1,3-Dipolar Cycloaddition Reactions of Triene-Conjugated Nitrile Ylides and Diazoalkanes

by Alastair G. Cessford

A thesis presented for the degree of Doctor of Philosophy

University of Edinburgh

2002

Dedication

This thesis is dedicated to Sorcha, my family and Dr. J. T. Sharp.

Declaration

I declare that this thesis is my own composition and that the work of which it is a record was carried out by myself unless otherwise acknowledged. No part of this thesis has been submitted in any other application for a higher degree.

Courses Attended

1. Royal Society of Chemistry, Perkin Division (Scottish Section), annual meetings, various speakers, 3 years attendance.
2. Current Topics in Organic Chemistry, various speakers, Department of Chemistry, University of Edinburgh, 2 years attendance.
3. Organic Research Seminars, various speakers, Department of Chemistry, University of Edinburgh, 3 years attendance.
4. Molecular Machines, Prof. D. Leigh, University of Edinburgh, 2001.
5. Introduction to Solid Phase Synthesis and Combinatorial Chemistry, GlaxoSmithKline, various speakers, University of Edinburgh, 2001.
6. Developments in Drug Design, Merck, Sharp and Dohme, various speakers, University of Edinburgh, 1999.
7. Walker Memorial Lecture, Prof. Sir Harry Kroto, University of Edinburgh, 2001.

Acknowledgements

I would firstly like to thank Dr. John Sharp for his excellent guidance, encouragement and patience and also for giving me the benefit of his experience and expertise throughout the course of my studies.

I am also grateful to the various members of staff in the Chemistry department without whose help this work would not have been possible. In particular I thank John Millar and Wesley Kerr for efficiently obtaining almost all of the NMR data for this work. I would also like to thank Dr. David Reed for more specialised help with NMR. Similarly, I thank Mr. Alan Taylor and Mr. Harry MacKenzie for their work in obtaining mass spectra. I also appreciate the help of Mr. Derek Burgess and the staff of the chemistry stores. I am also grateful to the EPSRC for funding.

I would like to thank my friends and colleagues from the Decanting Block, especially Ken Baker and Andrew March, for making my time there enjoyable and for lightening the mood whenever frustration crept in. Also for many interesting discussions, occasionally chemistry based.

Special thanks are due to my parents Robin and Sheila and to my brother Andrew and to Sorcha, for their constant love, support and understanding. Without them this would not have been possible.

Abstract

The cycloaddition reactions of a number of triene-conjugated nitrile ylides and diazoalkanes were studied. In all cases the α,β unsaturation was part of a benzene or thiophene ring and the γ,δ;ε,ζ double bonds were olefinic.

The nitrile ylides in which the trienyl system was in the *trans* configuration reacted exclusively *via* 1,1-cycloadditions to yield the corresponding 1-alkenyl-*exo*-cyclopropa[*c*]isoquinolines. These primary products were found to undergo intramolecular rearrangement reactions of three types to yield 4-alkenyl-1*H*-2-azepines, propenyl-bridged isoquinolines (or the thiophene analogue) or azabenzobabaralanes. It was found that the proportions of these products obtained were dictated by the substitution pattern of the precursor cyclopropa[*c*]isoquinoline, and, in each case, the observed reaction modes are rationalised in terms of substituent effects.

Triene-conjugated diazoalkanes where the *cis* δ substituent was hydrogen were found to yield exclusively the 4-alkenyl-1*H*-2,3-diazepines, presumably *via* a 1.7-electrocyclisation process. Where the *cis* δ substituent was a phenyl ring and the ζ-substituent was an aryl group a 1,1-cycloaddition occurred, ultimately yielding the pyrrolophthalazines. Where either the δ- or ζ-substituent of the diazoalkane was non-aromatic, carbene-derived products were formed *via* intermolecular reactions.

Where the trienyl system was in the *cis* configuration at the γ,δ-bond the 1,1-cycloaddition process became less competitive and the major or exclusive products were the carbene-derived cyclopropa[*a*]naphthalenes. Greater proportions of the phthalazines were obtained where the ζ-substituent was aromatic. This effect is rationalised in terms of the stability of a proposed diradical intermediate for rearrangement of the primary cycloaddition product.

Contents

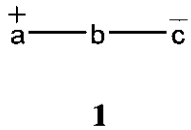
Introduction

Section 1

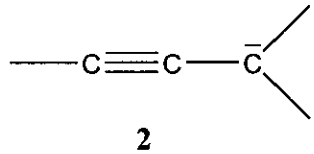
1,3-Dipoles

1.1 Structure

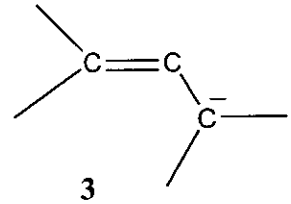
1,3-Dipoles[1] are 3-atom moieties (*i.e.* **1**) which, as the name suggests, possess both a formal positive charge at one of the terminal atoms (**a**) and a formal negative charge at the other (**c**). In terms of electrons, this means that the atom **a** has an electron sextet and **c** possesses an unshared pair of electrons. Overall, 1,3-dipoles possess 4 π-electrons spread over 3 atoms, making them isoelectronic with both the propargyl and allyl anions, **2** and **3** respectively.



1

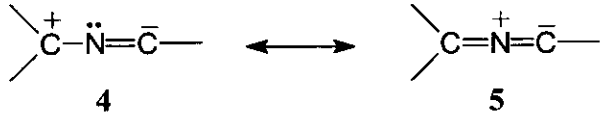


2



3

As depicted above the 1,3-dipole is unstable if the atom bearing the positive charge is an electron-deficient carbon, nitrogen or oxygen atom. They can, however, be stabilised when the central atom (**b**) is capable of donating a pair of electrons. This is the case where **b** = N, in *e.g.* nitrile ylides (**4**), when the neutral trivalent nitrogen atom can donate its lone pair of electrons into the dipolar system. Upon this donation the central nitrogen atom develops a formal positive charge and the previously positively-charged terminal atom (**a** as illustrated above) becomes neutral. This leads to the more stable "all octet" structure (**5**) depicted in figure **1**.



4 **5**

Figure 1

As stated, the central atom in a 1,3-dipole must be capable of donation of a pair of electrons in order for the extra stabilisation of the "all-octet" forms to be conferred and for the dipole to be stable enough to exist. Commonly, the central atom will be

nitrogen or oxygen and the differing valencies of these atoms partly lead to a distinction between two types of 1,3-dipoles.

Where the central atom is oxygen or trisubstituted nitrogen then the dipole is classified as belonging to the "allyl" family. Where the central atom is a **di**substituted nitrogen atom the resulting dipole falls into the propargyl-allenyl category. This distinction arises from the fact that a disubstituted nitrogen atom allows the formation of an orthogonal π-bond in the 3-atom system. Formation of this bond is precluded where the nitrogen has an "extra", third, substituent and in cases where the central atom is oxygen, which has a maximum valency of three in its oxonium form. Examples of both types of 1,3-dipoles are given in figure **2**.

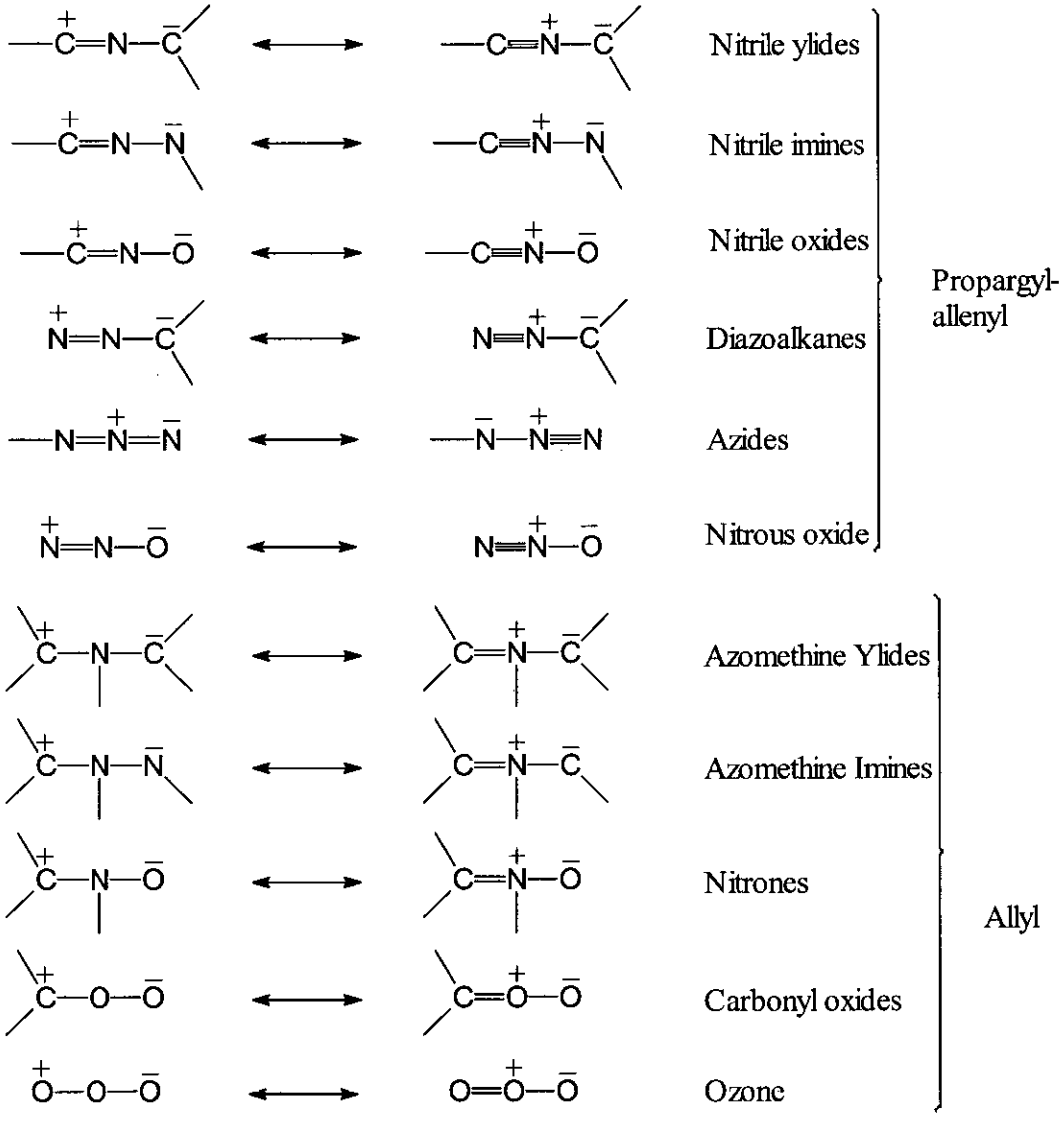
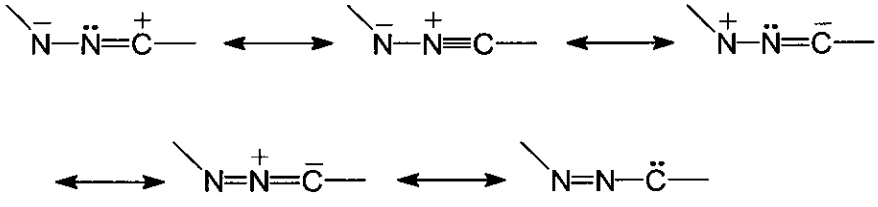


Figure 2

The depictions in figure **2** reflect another consequence of the identity of the central atom of the dipole. Where this atom is disubstituted nitrogen and the extra π-bond can form (*i.e.* the propargyl-allenyl family) then the dipoles are necessarily linear[2]. Those dipoles that have oxygen or trisubstituted nitrogen as the central atom belong to the allyl class and have a bent shape. The fine-structures of 1,3-dipoles have been the subject of calculations to determine the lowest-energy structures of various dipoles.

The structures of 1,3-dipoles are best represented as combinations of canonical structures, reflecting the fact that the π-electrons in the systems are delocalised over all three atoms. Any representation alone is not strictly accurate and may not reflect the observed reactivity of a dipole; only by consideration of all possible canonical forms of a dipole can these reactive intermediates be accurately represented, although they do not necessarily make equal contributions to the composite, observed behaviour of the dipole. Scheme **1** shows the possible resonance structures of a nitrile imine.

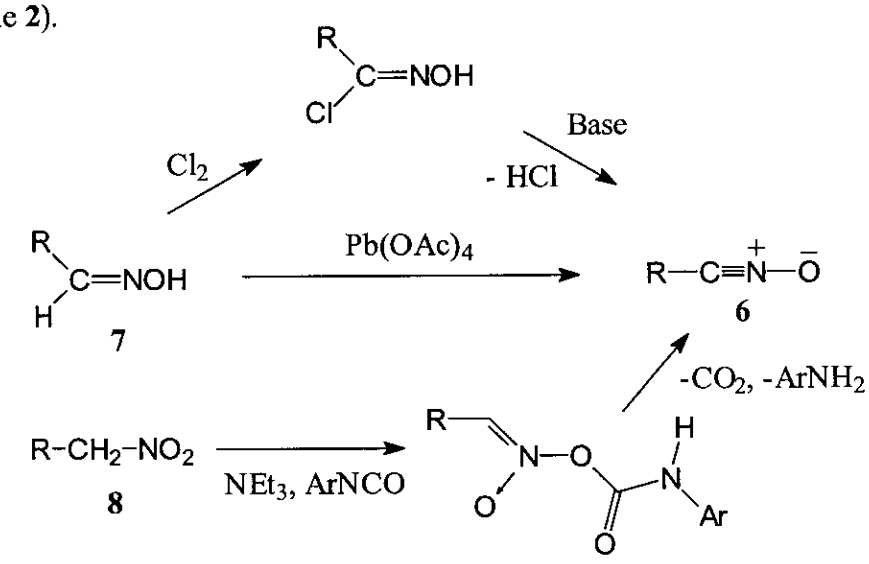


Scheme 1

It should be noted that only the representations where both of the terminal atoms bear a formal charge strictly can be called 1,3-dipoles, and that neither of these structures have the more stable all-octet electronic configuration. The reactivity of the molecule, however, can often be best explained only by consideration of one of the five canonical forms, not necessarily one of the most stable forms or the strictly 1,3-dipolar forms.

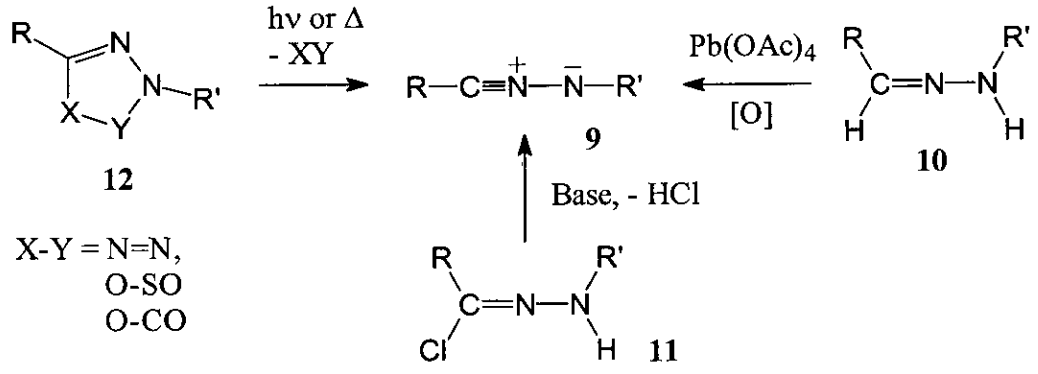
1.2 Generation

1,3-Dipoles can be generated in a variety of ways, some general and some specific to the particular nature of the dipole precursor. Chemical, photolytic and thermal techniques have all been utilised in the vast reported literature concerning 1,3-dipolar cycloadditions. Nitrile oxides (**6**), for example, are generally derived from stable oximes (**2**)[3,4] or nitroalkyl compounds (**8**)[5] by appropriate chemical manipulations (scheme **2**).



Scheme 2

Nitrile imines (**9**) can be generated chemically, either by oxidation of the appropriate hydrazone (**10**) with lead acetate or mercuric dioxide[6], or by dehydrochlorination of the hydrazidoyl halide[7] (**11**). They can also be generated thermally or photochemically, by heat- or light-promoted extrusion of a stable fragment such as nitrogen[8], sulfur dioxide[9] or carbon dioxide[10] from precursors of the type **12**.



Scheme 3

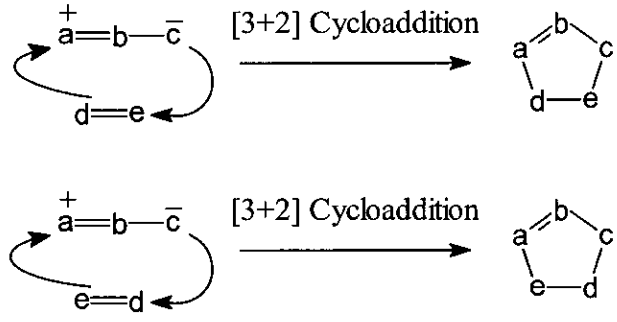
Nitrile ylides and diazoalkanes are available *via* chemical, photolytic and thermal techniques, depending on the precursors they are to be derived from. Examples of all of these conversions will be given in sections **2.2** and **3.2** of this introduction.

1.3 Reactions

1.3.1 Intermolecular Reactions

An enormous catalogue of examples of 1,3-dipolar cycloadditions exists in the literature and many reviews and books on the subject have been written[11]. These accounts reflect the usefulness of this type of reaction and the huge variety of products which can be obtained by utilising 1,3-dipolar cycloadditions.

1,3-Dipoles react with multiple bonds (dipolarophiles, **d=e** as illustrated in scheme **4)** to yield neutral products containing both the dipole and the dipolarophile atoms, often in the form of heterocycles[12]. The simplest way in which this occurs is *via* the [3+2] cycloaddition where the dipole and the dipolarophile react with each other *via* a concerted, pericyclic process. The net result of this is the formation of two new σ-bonds at the expense of a π-bond, giving an uncharged, 5-membered heterocycle.



Scheme 4

There are several features which are common between cycloaddition reactions;

1. They are stereospecific processes, *i.e.* substituents which are *trans*-related in a dipolarophile will also be *trans*-related in the product of a cycloaddition.

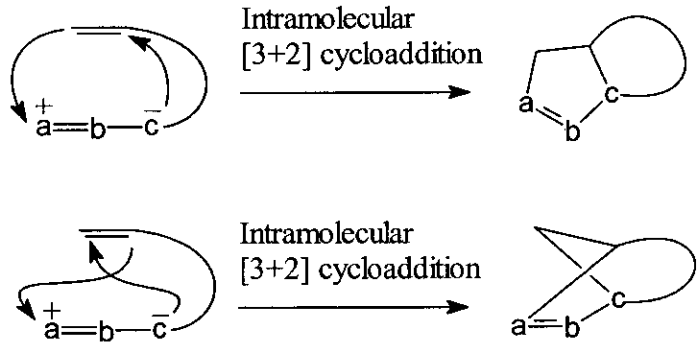
2. The rate and stereoselectivity of cycloadditions are insensitive to solvent polarity.

3. Cycloaddition reactions have large negative entropies of activation and small enthalpies of activation.

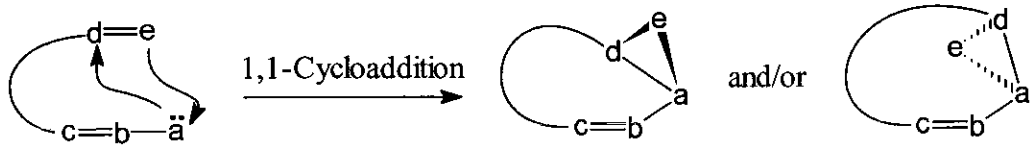
4. Bulky substituents about either participant in a cycloaddition decrease the rate of reaction, while conjugating substituents increase the rate.

