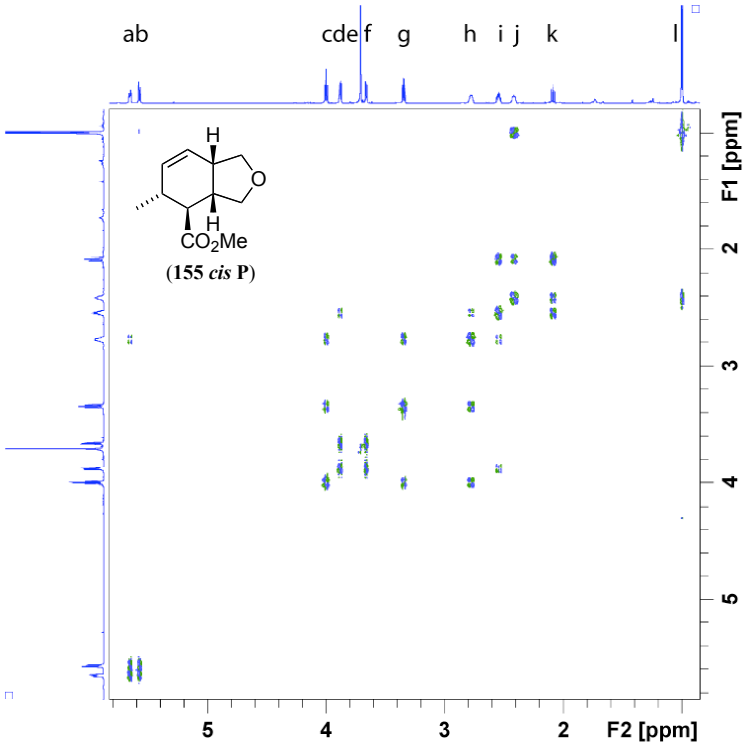


Figure 6.1 *800 MHz ^{1}H COSY spectrum of cycloadduct (**155 cis P**), obtained from intramolecular Diels-Alder reactions of 1,3,8-nonatriene (**155**).*

The connectivity of the compound is depicted in the left hand structure in (**Figure 6.2**). The coupling constant between the protons at the site of ring fusion, H_h and H_i, is 7.7 Hz, indicative of a *cis* fused ring junction. The stereochemical information missing from the left hand structure was obtained from coupling constant data and through one dimensional nOe experiments summarised in the right hand structure.

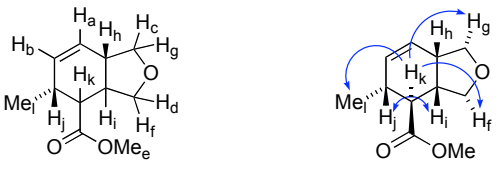


Figure 6.2 *Left: Connectivity of intramolecular Diels-Alder adduct (**155 cis P**) derived from inspection of the 800 MHz ^{1}H COSY spectrum of (**155 cis P**) in $CDCl_3$. Right: Nuclear Overhauser effect data obtained from one dimensional nOe experiments with cycloadduct (**155 cis P**) in $CDCl_3$.*

The three dimensional configuration of the molecule is clear from the coupling constant and nOe data. Strong nOes were observed between H_k and H_g, and H_k and H_f, indicating that the ring system is *cis* fused. These data, combined with effects observed between H_j and H_i, and H_k and H_l, prove that the configuration of the dienophile in (**155**) is conserved in the IMDA adduct (**155 *cis* P**).

6.2.2 Cycloadduct (155 trans P)

The connectivity of IMDA adduct (**155 *trans* P**) was obtained from inspection of the 800 MHz ^{1}H COSY spectrum of this compound in $CDCl_3$ solution (**Figure 6.3**). The doublet corresponding to the methyl group at 1.0 ppm, H_l, is linked to the signals corresponding to the ring junction methine units, H_j and H_k, by three bond couplings; H_l couples to H_h, H_h couples to H_i, H_i couples to H_k, and H_k couples to H_j. The signals corresponding to the methylene units adjacent to H_j and H_k, the alkene interposed between H_j and H_h, and the methyl ester, H_e, are well resolved and easily identified.