1.3.2 Intramolecular Reactions

Cycloaddition reactions are also viable where the dipole and the dipolarophile are connected as parts of the same molecule, provided that the tether allows them to approach each other in a suitable geometric arrangement (schemes **5** and **6**). This type of reaction is called an intramolecular cycloaddition. These reactions also provide 5- membered heterocycles, but in these intramolecular cases they are fused to the linking group, which necessarily forms another ring.



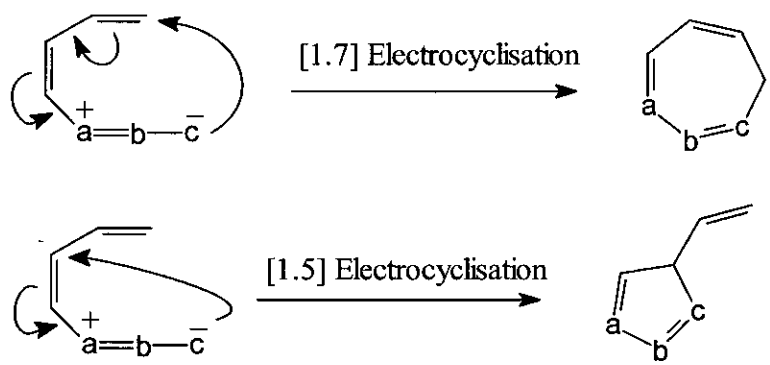
Scheme 5



Scheme 6

Intramolecular reactions other than cycloadditions are also possible, providing the dipole and dipolarophile are able to attain suitable geometry with one another.

Where the dipole and dipolarophile are part of the same molecule and are connected by a conjugating system then they can also react *via* an electrocyclic process[13,14], again yielding heterocyclic products (scheme 7). These processes are thermally promoted and proceed in a conrotatory manner to conserve orbital symmetry.

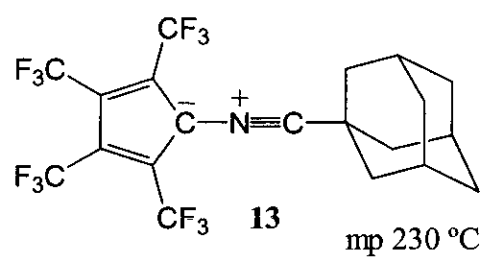


Scheme 7

2. Nitrile Ylides

2.1 Structure

Nitrile ylides are based on the system R_2C—N—CR; they are nitrilium betaines and belong to the propargyl-allenyl class of 1,3-dipoles, possessing an orthogonal π-bond. Although the nitrile ylides are inherently unstable, an example (**13**) has been designed[15] in which the steric hindrance about the dipole is so great that reaction is precluded and the compound has been rendered isolable, to the extent that a melting point has been measured.



13 mp 230 °C

The dipolar nitrile ylide moiety can be represented by the five isoelectronic structures depicted in figure 3.

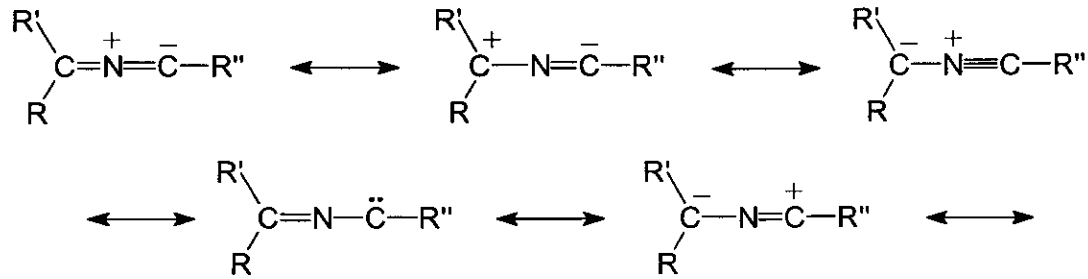
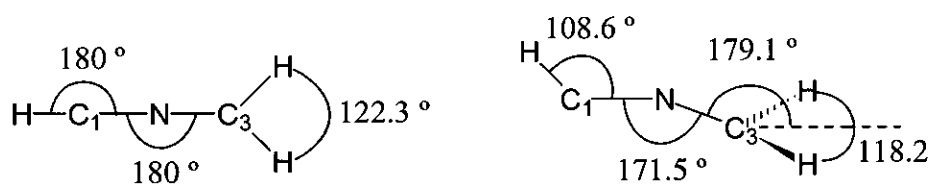


Figure 3

The spatial structure of nitrile ylides has been the subject of much investigation. The importance of the shape of the nitrile ylide stems from the effect that this has on the natures, forms and magnitudes of the molecular orbitals of the three atoms of the dipole, which in turn have a fundamental influence on the regio- and stereoselectivity observed in cycloaddition reactions of 1,3-dipoles.

The results of *ab initio* calculations carried out by Houk [16,17] on the basis that nitrile ylides took a linear-planar form[18] (*i.e.* **14**) suggested that the regioselectivity of some cycloaddition reactions should be the opposite of that actually observed. This obviously suggested that an unwarranted assumption had been made. When further *ab initio* calculations were made using geometry optimisation [2] it became apparent that the assumption that the nitrile ylide adopted a linear-planar form had been wrong. It appeared that the lowest energy conformation was significantly distorted from linear-planar, with the parameters shown in structure **15** (figure **4**) representing a conformation that is 46.4 kJmol^{-1} lower in energy than the putative linear-planar form (**14**).



14 **15**

Figure 4

The geometry optimised calculations allowed evaluation of the molecular orbitals of the nitrile ylide. The largest coefficient in the HOMO of the bent nitrile ylide was found to be at the C-1 terminus, which bears one substituent. If this model were to be an accurate representation of the real world then the nitrile ylides would be expected to react with dipolarophiles by attack of the evidently more nucleophilic C-1 atom at the more electron-deficient terminal of the dipolarophile. As the dipolarophile must be unsymmetrical for there to **be** any regioselectivity, then the termini of the dipolarophile will necessarily be non-equivalent electronically to some extent and one terminal would possess a larger coefficient in the LUMO of the dipolarophile.

Another consequence of the results of these calculations was the opportunity to note the similarity between the $HO_{(dipole)}$ and $SLU_{(dipole)}$ molecular orbitals of formonitrile methylide and the HO and LU molecular orbitals of singlet carbenes [2] (figure **5**). The significance of this resemblance will become apparent later.

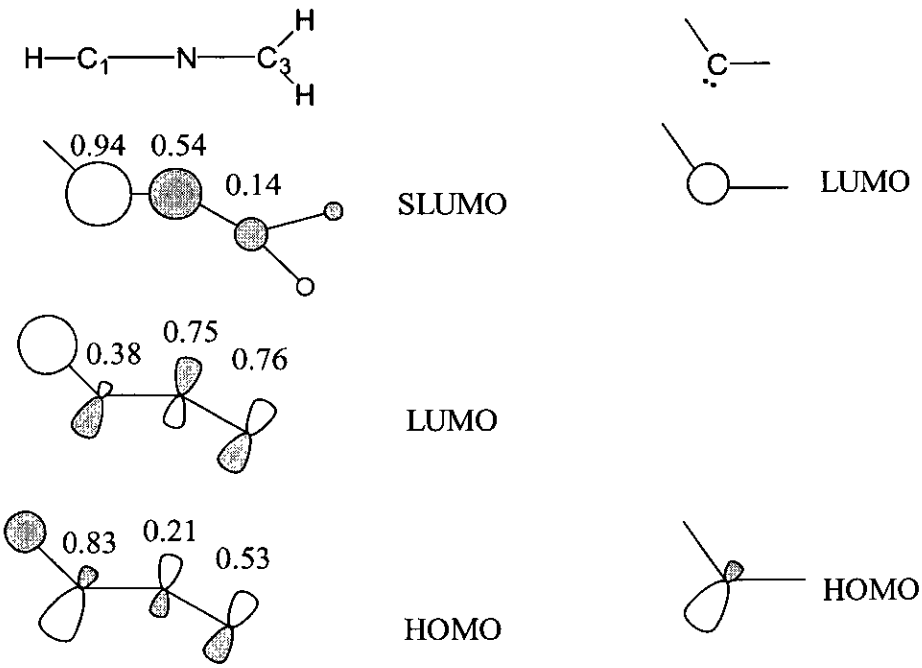


Figure 5

Predictions based on the results of calculations using the MO coefficients estimated for the bent form of the nitrile ylide were in accordance with the regioselectivity observed in practice when the experiments were carried out. This provided further evidence for the bent form of the nitrile ylide being an accurate model. These predictions were based on the products which would be obtained by combination of the dipole and dipolarophile *via* interaction of the centres with the largest MO coefficients on each participant.

The major interaction between the molecular orbitals of nitrile ylides and dipolarophiles undergoing cycloadditions is between $HO_{(dipole)}$ and $LU_{(dipolarophile)}$, because the HOMO of nitrile ylides (in common with all Sustmann type I dipoles) is high-lying[19, 20, 21] (figure **6**, major interaction indicated as an arrow). Electron-attracting groups attached to the dipole decelerate cycloadditions by decreasing the energy of the HOMO and LUMO of the dipole and destabilising the transition state relative to the unsubstituted case. Electron-donating groups accelerate cycloadditions by increasing the stabilisation of the transition state, due to raising of the HOMO and LUMO of the dipole. Conjugating substituents raise the HOMO energy and lower the LUMO energy of the dipole and thus accelerate cycloadditions.

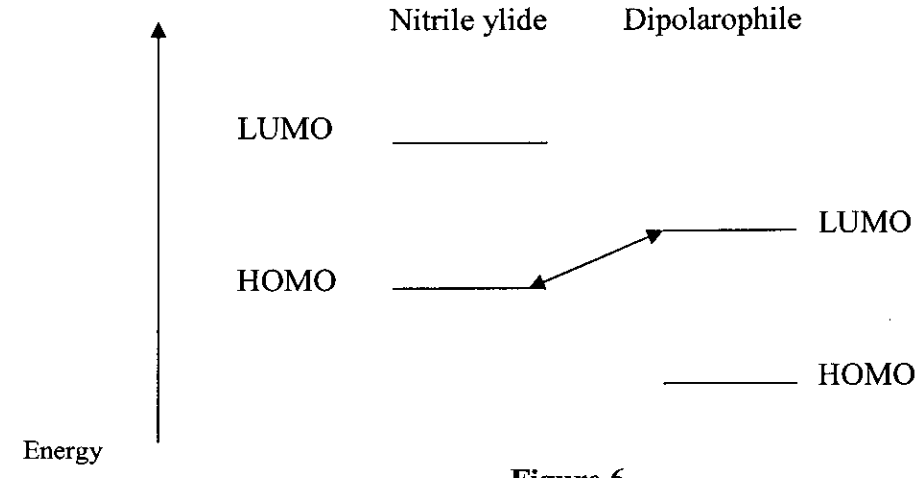


Figure 6

The opposite situation is true for substitution at the termini of the dipolarophile, for similar reasons. Electron-withdrawing groups lower the energies of HOMO and $LUMO_{(dipolarophile)}$, thus again stabilising the transition state relative to that for unsubstituted participants, while electron-donating groups raise HOMO and

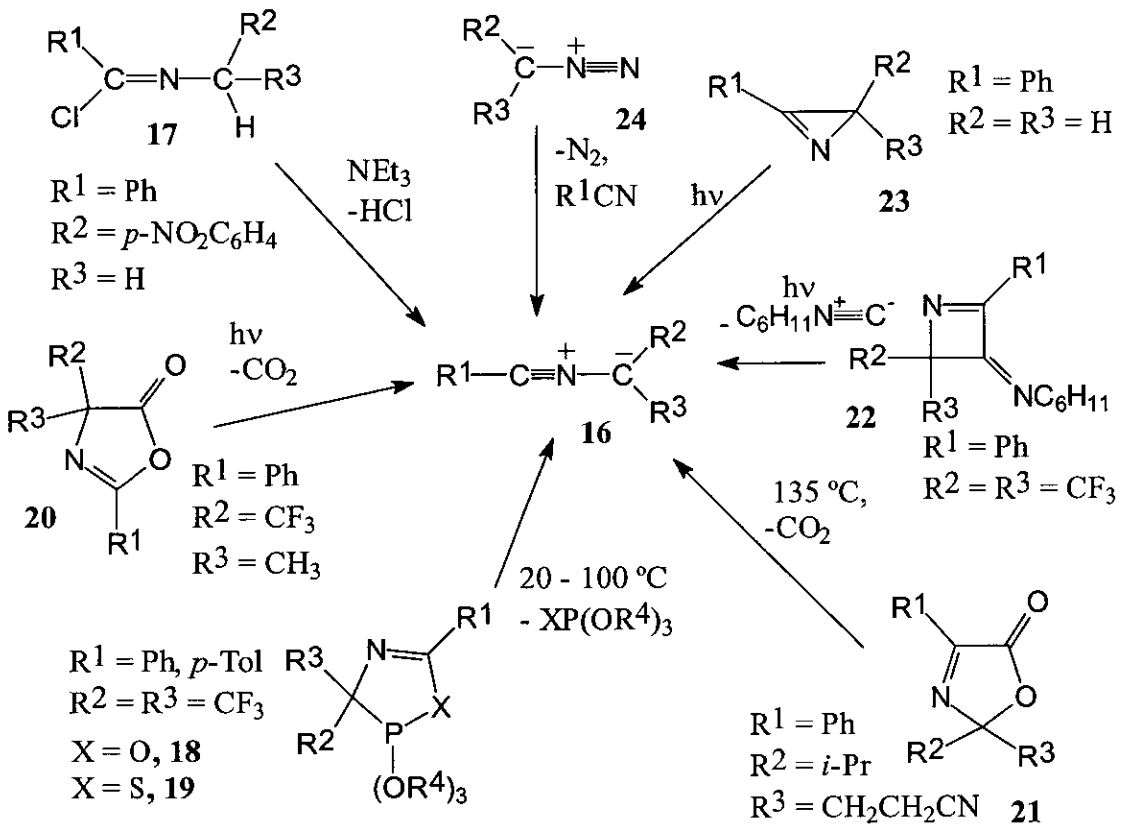
$LUMO_{(dipolarophile)}$ and decelerate cycloadditions. Groups in conjugation with the dipolarophile accelerate cycloadditions by lowering the energy of $LUMO_{(dipolarophile)}$.

2.2 Generation

An enormous battery of methodologies for the generation of nitrile ylides (**16**) is available[22]. The main chemical method involves dehydrohalogenation of imidoyl halides (*e.g.* **17**) by bases[23]. The imidoyl halides themselves are derived from halogenation of appropriately substituted amides[24] with reagents such as thionyl chloride, phosphoryl chloride or dimethylchloroformiminium chloride.

Elimination of stable fragments from a stable precursor compound is another popular method for nitrile ylide generation. The favoured types of precursor for this technique are oxazaphospholes **18** [25, 26, 27] and thiazaphospholes **19** [28], and 2- and 3-oxazolin-5-ones [29, 30] (**20** and **21** respectively). The stable fragments in the case of **20** and **21** are carbon dioxide, while compounds of the type **18** and **19** extrude trialkyl phosphates or thiophosphates.

These reactions are promoted by thermolysis or photolysis of the precursors. Some are substituent dependent, for example attempted nitrile ylide generations from 2-oxazolin-5-ones have been reported [31,32] to fail due to extrusion of carbon monoxide rather than CO_2. Obviously, this pathway does not lead to generation of the desired nitrile ylide. The most suitable method for generation of a particular nitrile ylide is partly dependant upon the identity of the substituents required about the dipole. A less widely used method is the photochemically induced extrusion of cyclohexyl isocyanide from 3-imino-1-azetines [33,34] (**22**), which are themselves generated as the product of the nitrile ylide reacting with cyclohexyl isocyanide.

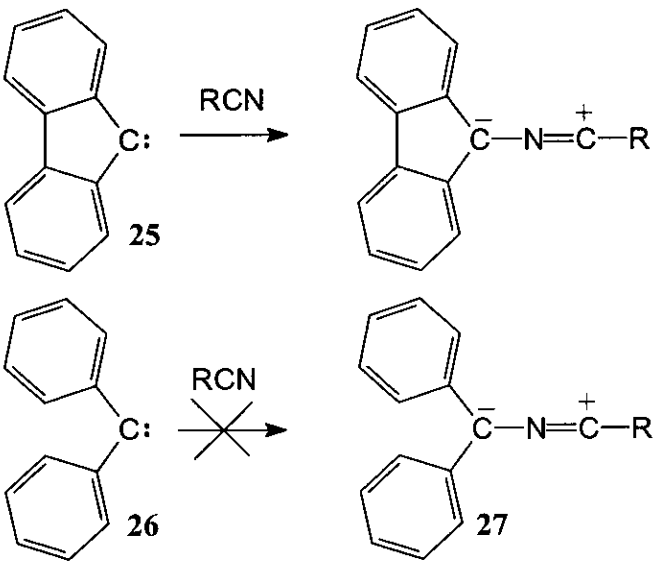


Scheme 8

The other most common method of nitrile ylide generation is photolysis of 2*H*-azirines[35] **23**. A photochemically induced 1,3-retro electrocyclisation of the appropriate 2*H*-azirine yields the nitrile ylide. This reaction is reversible[36] and solutions of the 2*H*-azirines can be racemised by irradiation in the absence of a dipolarophile, *via* a retro electrocyclisation to yield the dipole followed by electrocyclic ring-closure to reform the 2*H*-azirine, with possible scrambling of R^2 and R^3.

A more recent development in the generation of nitrile ylides is the bimolecular assembly of the dipole from a carbene and a nitrile [37,38,39] (scheme **9**). The carbenes can be generated *via* the corresponding diazoalkane (**24**), or by other methods. Advantages of the approach illustrated below are that both types of component are readily available and a wide variety of substitution patterns are possible. In the work

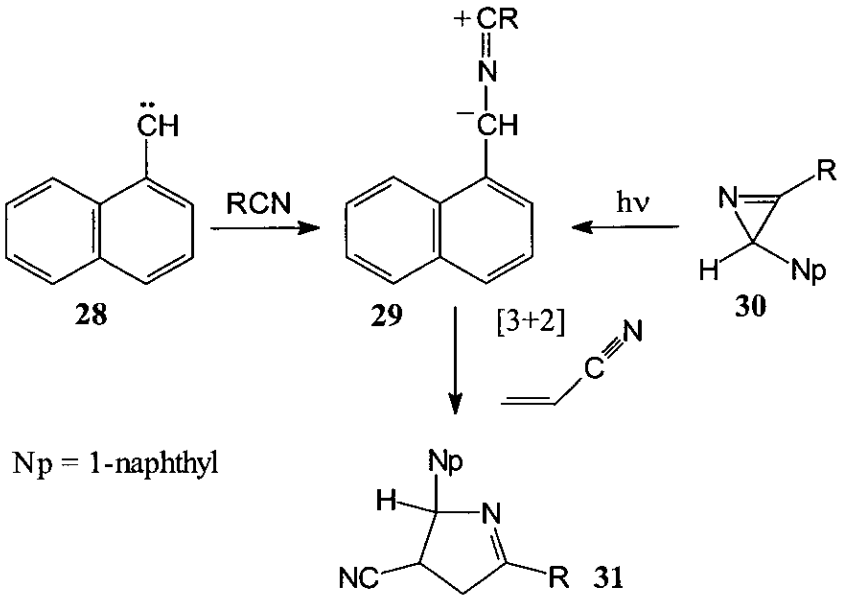
reported to date the carbene has generally been generated photolytically, by laser flash photolysis.



Scheme 9

Initial reports of this method of nitrile ylide generation utilised stabilised carbenes such fluoroylidene carbene (**25**). Subsequent work has shown that this appears to give the best results. Subsequent work has shown that it is a general route but that the equilibrium does not always lie in favour of the nitrile ylide. Thus for diphenylcarbene (**26**), no evidence for the presence of nitrile ylides was obtained by UV spectrophotometry.

The example illustrated in scheme **10**, with naphthylcarbene (**28**), has been proven to proceed *via* the nitrile ylide **29** by trapping experiments [40,41]. Generation of the nitrile ylide **29** from the azirine **30** and trapping in an identical manner gave the same product (**31**) to that obtained by when the dipole was generated from the carbene **28**.

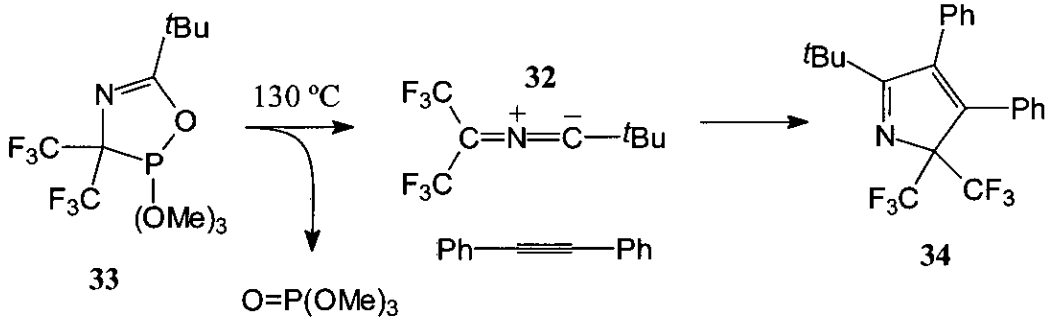


Scheme 10

2.3 Reactions

2.3.1 Intermolecular Reactions

One of the most straightforward reactions of nitrile ylides is the intermolecular [3+2] cycloaddition with a symmetrical dipolarophile. For example, when the nitrile ylide **32** is generated thermally from oxazaphosphole **33** in the presence of diphenylacetylene then the product is the 2*H*-pyrrole **34** [42].

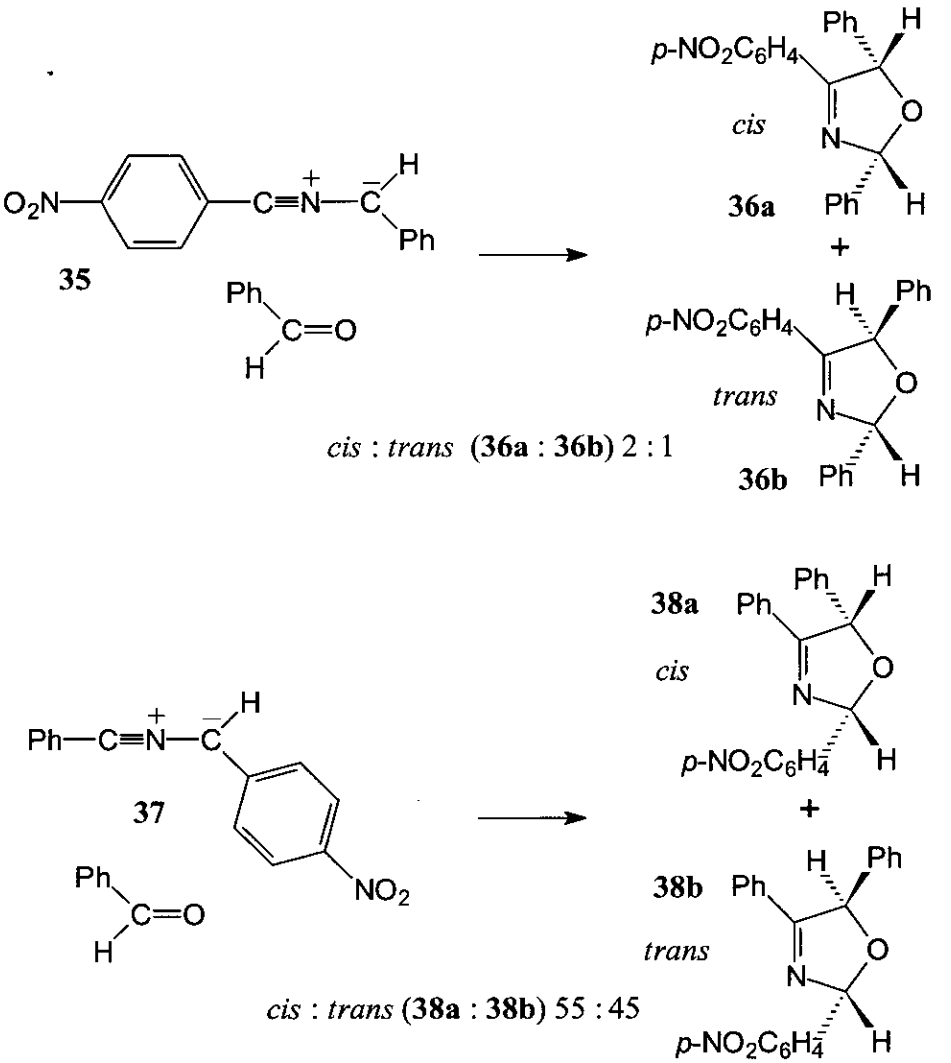


Scheme 11

As the dipolarophile is a symmetrical alkyne no regioisomerism is possible and, as the two phenyl rings are both attached to trigonal carbon atoms of a carbon-carbon double-bond in the product, stereoselectivity is not an issue either.

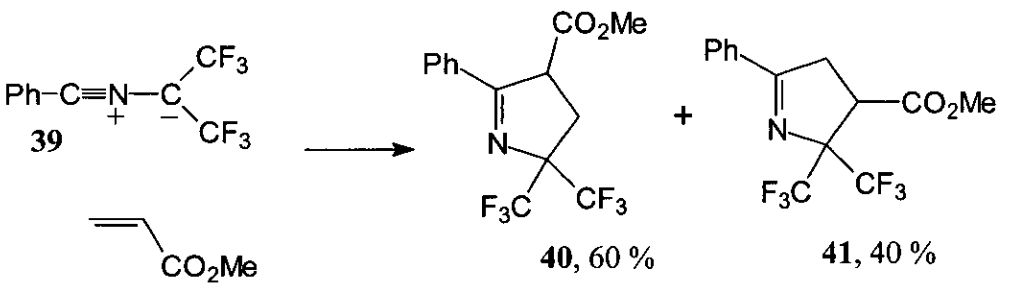
More complex results are obtained where the dipolarophile is unsymmetrical. The following example (scheme **12**) also illustrates the capability of nitrile ylides, along with 1,3-dipoles in general, to react with multiple bonds which include elements other than carbon[43]. Nitrile ylides can also react with imines, nitriles, aldehydes, ketones, esters and thiones. In the reactions depicted in scheme **12**, transferring the nitro group from the phenyl ring at C-3 to that on C-1 of the nitrile ylide has altered the stereoselectivity of the reaction to cause formation of more of the *trans* isomer (**38b**) of the product. The regioselectivity remains unchanged in this case.

Although the stereochemistry of the major product obtained from cycloadditions of **35** and **37** with benzaldehyde is not entirely reversed, this example still illustrates the fundamental importance that substituents have in dictating the favoured course of cycloaddition reactions.



Scheme 12

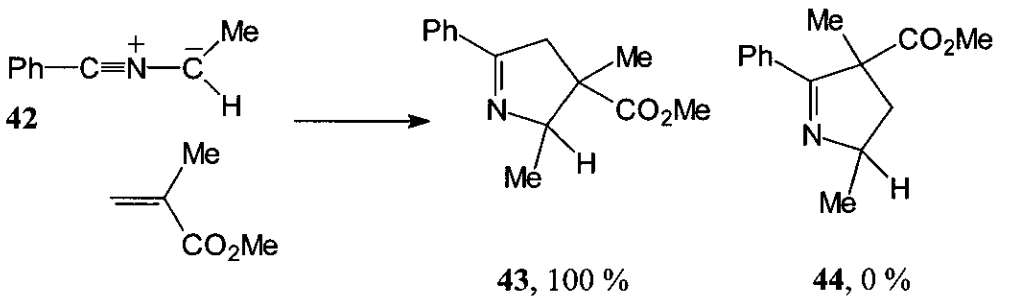
Regiochemistry can also become an issue where the dipolarophile is an unsymmetrically substituted multiple bond. The cycloaddition between nitrile ylide **39** and methyl acrylate depicted in scheme **13** does not show a strong preference for formation of either regioisomer[44].



40, 60 % **41**, 40 %

Scheme 13

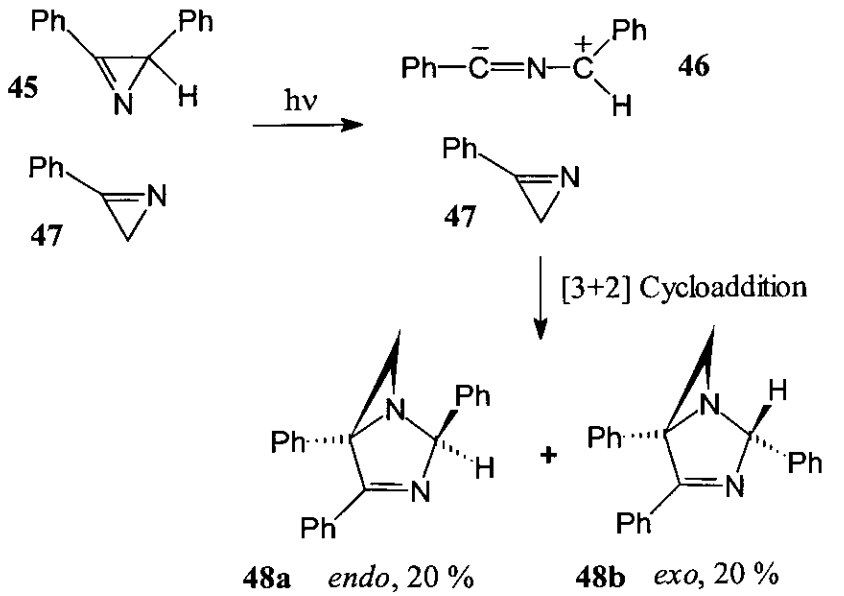
The cycloaddition between nitrile ylide **42** and methyl α-methacrylate (scheme **14**), however, proceeds to yield exclusively[45] the isomer **43**, which is analogous with the disfavoured product **41** in the previous example. The two examples shown above demonstrate the marked influence that the nature of the substituents on the participants in a cycloaddition reaction can have over the regio- and stereoselectivity of the process. This influence derives, as previously outlined, from the relative magnitudes of the HO/LU coefficients of the FMO's of both the dipole and the dipolarophile, which are altered by substitution at the centres concerned.



43, 100 % **44**, 0 %

Scheme 14

Nitrile ylides can, in some cases, also react with nitrile ylide precursors [46]. When the 2*H*-azirine **45** is selectively excited to give the nitrile ylide **46** in the presence of the 2*H*-azirine **47** a [3+2] cycloaddition occurs between the dipole and the C=N bond of **47** (scheme **15**), yielding both the *exo*- and *endo*-isomers of the heterocyclic product (**48a** and **48b**).



Scheme 15

It has been proposed [1,46,47] that, for 1,3-dipolar cycloadditions to occur, the components must approach each other in a specific manner (figure 7). Obviously, the two termini of the dipole must come into proximity with the dipolarophile, and the five centres involved in the coordination complex arrange themselves into the form of the 5-membered heterocycle as the electrons rearrange to form the new bonds. In this intermediate form the nitrile ylide must have a bent shape and thus the orthogonal π-bond possessed by propargyl-allenyl dipoles such as nitrile ylides becomes disrupted.

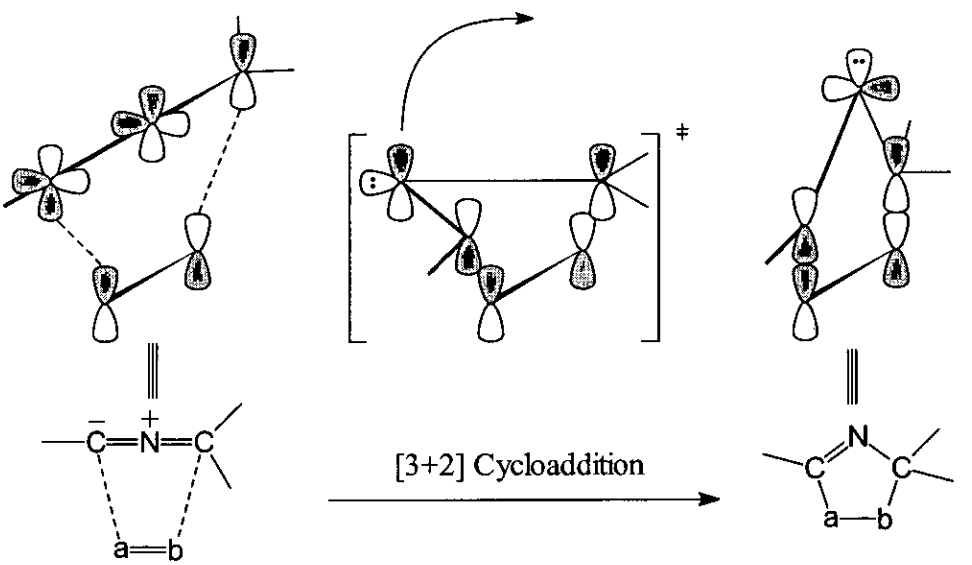
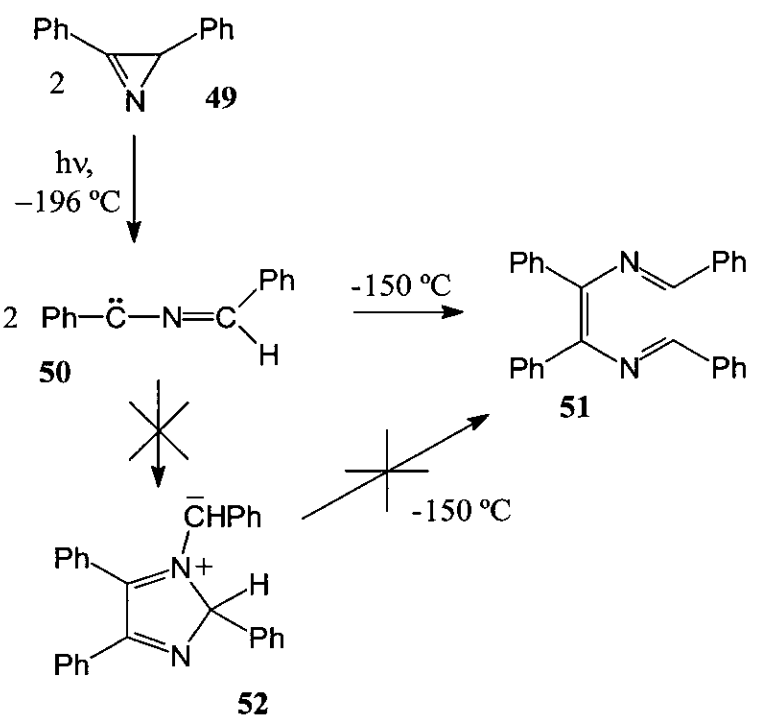


Figure 7

Bringing five atoms into the requisite orientations for this orientation complex to form can prove sterically demanding, depending on substitution patterns about both participants, and in some cases alternative processes become more favourable than the [3+2] cycloaddition. The 1,1-cycloaddition, for instance, only requires three centres to attain a particular geometry relative to each other – two from the dipolarophile and one from the dipole. Formally, the 1,1-cycloaddition has a smaller negative entropy of activation than the [3+2] cycloaddition.

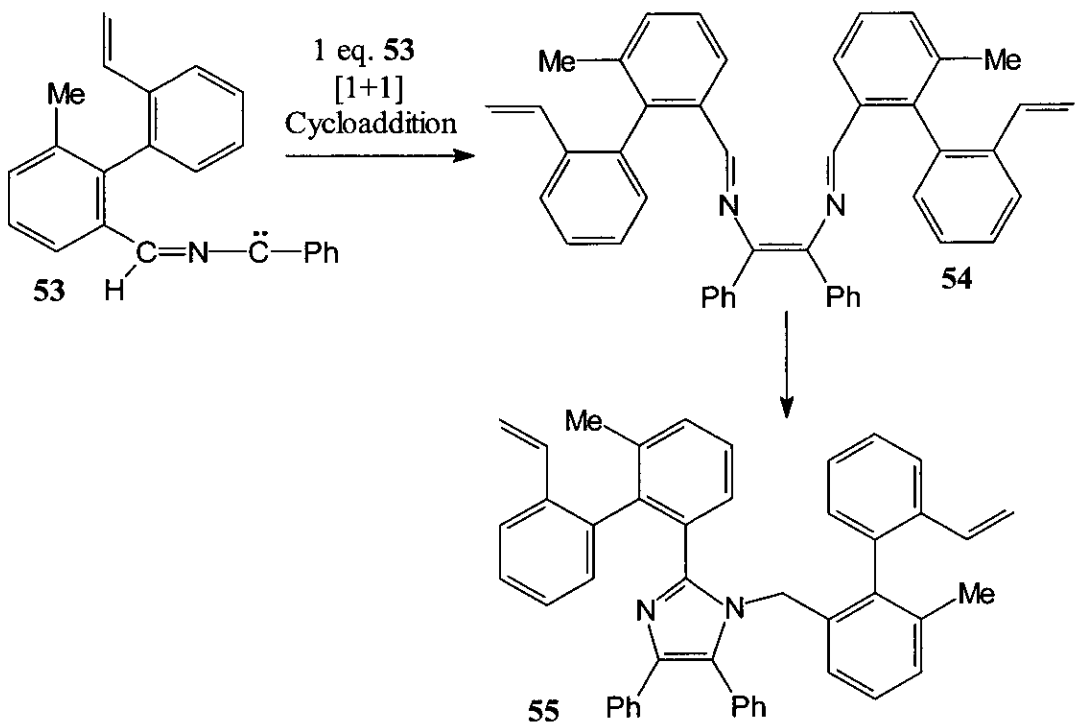
Nitrile ylides are also capable of dimerization reactions when generated in the absence of dipolarophiles[48, 49, 50] (scheme **16**). When the 2*H*-azirine **49** was irradiated in a glassy matrix at –196 °C the dipole generated (**50**) could be observed and was found to be unreactive to dipolarophiles included in the matrix at the low temperatures used. When the dipole (**50**) was the sole reactant included in the matrix (*i.e.* no dipolarophile was added and all azirine **49** had been photolysed) a reaction was observed when the matrix was warmed to *ca.* –150 °C.



Scheme 16

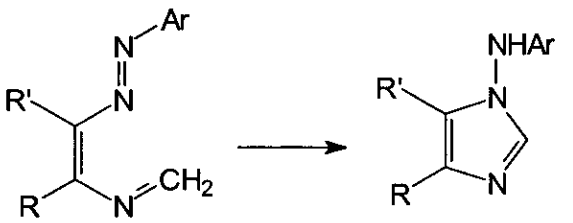
The product was found to be the dimer **51**, thought to form *via* [1+1] cycloaddition of two equivalents of the nitrile ylide **50** (scheme **16**), in a head-to-head manner. The alternative mechanism depicted in scheme **16** was demonstrated not to be active under the conditions used in an independent experiment, generating the intermediate **52** by another route.

The reaction conditions required for these dimerisations to occur can be more mundane than those outlined in the foregoing example. The nitrile ylide **53** was generated from the corresponding imidoyl chloride by treatment with potassium *tert*-butoxide at 0 °C in THF[51] (scheme **17**).