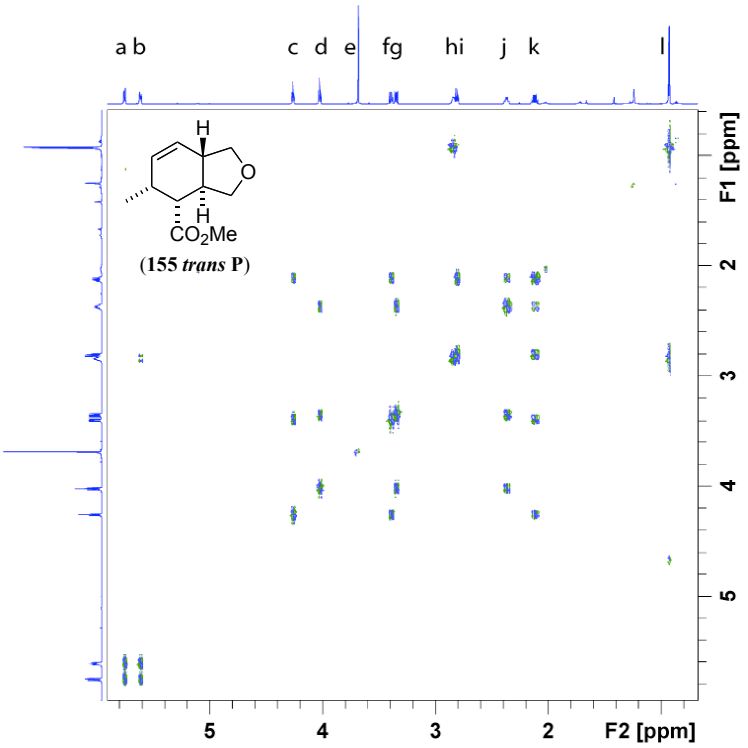


Figure 6.3 *800 MHz ^{1}H COSY spectrum of cycloadduct (**155 trans P**), obtained from intramolecular Diels-Alder reactions of triene (**155**).*

Signals in the 800 MHz ^{1}H COSY spectrum of IMDA adduct (**155 *trans* P**) were assigned letters of the alphabet, allowing the connectivity of the compound to be depicted in the left hand structure in (**Figure 6.4**). The coupling constant between the

protons at the site of ring fusion, H_j and H_k, was 12.5 Hz, indicative of a *trans* fused ring junction. The stereochemical information missing from the left hand structure was obtained from coupling constant data and through one dimensional nOe experiments summarised in the right hand structure.

(155 *trans* P) **(155 *trans* P)**

Figure 6.4 *Left: Connectivity of cycloadduct (**155 trans P**) derived from inspection of the 800 MHz ^1H COSY spectrum of (**155 trans P**) in $CDCl_3$. Right: Nuclear Overhauser effect data obtained from one dimensional nOe experiments with (**155 trans P**) in $CDCl_3$.*

The nOe data, and in particular the effect observed between H_k and H_l, confirm that the ring system in this IMDA adduct is *trans* fused. A strong effect was also observed between H_j and H_i, indicating that the configuration of the dienophile in (**155**) is conserved in the IMDA adduct (**155 *trans* P**).

6.2.3 Cycloadduct (65 cis P)

The adducts obtained from IMDA reactions of 1,3,8-nonatriene (**65 *cis* P**) were separated by HPLC and analysed by 800 MNz NMR. A number of solvents were screened for the NMR analysis of adduct (**65 *cis* P**). CD_3OD gave the best distribution of resonances and was employed in further NMR spectroscopy with this adduct. NMR analysis of adduct (**65 *trans* P**) was carried out using samples in $CDCl_3$ solution.

The connectivity of IMDA adduct (**65 *cis* P**) was obtained from inspection of the 800 MHz ^1H COSY spectrum of the compound in CD_3OD solution (**Figure 6.5**). The proton signals were assigned letters of the alphabet. The doublet corresponding to the methyl group at 1.0 ppm, H_k, is linked to the signals corresponding to the ring junction methine units, H_i and H_h, by three bond couplings; H_k couples to H_j, H_j couples to H_g, H_g couples to H_i, and H_i couples to H_h. The signals corresponding to the methylene units adjacent to H_h and H_i, the alkene interposed between H_j and H_h, and the methyl ester, H_e, are adequately resolved and easily identified.

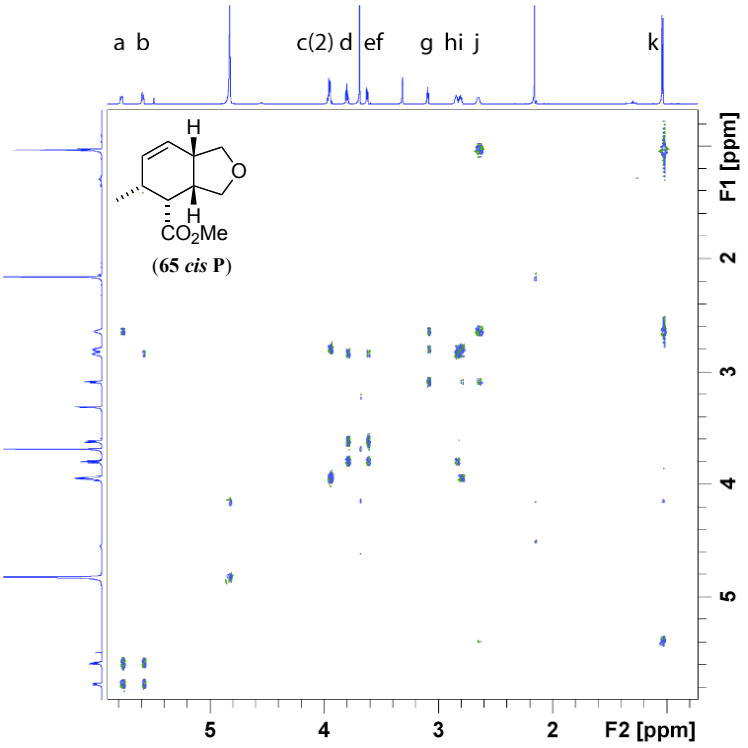
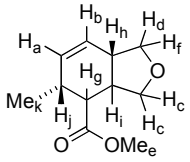
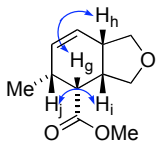


Figure 6.5 *800 MHz ^{1}H COSY spectrum of cycloadduct (**65 cis P**), obtained from intramolecular Diels-Alder reactions of triene (**65**).*

Signals in the 800 MHz ^{1}H COSY spectrum of adduct (**65 *cis* P**) were assigned letters of the alphabet, allowing the connectivity of the compound to be depicted in the left hand structure in (**Figure 6.6**). The coupling constant between the protons at the site of ring fusion, H_h and H_i, was 8.3 Hz, indicative of a *cis* fused ring junction. The stereochemical information missing from the left hand structure was obtained from coupling constant data and through one dimensional nOe experiments summarised in the right hand structure.



(65 *cis* P)



(65 *cis* P)

Figure 6.6 *Left: Connectivity of cycloadduct (**65 cis P**) derived from inspection of the 800 MHz ^{1}H COSY spectrum of (**65 cis P**) in CD_3OD. Right: Nuclear Overhauser effect data obtained from one dimensional nOe experiments with (**65 cis P**) in CD_3OD solution.*

The nOe observed between H_i and H_j indicates that the ring system in this adduct is *cis* fused, and this conclusion is confirmed by the observation of a nOe between H_h and H_g.

Further, the nOe between H_h and H_g demonstrates that the geometry of the dienophile is conserved in the adduct.

6.2.4 Cycloadduct (65 trans P)

The connectivity of IMDA adduct (**65 *trans* P**) was obtained from inspection of the 800 MHz ^{1}H COSY spectrum of the compound in $CDCl_3$ (**Figure 6.7**). The proton signals were assigned letters of the alphabet. The doublet corresponding to the methyl group at 1.0 ppm, H_l, is linked to the signals corresponding to the ring junction methine units, H_j and H_k, by three bond couplings; H_l couples to H_h, H_h couples to H_i, H_i couples to H_k, and H_k couples to H_j. The signals corresponding to the methylene units adjacent to H_j and H_k, the alkene interposed between H_j and H_h, and the methyl ester, H_e, are well resolved and easily identified.