Scheme 17

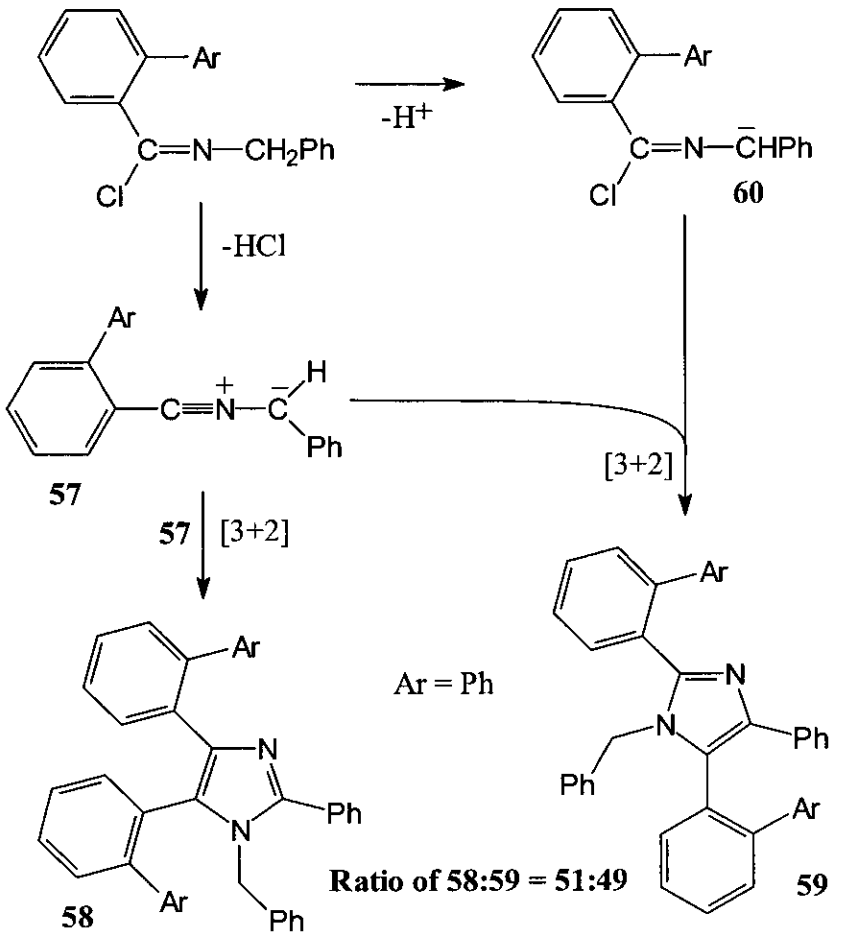
As all "normal" cycloaddition processes were apparently disfavoured the initial reaction was a [1+1] cycloaddition between two equivalents of the nitrile ylide **53**, resulting in a head-to-head dimerisation to give the 2,5-diazahexa-1,3,5-triene **54**. These types of compound have been shown to be capable of rearranging to yield 1-anilinoimidazoles[52] **56** (scheme **18**). A similar rearrangement was observed to occur in the example above, with the isolated product being identified as **55**.



56

Scheme 18

A similar example has been reported more recently[53]. In that case the substituted nitrile ylide **57** reacted to yield two different products (scheme **19**). One of these (**58**) was the product of [3+2] cycloaddition of two equivalents of the nitrile ylide **57**, *i.e.* that predicted by maximum possible overlap between the frontier MO's of two equivalents of the nitrile ylide. The other product was the regioisomer not predicted by FMO theory. The formation of the unexpected product (**59**) was rationalised by proposal of reaction of the nitrile ylide with the deprotonated form of the precursor imidoyl chloride (**60**).

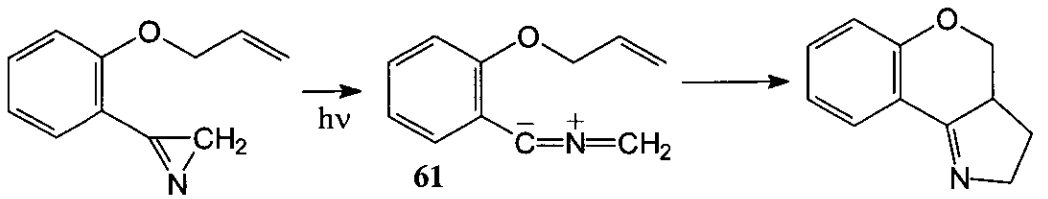


Scheme 19

2.3.2 Intramolecular Reactions

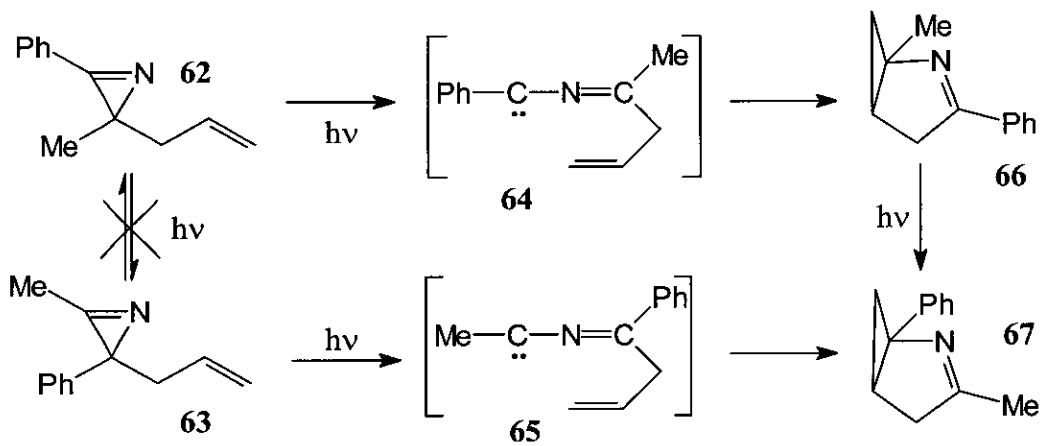
Many examples of cycloadditions between nitrile ylides and dipolarophiles which form part of the same molecule have been reported in the past and a number of reviews and articles have been published[54,55] detailing the application of these reactions as steps in the overall synthesis of natural products. These syntheses often capitalise on the degree of regio- and stereochemical control provided by 1,3-dipolar cycloaddition reactions. The construction of ring-systems is an aspect of synthetic chemistry for which 1,3-dipolar cycloadditions are ideally suited.

The example of an intramolecular [3+2] cycloaddition shown in scheme **20** demonstrates the complexity which can be attained in products from relatively easily synthesised precursors [26, 27].



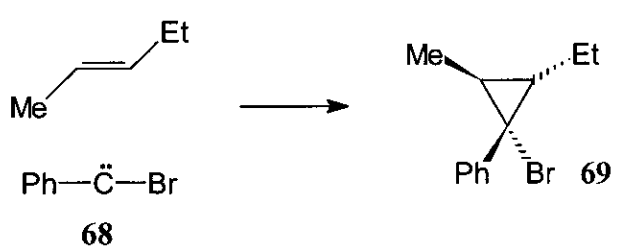
Scheme 20

The first example of an intramolecular 1,1-cycloaddition of a nitrile ylide was reported in 1977 by Padwa and Carlsen[56] (scheme **21**).



Scheme 21

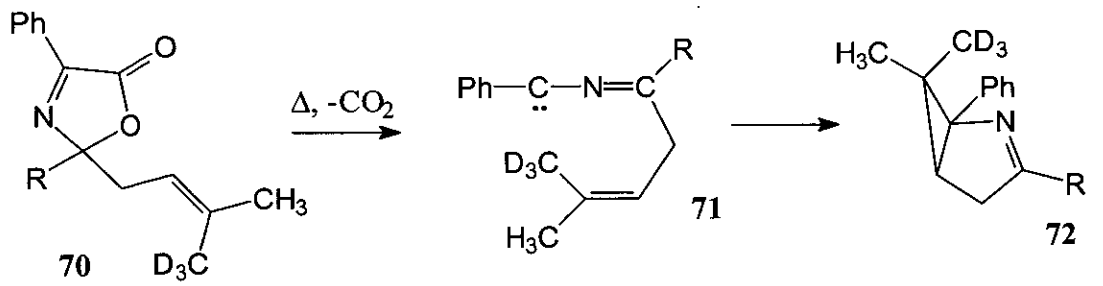
The photolyses of both 2*H*-azirines **62** and **63** depicted in scheme **21** were found to progress smoothly to yield compound **67**. This mode of reaction was rationalised by consideration of the carbenoid resonance representation of nitrile ylides, as analogous singlet carbenes (**68**) are known to react similarly in a concerted manner with alkenes to yield cyclopropanes (**69**)[57].



Scheme 22

The intermediacy of the 1,3-dipoles **64** and **65** was proven by control experiments carried out in the presence of methyl trifluoroacetate, a highly reactive dipolarophile which was shown to trap the dipoles as adducts derived from intermolecular [3+2] cycloadditions. The fact that both of the isomeric dipole precursors **62** and **63** gave the same ultimate product (**67**) upon photolysis complicated interpretation of the results of these experiments, but the precursors **62** and **63** were demonstrated not to interconvert under the reaction conditions used. Halting irradiation of **62** prematurely allowed isolation of a mixture of **62** and **66**, with **66** isomerising to **67** when irradiation was recommenced.

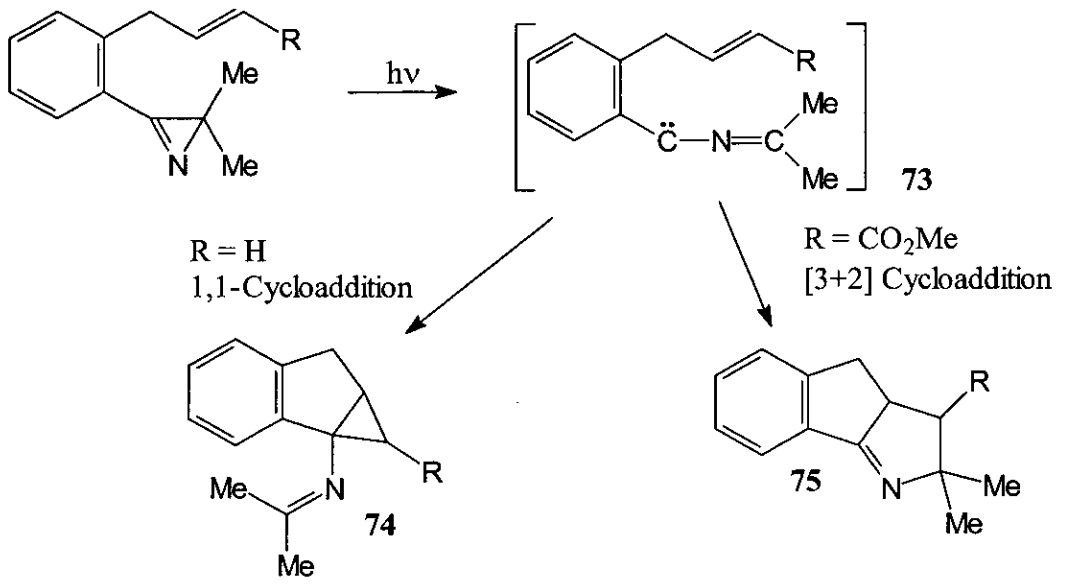
Fischer and Steglich later examined the cycloadditions of a similar system[58] (scheme **23**).



Scheme 23

Again, the intermediacy of the 1,3-dipole was proven by repeating the thermolysis of **70** in the presence of an added intermolecular dipolarophile. This result was of enormous importance, as it proved that the 1,1-cycloaddition has a concerted mechanism. This conclusion was drawn from the fact the reaction proceeded with complete retention of stereochemistry about the olefin, with the *cis* substituent of the olefin (CD_3) adopting the *endo* position on the cyclopropyl ring in compound **72**.

In some cases the switch between the competing modes of cycloaddition that a dipole will undergo is dramatic. This is strikingly exemplified by the reactions[59] shown in scheme **24**.



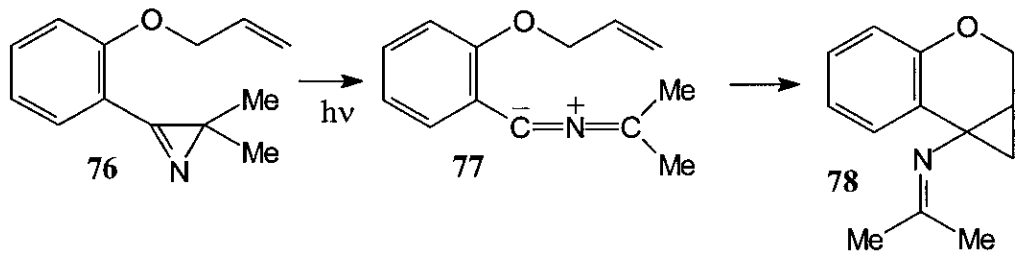
Scheme 24

Photochemical generation of the nitrile ylide **73** is followed by a cycloaddition reaction, the product of which is dictated, in this case, by the identity of the substituent R on the olefin. Where R = H then the 1,1-cycloaddition leading to **74** is the entirely dominant reaction, *via* the carbenoid resonance form of the nitrile ylide. This observation can be rationalised by consideration of the geometrical requirements of the 1,1-cycloaddition. This type of reaction only requires three centres to be correctly aligned to occur, while the [3+2] cycloaddition mechanism requires five centres to be arranged in the two-plane complex detailed previously. These lower geometric requirements for 1,1-cycloaddition mean that it can occur more easily.

On the other hand, when the dipolarophile is activated by the imposition of a methyl ester (*i.e.* R = CO_2Me) then the cycloaddition is massively accelerated and the only product recovered (**75**) is derived from the [3+2] mechanism [27]. This mechanistic switch reflects the strong influence that substituents on the dipole or the dipolarophile can exert.

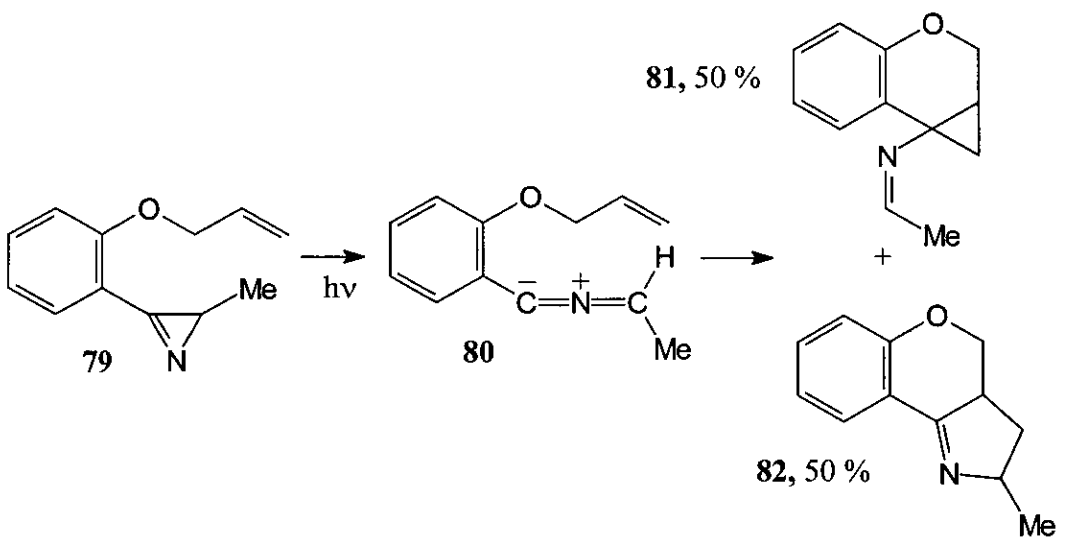
An interesting epilogue to the example of the intramolecular [3+2] cycloaddition of nitrile ylide **61** given at the beginning of this section (scheme **20**) is worthy of note

here. When the nitrile ylide **77**, derived photochemically from dimethyl 2*H*-azirine **76**, cyclised the sole product was found to be the 1,1-cycloadduct **78**. None of the [3+2] cycloadduct was found to form, in complete contrast to the analogous nitrile ylide **61**, which cyclised exclusively *via* the [3+2] mechanism. This shows how substitution at the dipole can cause complete diversion from one mechanism to another, in extreme cases.



Scheme 25

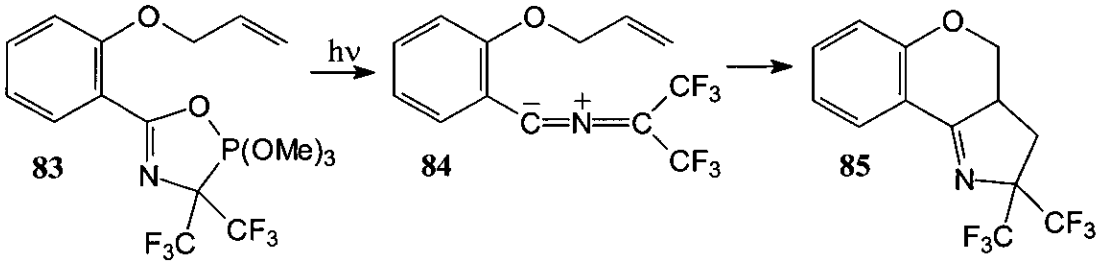
In a neat example of how these cycloaddition processes are balanced [26], when the monomethyl 2*H*-azirine **79** was photolysed to generate nitrile ylide **80** the product mixture of the intramolecular reaction was found to be composed of equal amounts of the 1,1- and [3+2]-cycloadducts (**81** and **82** respectively).



Scheme 26

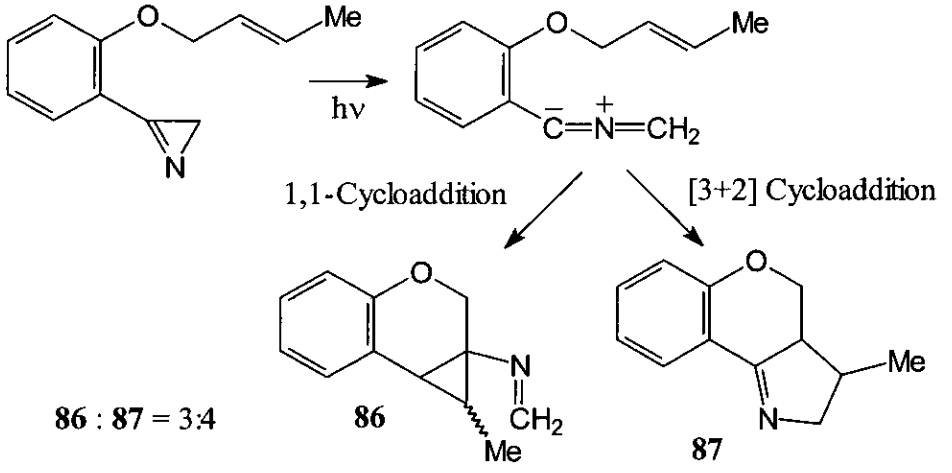
A further fascinating addend to this series of reactions came with generation of the nitrile ylide **84** derived from the di(trifluoromethyl) 2*H*-azirine **83**. Intramolecular reaction of this dipole was found [27] to proceed exclusively by the [3+2] cycloaddition

pathway to yield **85** only (scheme **27**). This finding was ascribed to the electron-withdrawing CF_3 groups favouring the linear, dipolar (as opposed to bent, carbenoid) form of the nitrile ylide moiety and thus favouring 1,3-cycloadditions. The electron-donating methyl groups have the opposite effect, and thus favour 1,1-cycloadditions of the dipole.