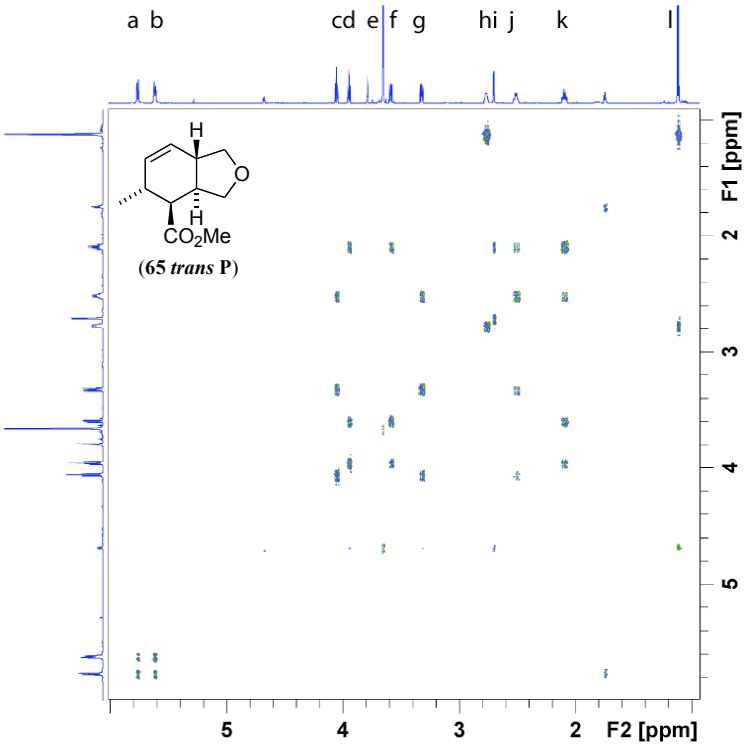
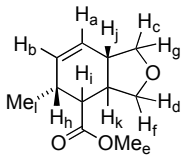


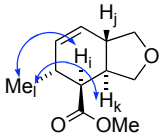
Figure 6.7 *800 MHz ^{1}H COSY spectrum of cycloadduct, (**65 trans P**), obtained from intramolecular Diels-Alder reactions of triene (**65**).*

Signals in the 800 MHz ^{1}H COSY spectrum of adduct (**65 *trans* P**) were assigned letters of the alphabet, allowing the connectivity of the compound to be depicted in the left hand structure in (**Figure 6.8**). The coupling constant between the protons at the site of ring fusion, H_j and H_k, was 12.8 Hz, indicative of a *trans* fused ring junction. The stereochemical information missing from the left hand structure was obtained from

coupling constant data and through one dimensional nOe experiments summarised in the right hand structure.



(**65** ***trans*** **P**)



(**65** ***trans*** **P**)

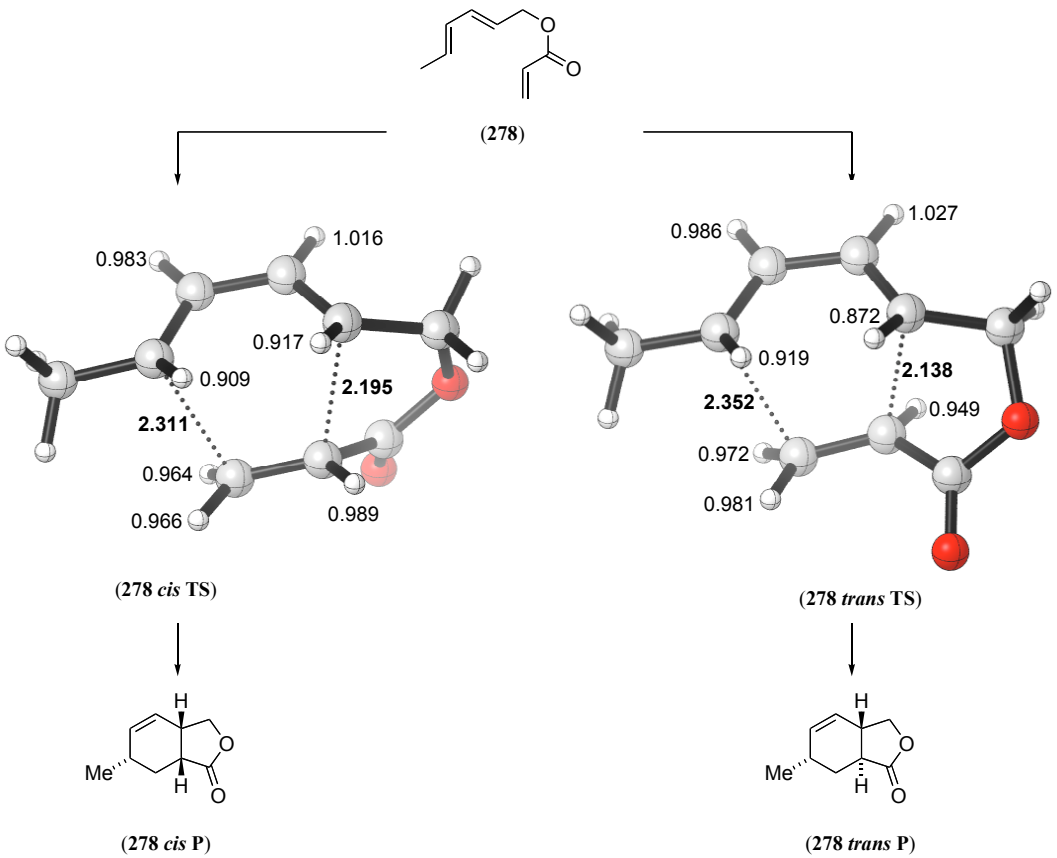
Figure 6.8 *Left: Connectivity of cycloadduct (**65 trans P**) derived from inspection of the 800 MHz ^{1}H COSY spectrum of (**65 trans P**) in $CDCl_3$. Right: Nuclear Overhauser effect data obtained from one dimensional nOe experiments with (**65 trans P**) in $CDCl_3$.*

The nOe observed between H_k and H_l indicates that the ring system in this adduct is *trans* fused, and this conclusion is confirmed by the magnitude of the coupling constant between H_j and H_k. Further, the nOe between H_i and H_l demonstrates that the geometry of the dienophile in (**65**) is conserved in the adduct (**65** ***trans*** **P**).

6.3 Calculated Kinetic Isotope Effect Data

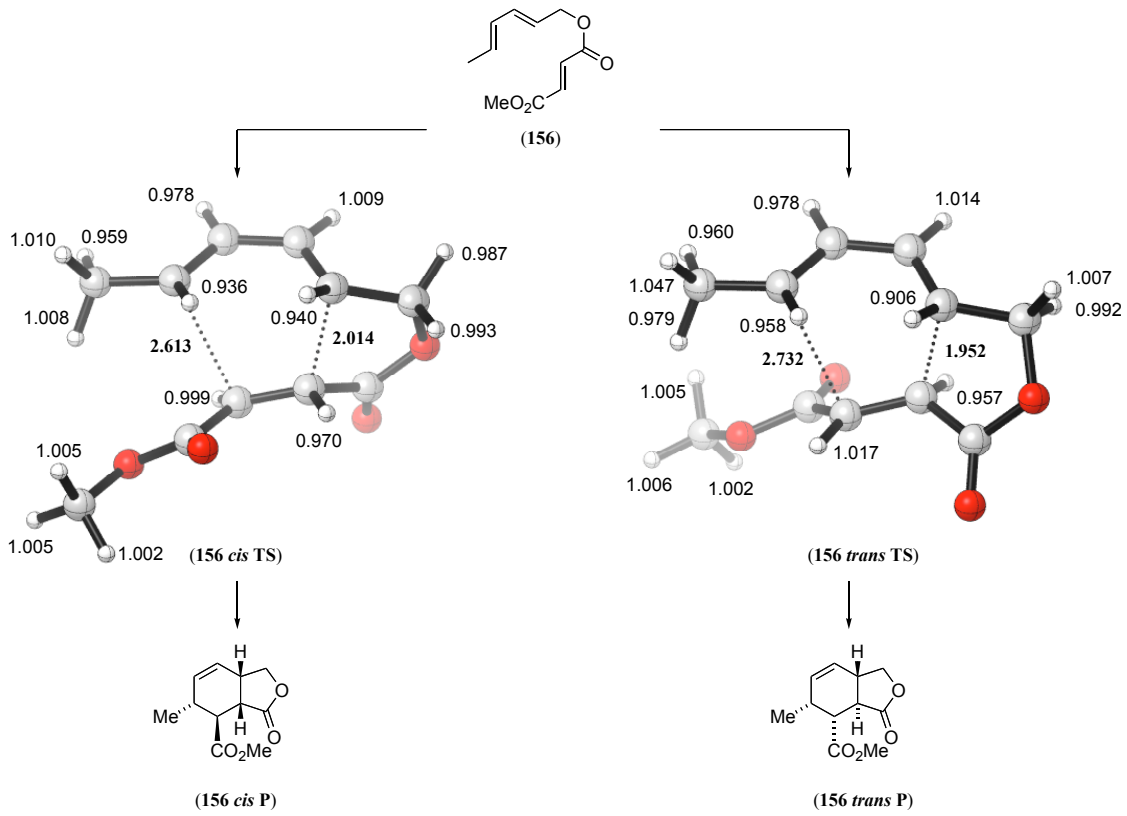
Prof. M. N. Paddon-Row has kindly supplied calculated KIE data and transition structures for the IMDA reactions of 1,3,8-nonatrienes (**278**) (**Scheme 6.2**), (**156**) (**Scheme 6.3**), (**157**) (**Scheme 6.4**) and (**158**) (**Scheme 6.5**) in chlorobenzene at 298.15 K. Calculated and experimental KIE data for the IMDA reaction of 1,3,8-nonatriene (**156**) in chlorobenzene at 405.15 K are discussed in (**Section 3.2.5**) of this thesis.[178].