Scheme 27

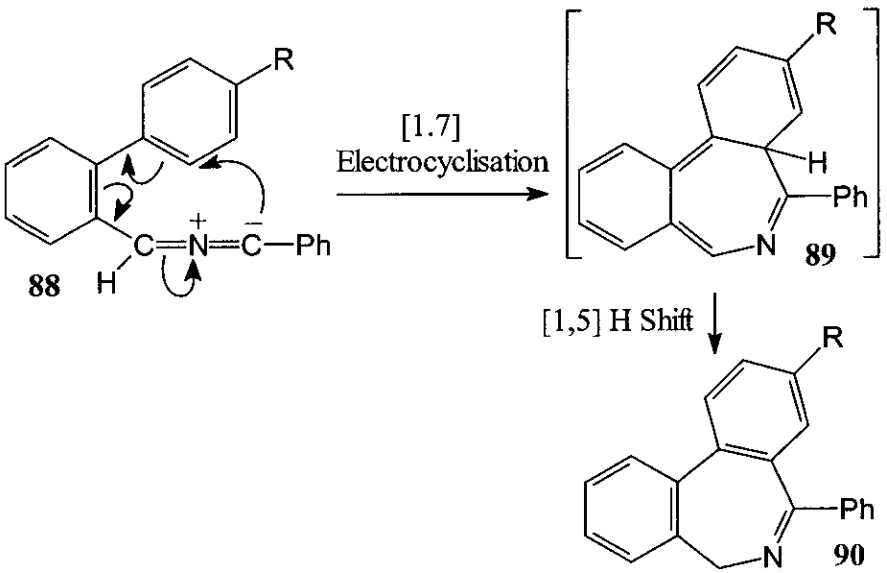
Similar effects were observed where a methyl group was situated on the dipolarophile instead of on the dipole (scheme **28**), with the 1,1-cycloaddition again becoming competitive relative to the [3+2] cycloaddition. These observations are all consistent with the classification of nitrile ylides as Sustmann Type I 1,3-dipoles.



Scheme 28

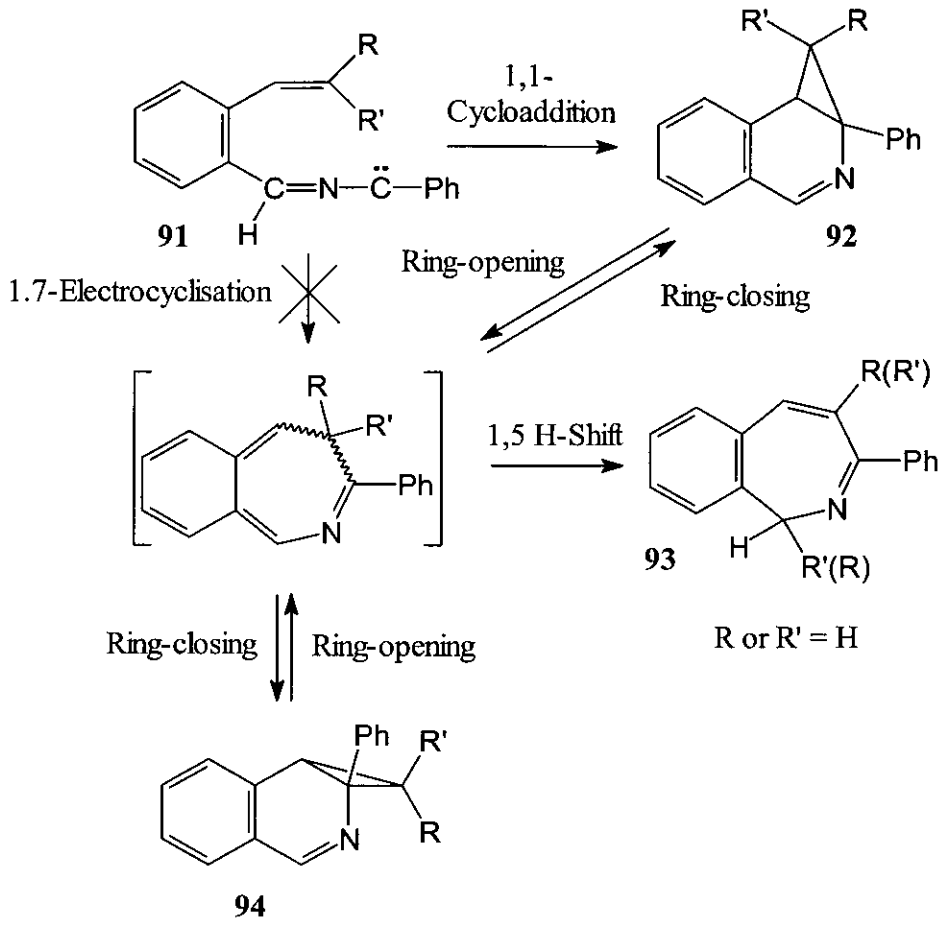
As stated previously, where the substituents and the dipole are in direct conjugation, processes other than the intramolecular [3+2]- and 1,1-cycloadditions detailed above become possible. These processes are electrocyclic reactions and also result in ring formation. Sharp and co-workers showed diene-conjugated nitrile ylides to

undergo these processes when the α,β;γ,δ unsaturations were aromatic (*e.g.* nitrile ylide **88**), with heterocycles in either position giving similar results to the biphenyl compounds[60]. In all cases the isolated products were the fused 1*H*-2,3-azepines **90**.



Scheme 29

Perhaps surprisingly, when the nitrile ylide is in conjugation with a diene where the α,β unsaturation is aromatic and the γ,δ unsaturation is olefinic the operative mechanism has been found[61] to be the 1,1-cycloaddition exclusively (scheme **30**), with no cases of nitrile ylides of the type **91** reacting by 1.7-electrocyclisations.



Scheme 30

Although this process ultimately yields the same products as a 1.7-electrocyclisation would, the intermediate cyclopropa[*c*]isoquinolines **92** can be isolated prior to their rearrangement to 1*H*-2-benzazepines (**93**). Again, these reactions have been proven to be stereospecific, with the *trans* substituent on the olefin occupying the *exo* position on the cyclopropyl ring in the product of the 1,1-cycloaddition and the *cis* group assuming the *endo* position. This *cis* group (R') may be hydrogen, alkyl or aryl.

These cyclopropa[*c*]isoquinolines undergo some very selective and interesting rearrangements upon heating, which will be discussed in sections **4.2.1** and **4.2.2**. The isomerism between the *exo*- and *endo*-isomers of the cyclopropa[*c*]isoquinolines (**92** and **94** respectively) is of integral importance to their subsequent reactivity and this will also be discussed in more depth later.

3 Diazoalkanes

3.1 Structure

Diazoalkanes have the structure shown in figure **8**.

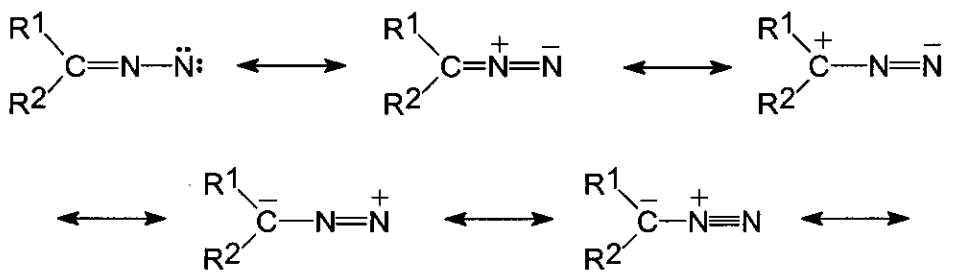


Figure 8

In common with the nitrile ylides, they possess a non-dipolar resonance form, the significance of which will be discussed later. They also belong to the nitrilium betaine family of 1,3-dipoles and are classified as Sustmann Type I dipoles, the HOMO and LUMO of diazoalkanes being relatively high-lying.

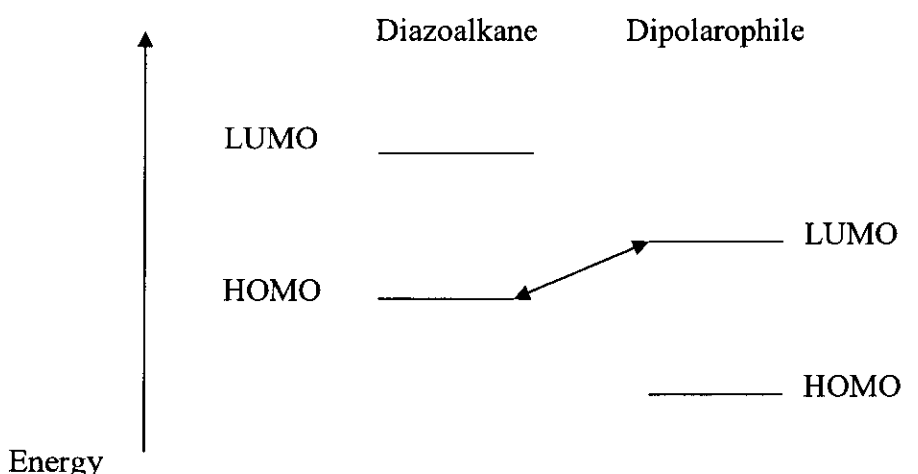


Figure 9

These characteristics mean that cycloadditions of diazoalkanes are affected by substituents in similar ways to nitrile ylides;

1) Imposition of an electron-donating group on the dipole accelerates cycloadditions (dipole HOMO + LUMO energies ↑).

2) Electron-withdrawing groups attached to the dipole decelerate cycloadditions (dipole HOMO + LUMO energies ↓).

3) Substituents in conjugation with the dipole accelerate cycloadditions (dipole HOMO energy ↑, LUMO energy ↓).

4) Electron-withdrawing substituents on the dipolarophile accelerate cycloadditions (dipolarophile HOMO + LUMO energies ↑).

5) Electron-donating substituents on the dipolarophile decelerate cycloadditions (dipolarophile HOMO and LUMO energies ↓).

In contrast to the nitrile ylides, calculations of the orbital coefficients of linear diazoalkanes allowed prediction of the regioisomers of the cycloadducts which would be obtained from reaction with dipolarophiles. The coefficients for the HO and LU molecular orbitals are shown in figure **10**. Electron diffraction studies[63] have shown diazomethane to have a linear-planar form and microwave quadrupole studies[64] have shown the electron density in the species to be highest at the terminal N atom.

C——N——N
0.51 -0.70 0.50 LUMO

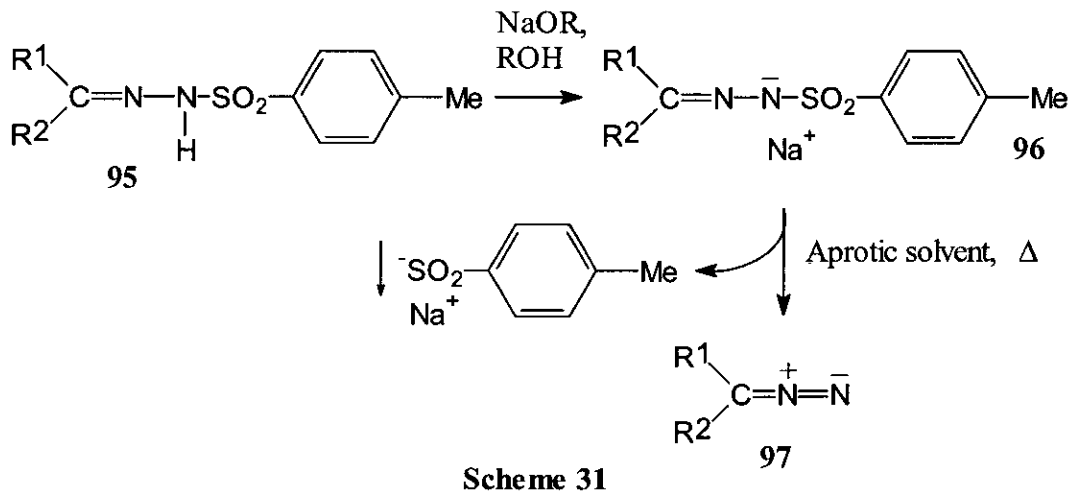
C——N——N
0.78 0.13 -0.61 HOMO

Figure 10

2.2 Generation

Diazoalkanes can be generated in a number of ways. The method which will be used exclusively in this work is the Bamford-Stevens reaction[65] (scheme **31**). This reaction entails synthesis of the tosylhydrazones (**95**), with the desired carbon

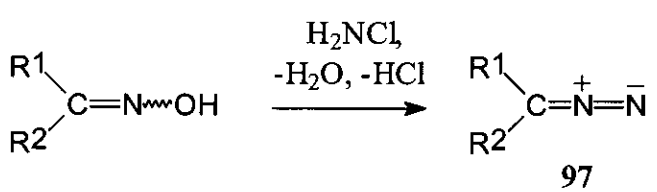
skeleton (R^1, R^2) in place. Treatment of this tosylhydrazone with a sodium alkoxide generates the sodium salt (**96**), which when dried and thermolysed or irradiated in aprotic solvents such as DME, cyclohexane or octane will yield the corresponding diazoalkane (**96**) following extrusion of sodium *p*-toluenesulfinate.



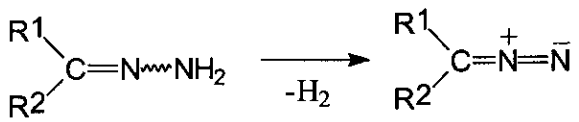
Scheme 31

The first observed reactions of this type yielded olefins and not nitrogen-containing heterocycles. This was due to the propensity of unstabilised diazoalkanes to extrude molecular nitrogen and react as the carbenes, which is an interesting, useful and important reaction pathway in itself. Improvements in the understanding of the reaction and refinements in reaction conditions, however, have allowed reactions to be carried out with retention of nitrogen in the product *via* diazoalkanes generated by this method.

Among the established methods developed and utilised by other workers are the Forster reaction[66,67] (scheme **32**), oxidation of hydrazones[68,69,70] (**98**, scheme **33**), deacylation of *N*-nitrosocarboxamides[71,72] (**99**, scheme **34**) and the route by which the first reported diazoalkane was generated, diazotisation of a primary or secondary amine[73, 74] (**100**, scheme **35**).

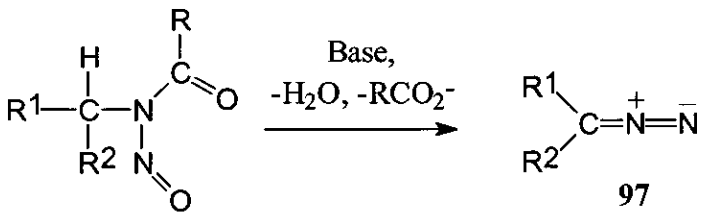


Scheme 32



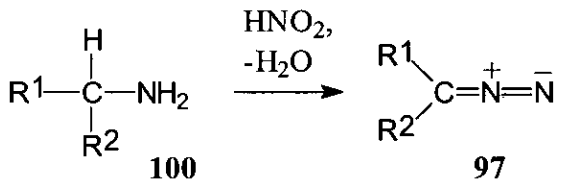
98 97

Scheme 33



99 97

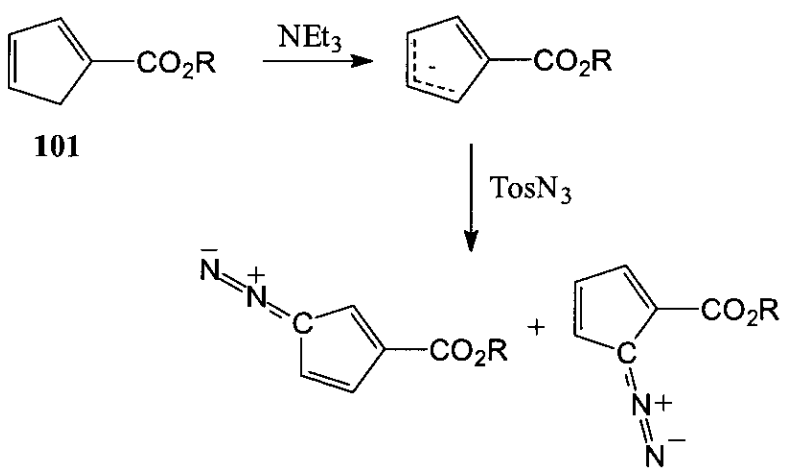
Scheme 34



100 97

Scheme 35

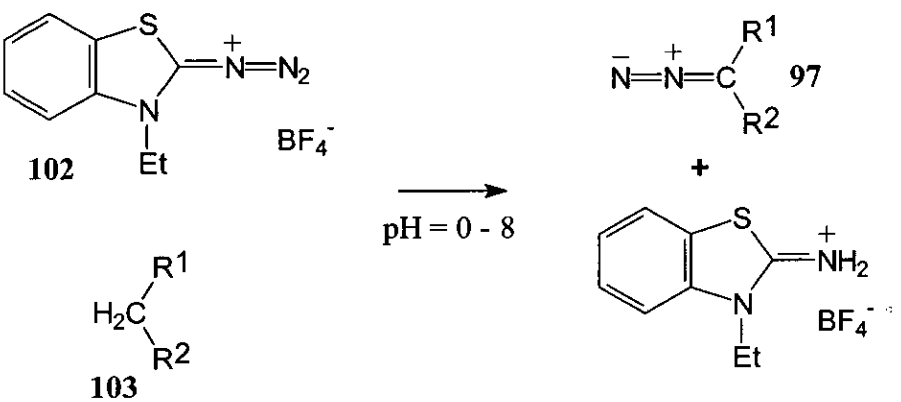
More recently, a route involving transfer of the diazo group from tosyl azide onto activated methylene groups (*e.g.* in compound **101**) has been developed[75] (scheme **36**).



101

Scheme 36

Azidinium salts (**102**) may also be used to provide the diazo group to be transferred[76] (scheme **37**). The necessity for the reaction to be carried out under acidic or neutral conditions means that the methylene group in reactant **103** must be especially active in order to form its anion, and also that the product derived from the generated diazoalkane must be acid-stable. An advantage, however, is that diazoalkanes such as diazonitro- and diazocyanomethanes (*i.e.* R^1 or R^2 = CN, NO_2) can be prepared by this method. Diazo transfer to nitromethanes and methanonitriles from tosyl azide is not possible.



Scheme 37

3.3 Reactions

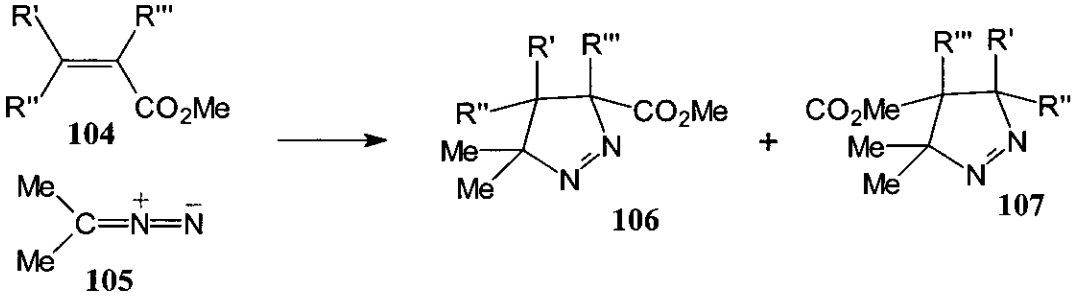
3.3.1 Intermolecular Reactions

The intermolecular reactions of diazoalkanes have been studied extensively in the past, partly due to their ease of generation, with Diazald (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide), a chemical precursor to diazomethane itself, being commercially available. This class of reaction is of such interest as it allows access to a huge variety of nitrogen-containing heterocyclic products, including diazepines, which are important pharmaceutically[77].

The simplest type of intermolecular reaction is the [3+2] cycloaddition between a dipole and a dipolarophile. Examples[78] of this are shown in scheme **38**. This series

of reactions, performed in the late 1960s, shows the complexity and subtlety which even the apparently straightforward combination of simple alkenes (**104**) and diazoalkanes (**105**) involves. The regioselectivity of the cycloaddition was found to be heavily influenced by the substitution pattern about the olefin, with excellent yields of one regioisomer being obtained in some situations and mediocre yields of the other regioisomer being obtained when the substitution pattern about the olefin was changed.