6.3.1 *Calculated kinetic isotope effect data for the intramolecular Diels-Alder reaction of triene (278)*



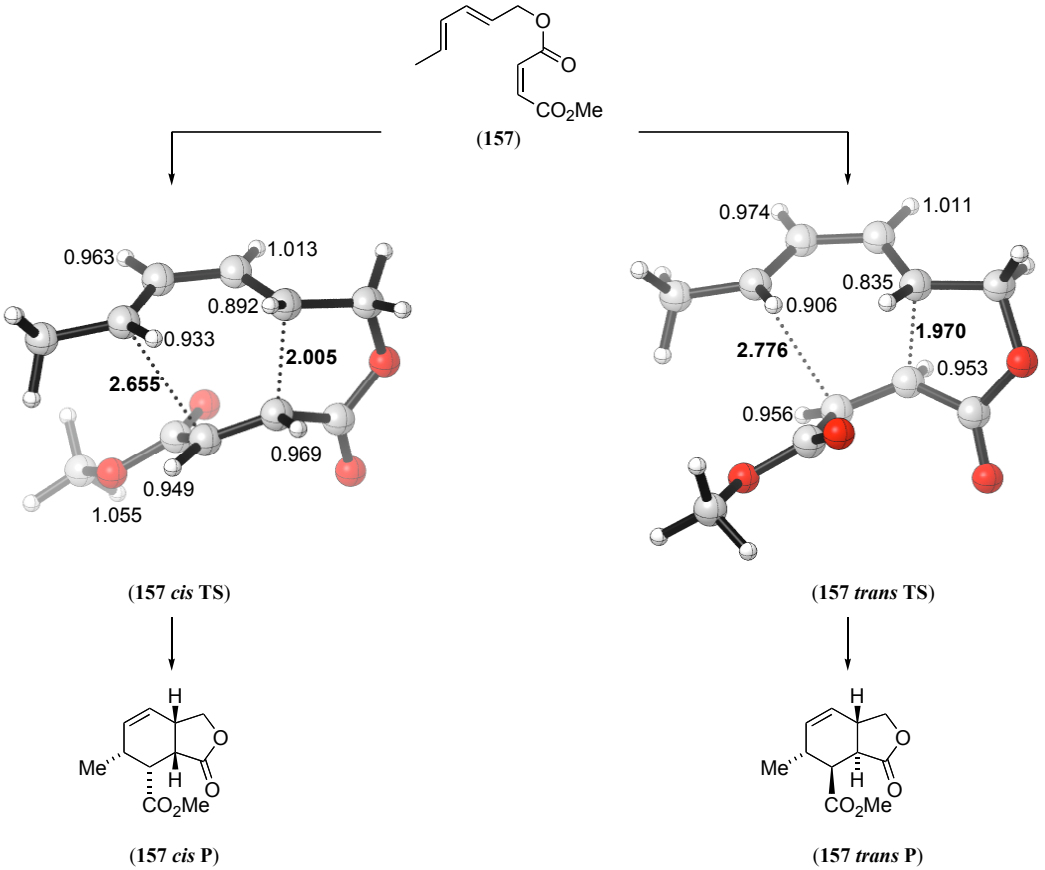
Scheme 6.2 *B3LYP/6-31G(d) calculated kinetic isotope effects for the intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**278**) in chlorobenzene at 298.15 K.*[178]

6.3.2 *Calculated kinetic isotope effect data for the intramolecular Diels-Alder reaction of triene (156)*