This perturbation of the reaction pathway is explicable by consideration of the frontier molecular orbitals of both the dipole and the dipolarophile, with the predominant product changing as the most favourable MO overlap changes. The most favourable overlap depends upon the relative coefficients at the termini of both participants in the cycloaddition, which alter as substituents are added or removed.



R'	R''	R'''	% 106	% 107
H	Me	Me	92	--
Me	H	Me	92	--
Me	Me	H	0.6	30
Me	Me	Me	--	--

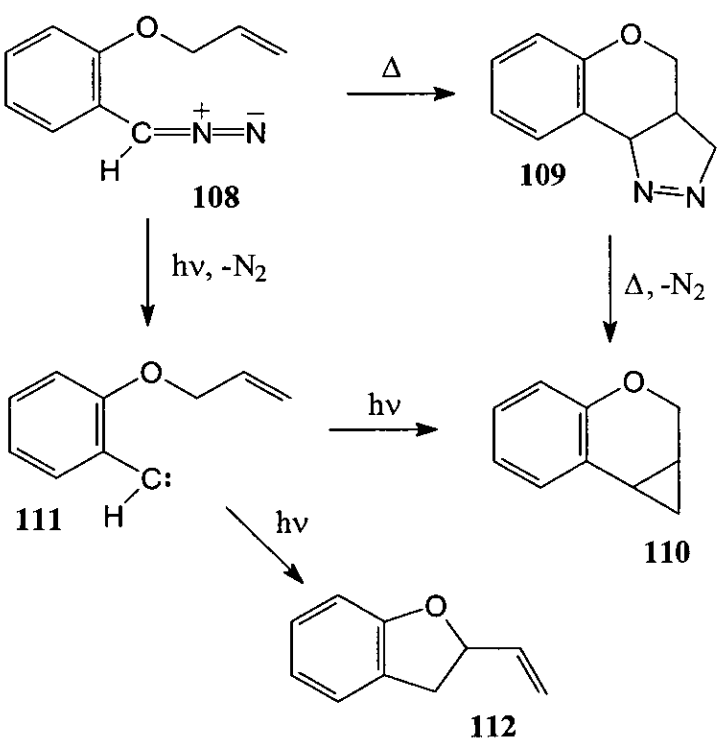
Scheme 38

The most favourable reaction is always that where the largest coefficient of the dipole and of the dipolarophile overlap. The difference between two orientations, however, is often not large and mixtures of products are often obtained.

3.3.2 Intramolecular Reactions

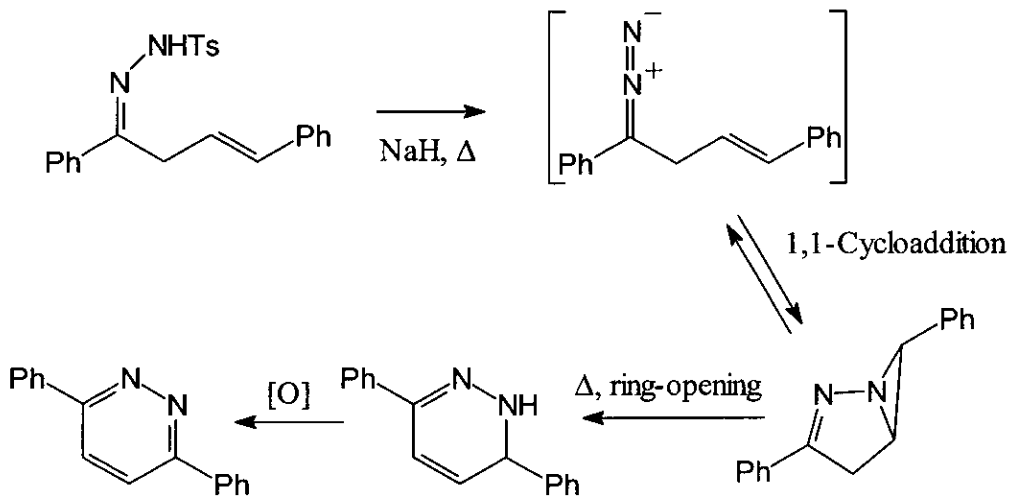
In contrast to the bimolecular cycloaddition reactions of diazoalkanes the intramolecular reactions were relatively neglected until much later. The early example depicted in scheme **39** exhibits some of the characteristic features of diazoalkane chemistry[79, 80].

When heated, the diazoalkane **108** reacts with the olefin in a [3+2] cycloaddition to yield the 1-pyrazoline **109**. Heating this product further resulted in loss of nitrogen and diradical ring-closure to yield **110**. Photolytic treatment of the dipole **108** resulted in two products, neither of which contained nitrogen. Both of these compounds were derived from the carbene obtained from loss of nitrogen from the dipole. The carbene **111** thus generated could react at either the methylene or the olefin of the allyl ether moiety (to give **112** or **110**, respectively), resulting in the product mixture observed.



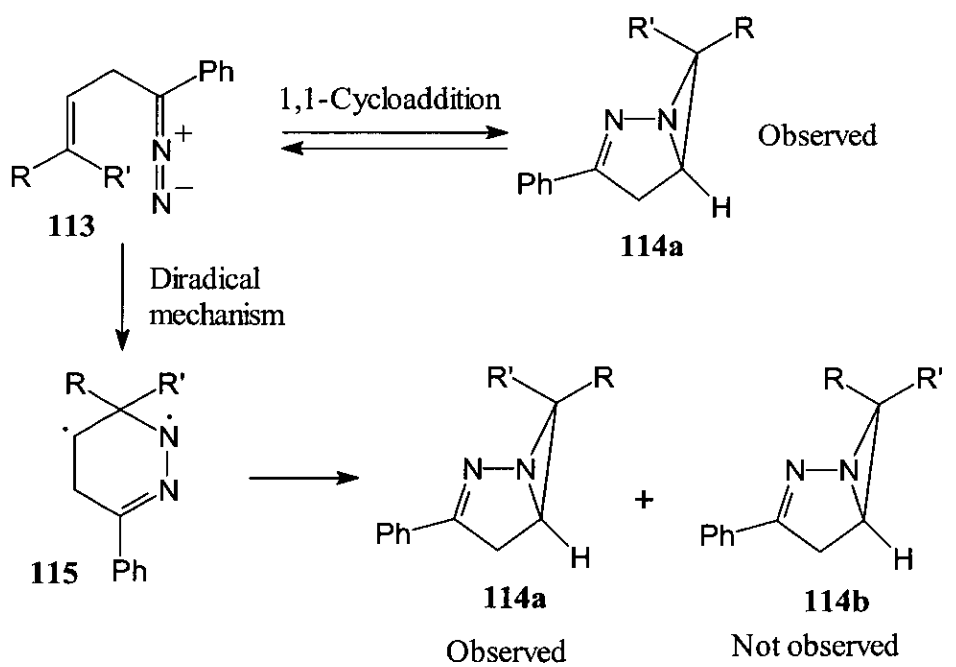
Scheme 39

The first examples of 1,1-cycloadditions of diazoalkanes were reported almost simultaneously in the early 1980s, by both Padwa[81] and Miyashi[82]. The example illustrated in scheme **40** bears strong similarities to the example given in scheme **21**, where the first intramolecular 1,1-cycloaddition of a nitrile ylide is depicted.



Scheme 40

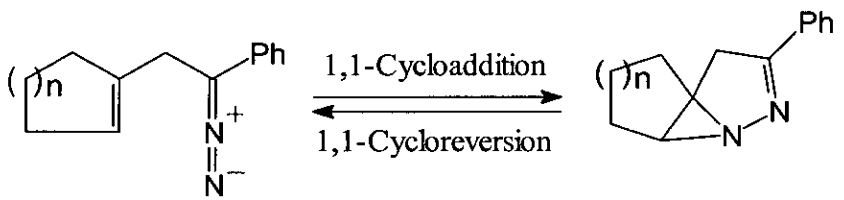
A further similarity between these reactions is that both proceed in a wholly stereospecific manner (scheme **41**), as demonstrated by Miyashi.



Scheme 41

The formation of only the *endo*-isomer of the product (**114a**) from diazoalkane **113** strongly suggested that the reaction proceeded by a stereospecific, concerted 1,1-cycloaddition mechanism[83] rather than a stepwise diradical mechanism, as had been suggested.

The 1,1-cycloaddition of diazoalkanes, however, shows one major difference to the analogous nitrile ylide reaction; the diazoalkane 1,1-cycloaddition has been demonstrated by Miyashi[84] to be reversible by variable-temperature NMR studies (scheme **42**). In the example illustrated in scheme **41** (**113** / **114a**) it was found that the stereochemistry of the alkene in **113** was retained upon 1,1-cycloreversion, *i.e.* R' maintained the *cis* position. This reversibility is obviously an unwelcome complication where the desired product derives from the 1,1-cycloaddition of a diazoalkane, as it is possible that the initial product would revert to the dipole, which could possibly undergo less favourable, but irreversible, cycloadditions to give undesirable products.

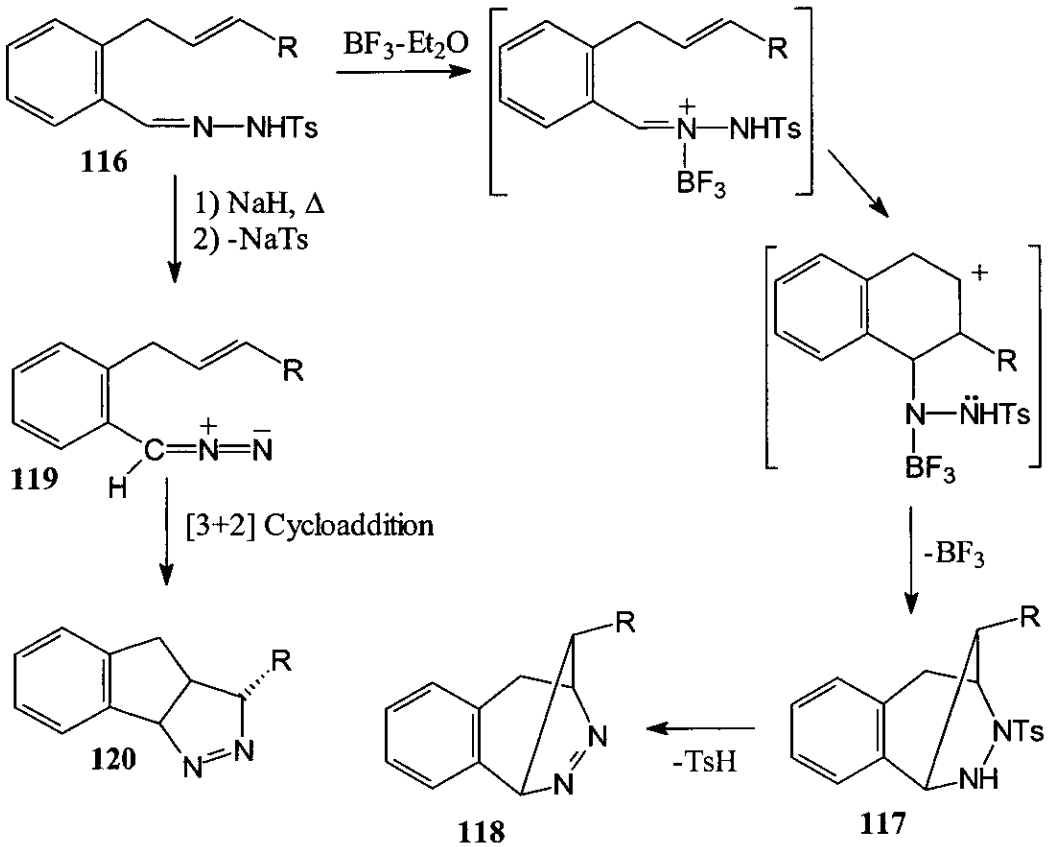


Scheme 42

The reaction conditions under which a dipole is generated and reacted can also have a profound effect on the mechanistic course which the reaction will take.

Treatment of the tosylhydrazone **116** with the Lewis acid boron trifluoride was found to have an interesting effect[85, 86] (scheme **43**). Complexation of boron with the imino nitrogen of **116** generates a cation at this nitrogen atom which is open to attack from the alkene. Ring-closure and loss of BF_3 generates the intermediate **117** which can expel tosic acid to yield the observed product **118**.

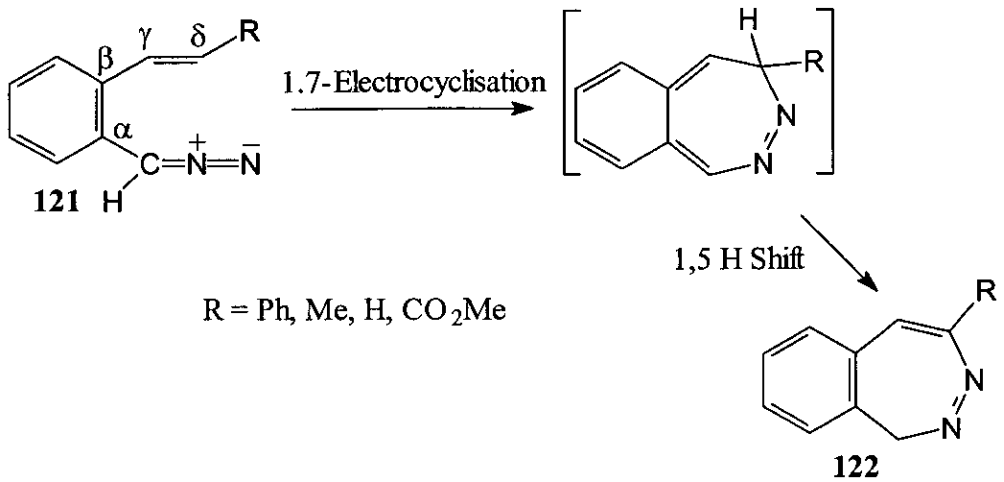
The conventional Bamford-Stevens method of diazoalkane generation, in the absence of Lewis acids, yielded the tetrahydronaphtho[1,2-c]pyrazole **120**.



Scheme 43

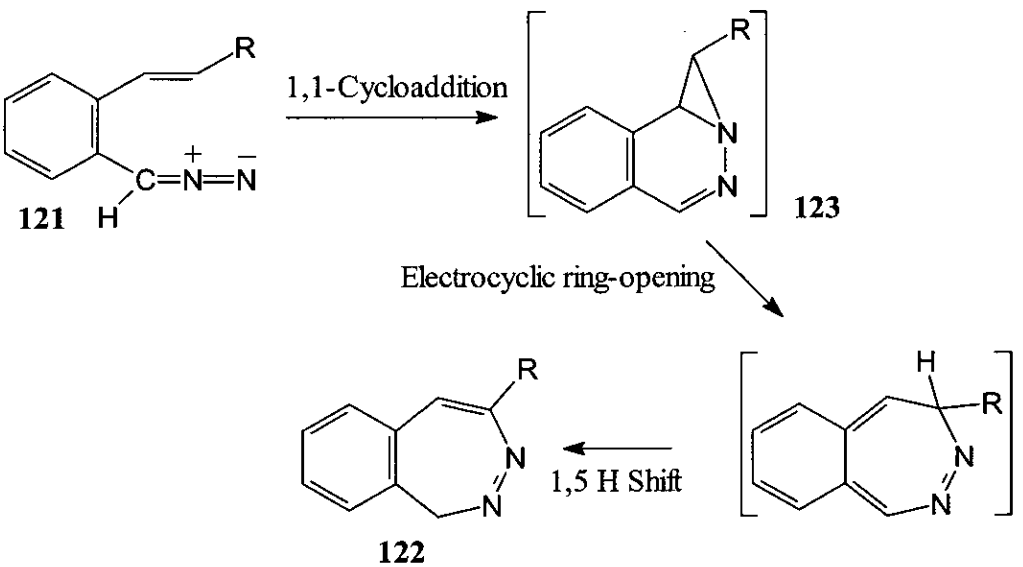
The cycloadditive characteristics of diazoalkanes which are in conjugation with diene systems have been studied extensively by Sharp and co-workers[87, 88]. The reactions observed to occur varied enormously, depending upon a number of factors.

In cases where the α,β unsaturation is aromatic and the γ,δ unsaturation is olefinic, two broad reaction pathways appear to be operational. Which of these two pathways is followed is governed by the substituents at the δ-carbon of the diene. Where the *cis* substituent is a hydrogen atom, then the diazoalkanes (**121**) undergo 1.7-electrocyclisation to yield the 1*H*-2,3-benzodiazepines **122** (scheme **44**).



Scheme 44

It could be easily envisaged that, rather than the 1.7-electrocyclisation, the reaction actually proceeds *via* a 1,1-cycloaddition of diazolkane **121,** in a manner analogous to the diene-conjugated nitrile ylides (scheme **45**).

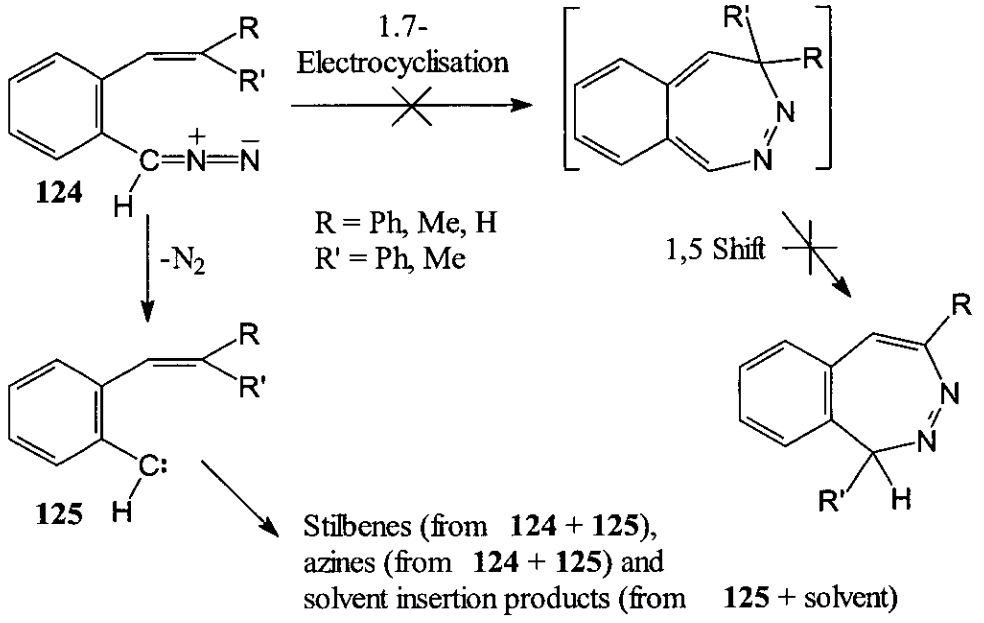


Scheme 45

The proposed intermediates (*e.g.* **123**), however, have not been isolated or detected to date.

The second of the two pathways mentioned is followed when the *cis* substituent at the δ-carbon of the diene is any substituent other than a hydrogen atom. In these cases the 1.7-electrocyclisation (or 1,1-cycloaddition) appears to be completely

precluded and the reactions proceed *via* loss of N_2 from the diazoalkane moiety of **124** to give the carbenes **125**. These can react in a number of ways, depending upon reaction conditions used.



Scheme 46

The rationalisation for these observations was provided by Sharp[89]. The helical transition state depicted in figure **11** was postulated. If this intermediate was involved, then in cases where the *cis*-substituent on the diene was a hydrogen atom the steric interaction between the terminal nitrogen atom of the dipole and that substituent would be minimised and the 1.7-electrocyclisation would proceed. This minimisation of steric interaction is important as the conjugation between the dipole and the dipolarophile will be undisturbed due to the small amount of distortion required of the dipole to accommodate the small hydrogen atom into the postulated transition form.

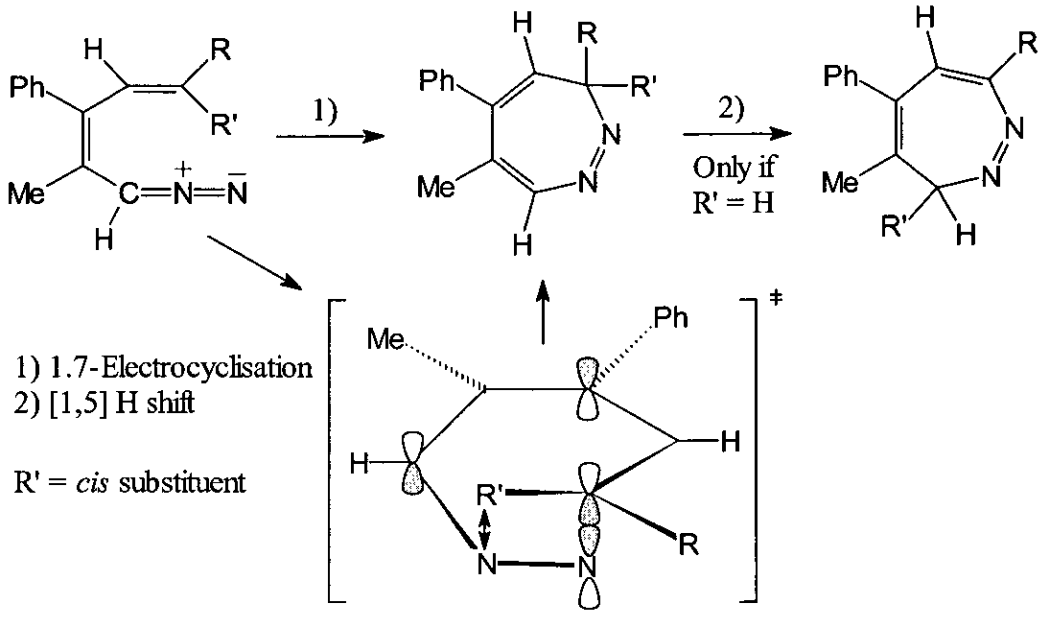
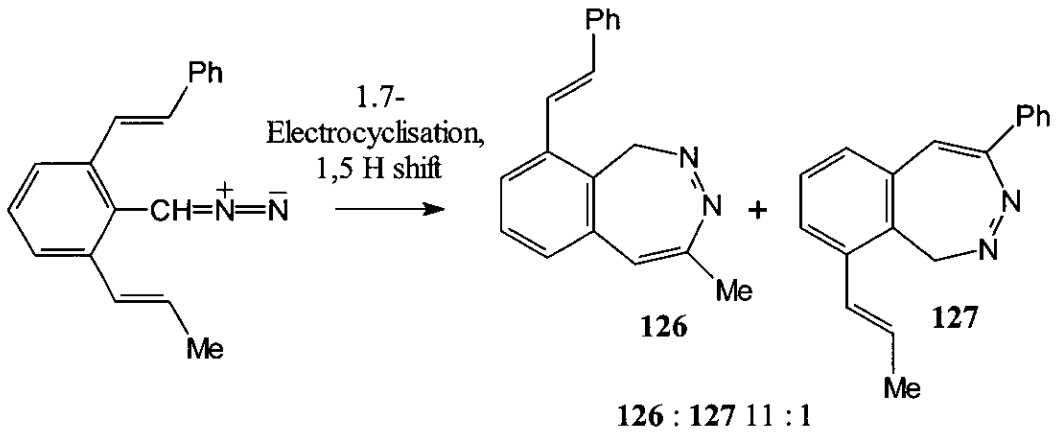


Figure 11

Where this *cis*-substituent (R') was larger than H then the steric interaction (indicated by an arrow in figure **11**) between this group and the diazo group would be increased. A consequence of this would be that 1.7-electrocyclisation would be disfavoured with respect to reactions *via* the carbene following loss of N_2. This can be attributed to loss of conjugation through the system due to the large amount of distortion required of the dipole to accommodate a bulky *cis*-substituent (R'). Comparison should be made with the example given later (in scheme **78**) where conjugation between a diazoalkane and an intramolecular dipolarophile is compromised by different means. Similar results were obtained where the α,β unsaturation was part of a thiophene ring rather than a benzene ring. These results will be touched upon in section 5.5.

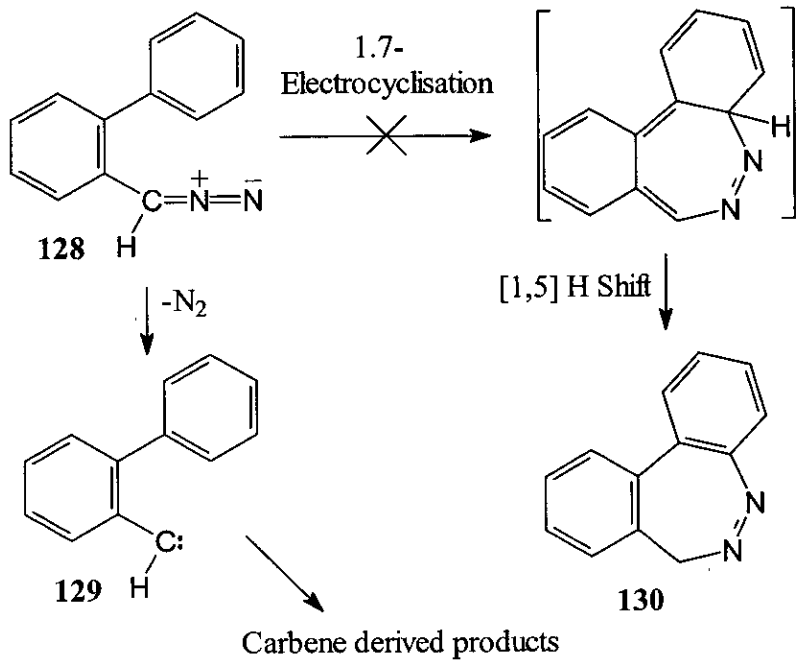
An illuminating example of the influence that substituents on the olefin can exert on their reactions with dipoles was provided by work carried out by Sharp's group[90]. Where there are two possible non-equivalent dipolarophiles for the internal dipole then the ratio of products derived from the 1.7-electrocyclisation reaction will be dependent on the ease of cyclisation onto each of these alkenes. The example depicted in scheme **47** demonstrates that an alkyl group hugely accelerates reaction

with the alkene bearing that substituent. Where this propenyl system is not present cyclisation onto an olefin bearing a phenyl ring occurs smoothly.



Scheme 47

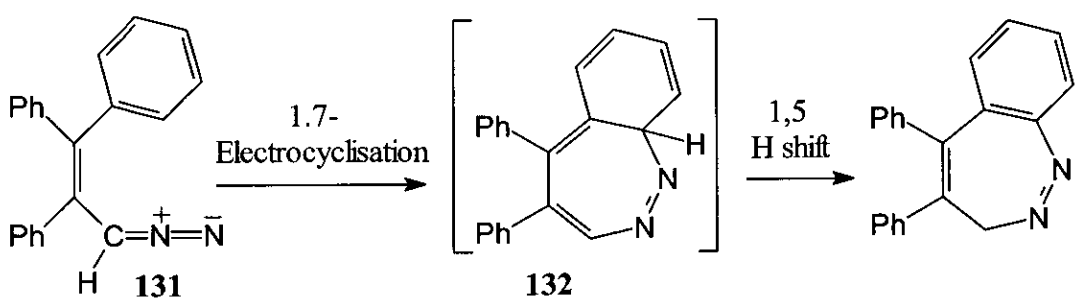
Examples of diene-conjugated diazoalkanes where both the α,β and δ,γ unsaturations are of aromatic nature have also been studied. In these cases it appears that the activation energy for the 1.7-electrocyclisation (and the 1,1-cycloaddition) is too high for the reaction to proceed, with interruption of aromaticity in the two benzene rings proving too high a price to pay for formation of **130**. In the absence of a facile dipolar reaction, nitrogen is lost from the dipole **128** and reaction proceeds *via* the carbene **129** (scheme **48**). Generation and reaction of this diazoalkane by photolytic means also results in the formation of carbene-derived products exclusively[91, 92]. This behaviour is in sharp contrast to reactions of analogous nitrile ylides (scheme **29**).



Scheme 48

These facts suggest either that E_{act} for the analogous nitrile ylide 1.7-electrocyclisations is lower than for the diazoalkane reaction or, more likely, that E_{act} for nitrogen loss from diazoalkanes of the type **128** is lower than that for 1.7-electrocyclisation in these systems.

Interestingly, where the α,β unsaturation is olefinic and the γ,δ unsaturation is aromatic (*e.g.* diazoalkane **131**), electrocyclic reactions between the dipole and the γ,δ bond have been shown to be feasible[93] (scheme **49**). This could be due to the fact that only one aromatic system has to be disrupted to form the intermediate **132**, whereas formation of **130** would require two benzene rings temporarily to lose their aromaticity.



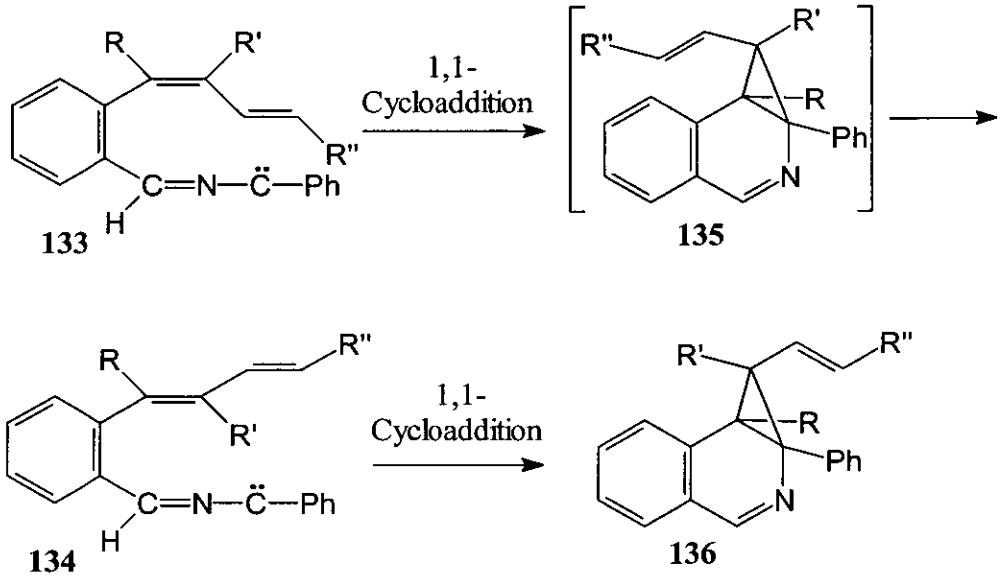
Scheme 49

4 Triene-Conjugated 1,3-Dipoles

4.1 Intramolecular Reactions of Triene-Conjugated Nitrile Ylides

As stated previously (section **2.3.2**), nitrile ylides can undergo intramolecular cycloaddition reactions to generate new heterocycles. Where the dipole is in conjugation with a triene system a number of cyclisation / cycloaddition pathways are open, with the relative favourabilities of these being dictated by a number of factors. Among these factors are the nature of the unsaturation, *i.e.* whether the dipolarophiles are aromatic or olefinic, and also the nature and position of any substituents on either the dipole or the dipolarophile.

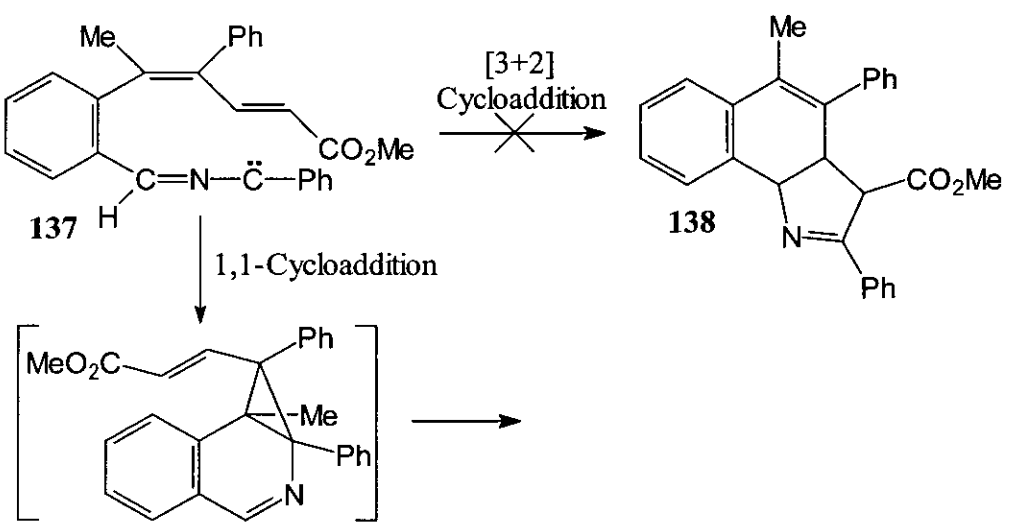
An interesting finding was made when the work on cycloaddition reactions of diene-conjugated nitrile ylides carried out by Sharp and co-workers was extended to triene-conjugated nitrile ylides[94].



Scheme 50

Isomers **133** and **134** were both observed to undergo initial 1,1-cycloadditions, but only in the case of **134** was the expected product (**136**) isolable. Even when the ε,ζ-olefin was strongly activated toward cycloadditions (R'' = CO_2Me) the 1,1-cycloaddition with the γ,δ double bond was the exclusive reaction pathway of the

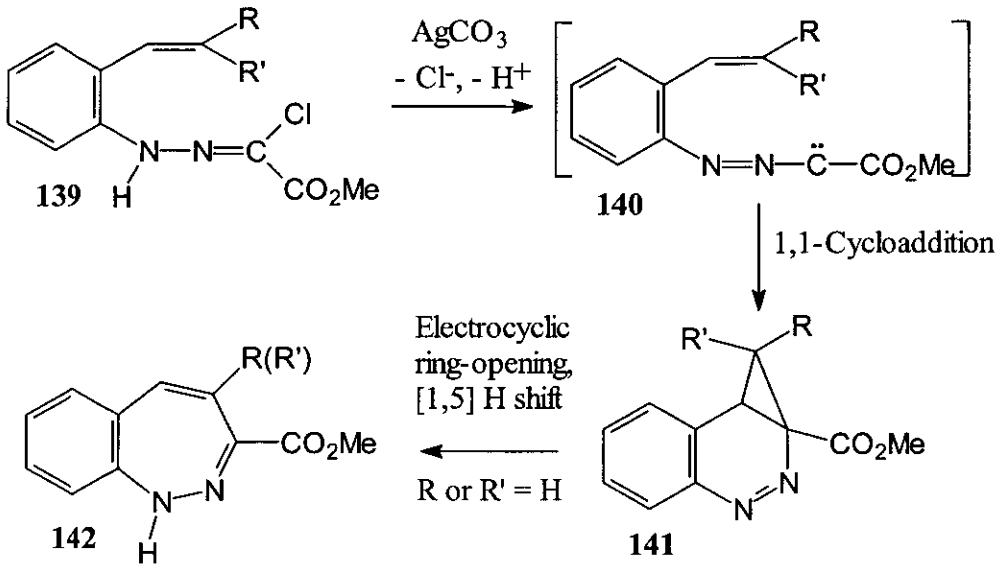
dipole and this analogue did *not* undergo [3+2] cycloaddition to give compound **138** (scheme **51**). The [3+2] cycloaddition had been expected[95] to occur due to the presence of the strongly activating ester group on the dipolarophile. In the case of analogues of the type **133** and **137** it was found that the primary cycloaddition product rearranged spontaneously and the product of this subsequent rearrangement was instead isolated in good yield. The processes involved here will be covered in more detail in the next section.



Scheme 51

4.2.1 Thermal Rearrangements of Cyclopropa[*c*]isoquinolines

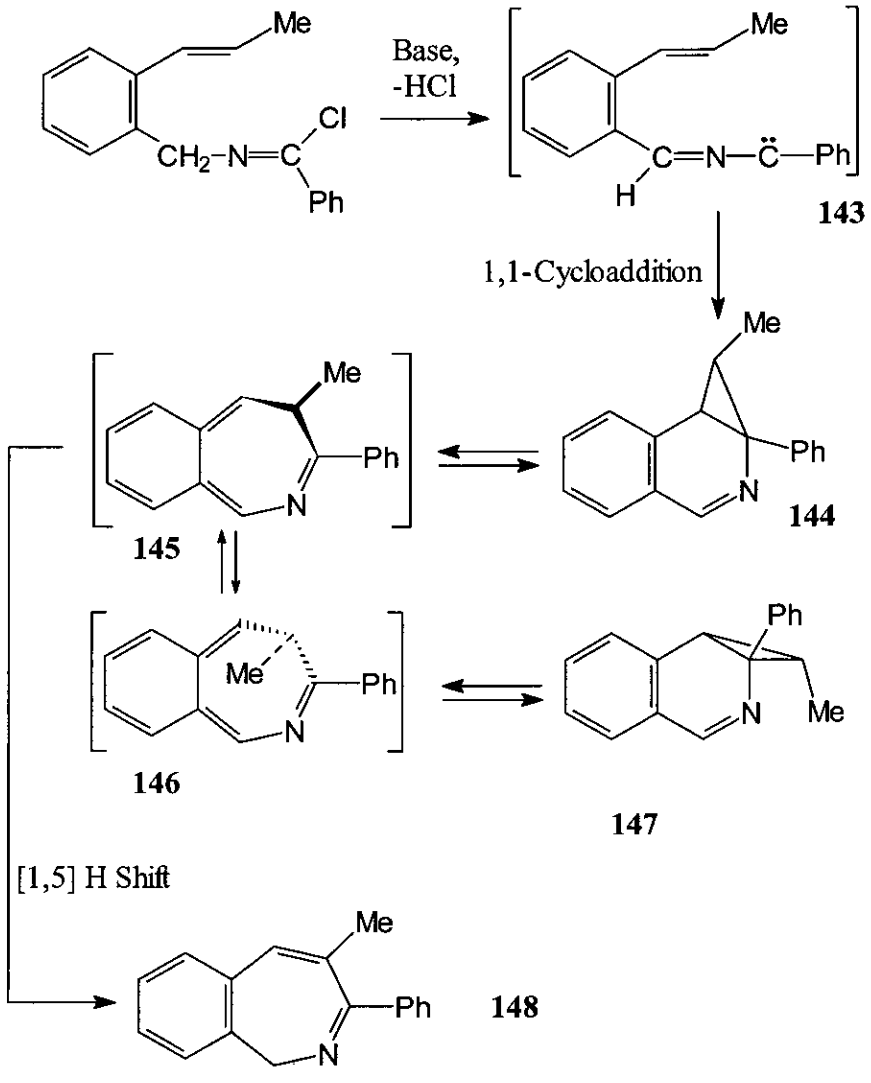
As previously described, cyclopropa[*c*]isoquinolines, with the same skeletal structure as *e.g.* **134** and analogues such as the cyclopropa[*c*]cinnolines[96,97,98] **141,** have been generated in the past (scheme **52**). The example shown where a nitrile imine **140** is cyclised to give an isolable cyclopropa[*c*]cinnoline **141** which rearranges to yield a 1*H*-1,2-benzodiazepine (**142**) illustrates one reaction pathway open to cyclopropa[*c*]isoquinolines. This example demonstrates the retention of stereochemistry in generating these cyclopropyl compounds, as a consequence of the concerted mechanism of 1,1-cycloadditions.