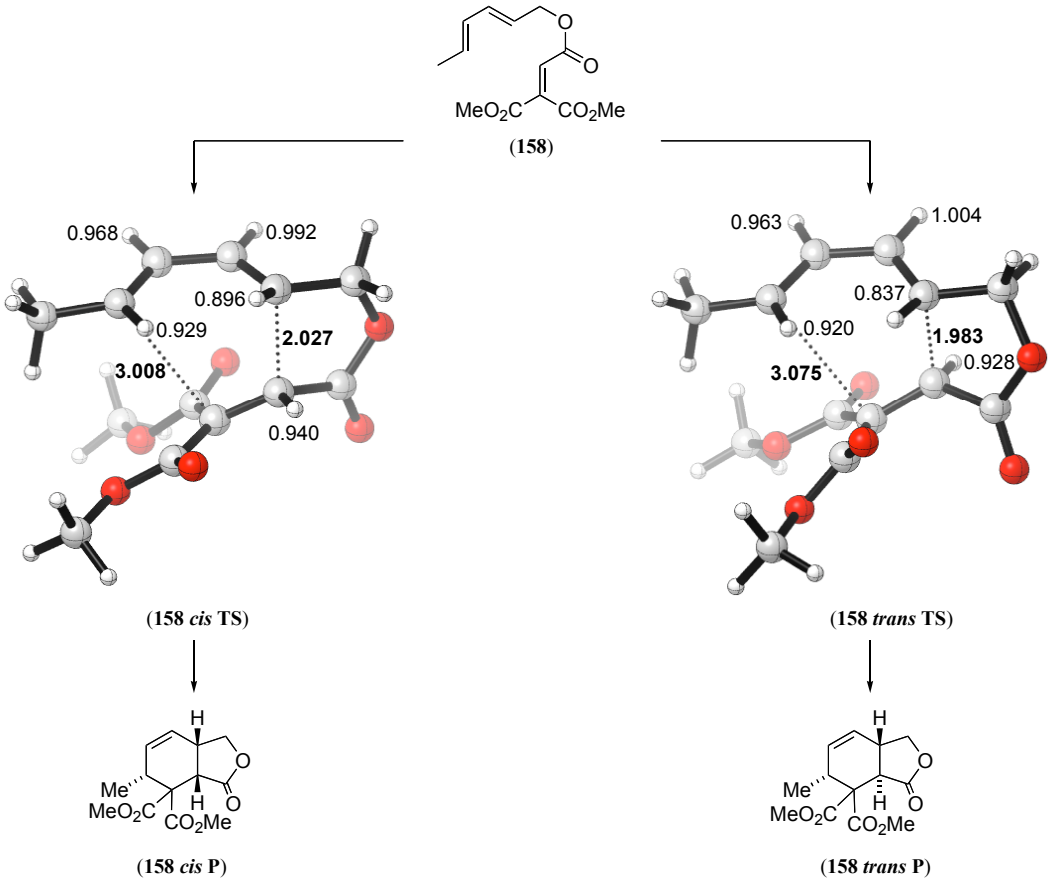
Scheme 6.3 *B3LYP/6-31G(d) calculated kinetic isotope effects for the intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**156**) in chlorobenzene at 405.15 K.*[178]

6.3.3 *Calculated kinetic isotope effect data for the intramolecular Diels-Alder reaction of triene (157)*



Scheme 6.4 *B3LYP/6-31G(d) calculated kinetic isotope effects for the intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**157**) in chlorobenzene at 298.15 K.*[178]

6.3.4 Calculated kinetic isotope effect data for the intramolecular Diels-Alder reaction of triene (158)



Scheme 6.5 *B3LYP/6-31G(d) calculated kinetic isotope effects for the intramolecular Diels-Alder reaction of 1,3,8-nonatriene (**158**) in chlorobenzene at 298.15 K.*[178]

6.4 Summary

Proofs of the structures of compounds (**155** ***cis*** **P**), (**155** ***trans*** **P**), (**155** ***cis*** **P**) and (**155** ***trans*** **P**) based on 800 MHz COSY, 600 MHz DQF-COSY and 800 MHz 1D nOe ^{1}H NMR spectra, and B3LYP/6-31G(d) calculated ^{2}H KIEs for the IMDA reactions of 1,3,8-nonatrienes (**278**), (**156**), (**157**) and (**158**) in chlorobenzene at 298.15 K have been presented.

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