Scheme 52

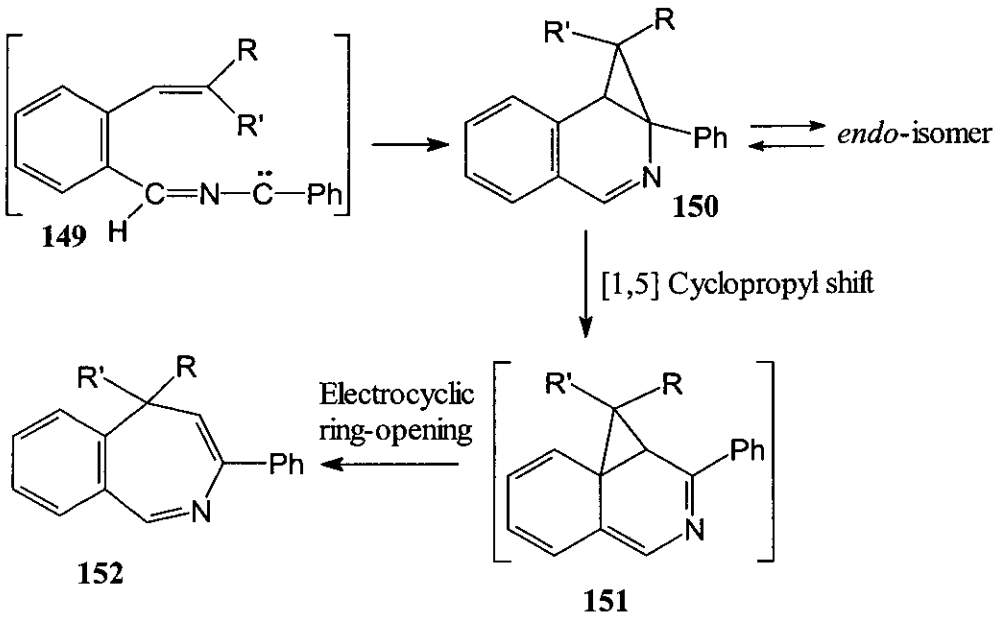
The example illustrated in scheme **53** demonstrates the isomerisation between *exo*- and *endo*-forms of cyclopropa[*c*]cinnolines and isoquinolines. This has been found to be crucial to the reactivity which some examples of these compounds exhibit.

The *exo*-cyclopropa[*c*]isoquinoline **144**, derived from the *trans*-substituted diene-conjugated nitrile ylide **143**, was isolated by Sharp[99]. It was found to undergo isomerisation to the *endo*-isomer **147** upon heating, and also to undergo a slower conversion to the 1*H*-2-benzazepine **148**. Both of these products derive from the non-aromatic intermediates **145** and **146**, with ring-inversion and electrocyclic ring closure of **146** forming **147** reversibly and an irreversible [1,5] H shift of **145** yielding the azepine **148**. The slower rate of the H-shift allowed observation of the *endo*-isomer **147**, which did not derive directly from the 1,1-cycloaddition of **143**.



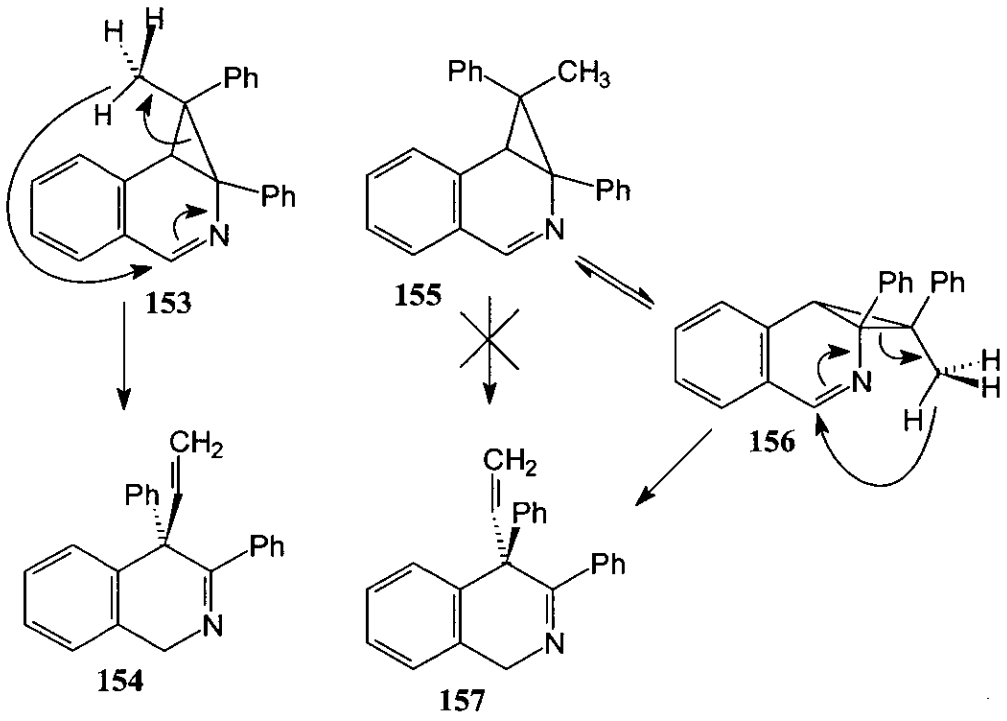
Scheme 53

The final step in this pathway is not possible in cases where the δ-position of the diene carries two non-H substituents (scheme **54**). The reaction then follows an alternative mechanism involving a [1,5] walk of the cyclopropyl ring in **150** to give the intermediate **151,** followed by a re-aromatising electrocyclic ring-opening. This process yields the 5*H*-2-benzazepines **152.**



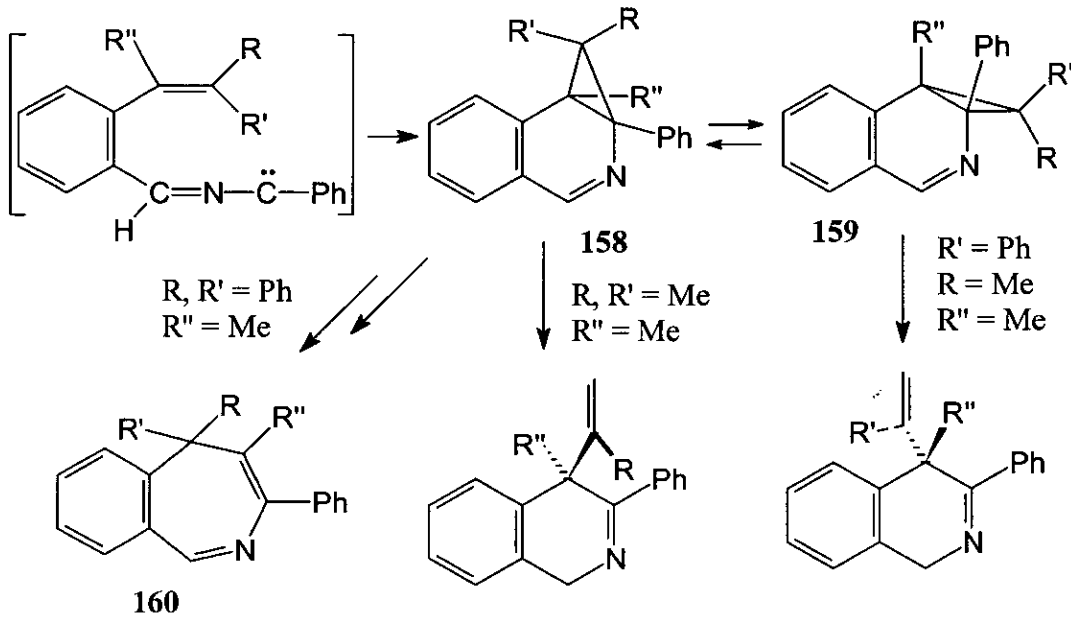
Scheme 54

A further alternative pathway was found when analogues of the nitrile ylides described above with methyl substituents at the γ-position of the diene were generated (scheme **55**). In these cases the final step was again a [1,5] H shift, but this time the hydrogen atom migrated from the methyl group in the *endo*-position of the *exo*-cyclopropa[*c*]isoquinolines **153**. If there was a phenyl group at this position and the methyl group was in the *exo*-position (*e.g.* compound **155**) then the cyclopropa[*c*]isoquinoline underwent the *exo-endo* ring-flipping to give structure **155** to bring the methyl group at C-1 into the correct orientation for the [1,5]-H shift to occur. In both cases the products were 4-alkenyl-1*H*-isoquinolines **154** or **157**.



Scheme 55

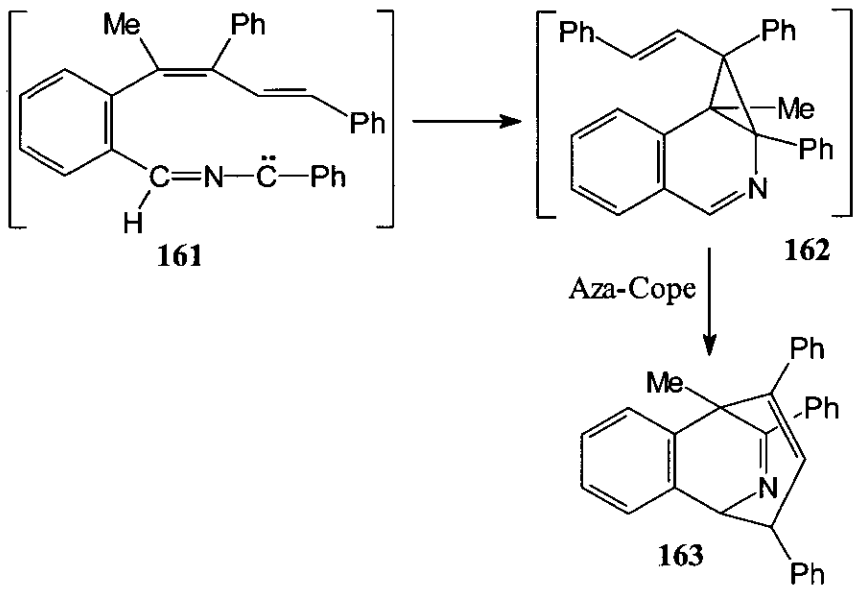
When the cyclopropa[*c*]isoquinolines (**158** / **159**) had no hydrogen or methyl groups at C-1, but two phenyl rings, then the hydrogen shifts became impossible and the rearrangement mechanism reverted to the [1,5] cyclopropyl walk outlined in scheme **56**, yielding 3,5,5-triphenyl-4-methyl-2-benzazepine **160.** This process appeared to be less favourable than either of the [1,5] H-shift mechanisms and the product degraded readily.



Scheme 56

4.2.2 Thermal Rearrangements of 1-Alkenyl Cyclopropa[*c*]isoquinolines

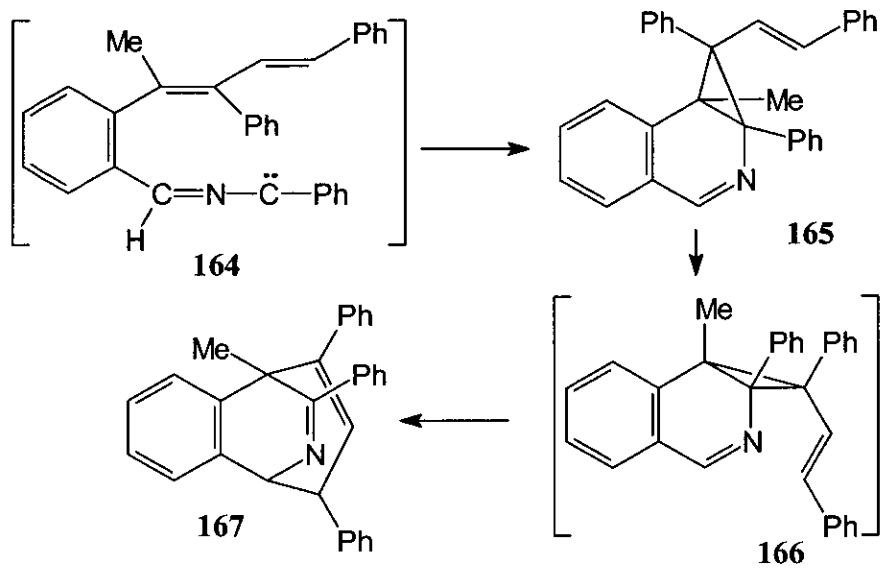
When the conjugated system was extended to a triene in which the γ,δ;ε,ζ unsaturations were olefinic some new rearrangement processes were discovered. Sharp found that when the nitrile ylide **161,** where the triene system is *cis* about the γ,δ olefin, was generated then the observed product was not the expected 1-alkenyl *endo*-cyclopropa[*c*]isoquinoline **162**, but rather the bridged isoquinoline **163**. This was postulated to derive from **162**, formed initially from the intramolecular 1,1-cycloaddition of **161** (scheme **57**), *via* an intramolecular aza-Cope rearrangement.



Scheme 57

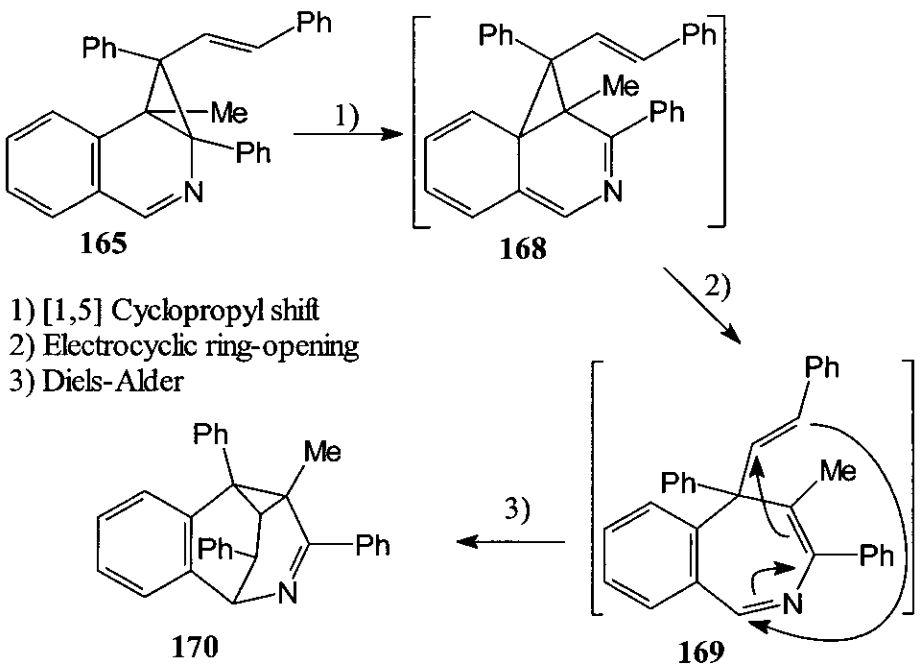
Verification of this theory was obtained when the nitrile ylide **164**, where the triene has *trans* geometry about the γ,δ olefin, was generated. 1,1-Cycloaddition of this dipole yielded the isolable *exo*-cyclopropa[*c*]isoquinoline **165**, where the residual ε,ζ olefin, which did not participate in the 1,1-cycloaddition, occupied the *exo* position at C-1. In this position it is too remote from the imine moiety of the isoquinoline ring to undergo the aza-Cope rearrangement. Consequently, the *exo*-isomer of the 1-alkenyl cyclopropa[*c*]isoquinoline **165** is stable while the *endo*-cyclopropa[*c*]isoquinoline **162** undergoes the intramolecular aza-Cope reaction spontaneously at room temperature.

As previously stated, an *exo-endo* isomerisation of cyclopropa[*c*]isoquinolines has been demonstrated. Accordingly, when compound **165** was heated it was found to isomerise to the *endo*-isomer which then underwent the aza-Cope rearrangement to yield the bridged isoquinoline **167** (scheme **58**).



Scheme 58

However the reaction also gave, as the major product, the babaralene **170**.



Scheme 59

Compound **170** was proposed to form *via* a mechanism analogous to that outlined in section **4.2** (scheme **54**). The mechanism proposed involved a [1,5] shift rearrangement, analogous to **150**? **152**, giving the 5-alkenyl-5*H*-2-benzazepine **169**.

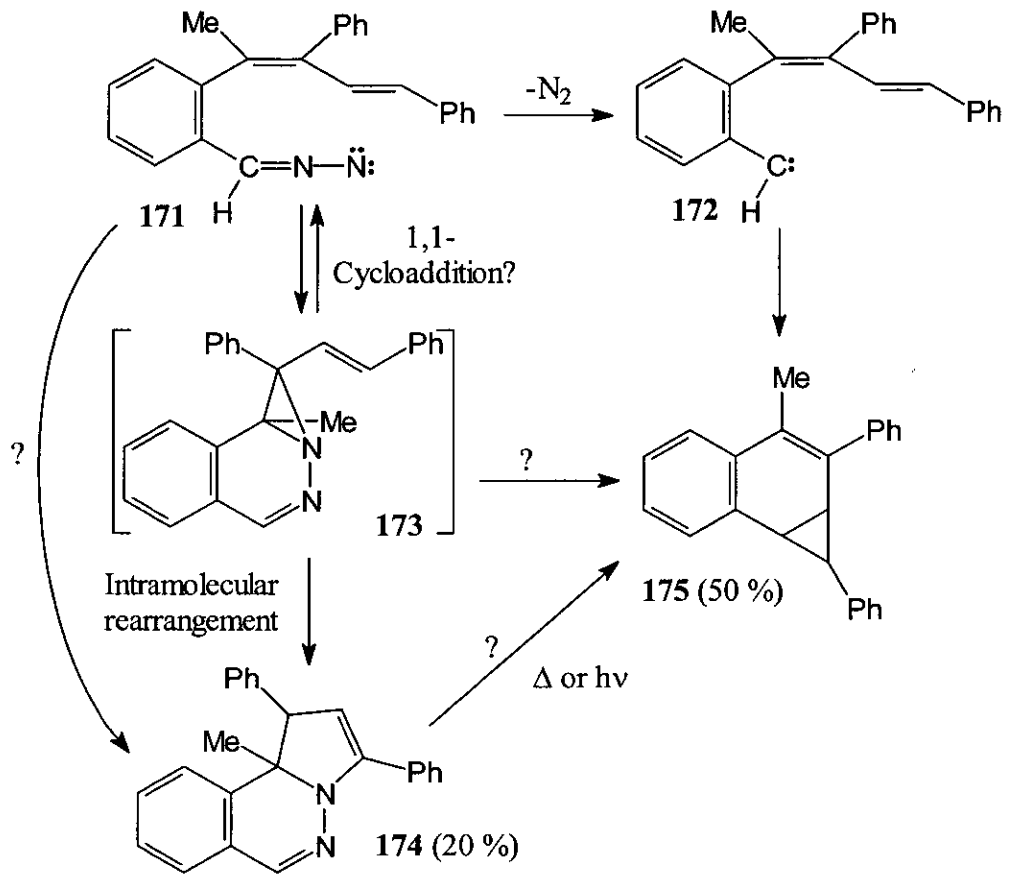
This is apparently unstable under the reaction conditions and undergoes an intramolecular Diels-Alder reaction to yield **170**.

4.3 Intramolecular Reactions of Triene-Conjugated Diazoalkanes

An investigation by Sharp and co-workers showed that triene-conjugated diazoalkanes undergo interesting cyclisation and rearrangement processes. This work was further complicated, relative to the study of analogous triene-conjugated nitrile ylides (also by Sharp), by the propensity of diazoalkanes to decompose with loss of N_2 and to then react as carbenes (scheme **60**). In these cases it can become difficult to ascertain whether a particular product is derived from loss of N_2 from the dipole or from loss of N_2 from an initial cyclisation product. Also, the reversibility of diazoalkane 1,1-cycloadditions can lead to added mechanistic complications.

The rationale behind the interest in compounds such as this is that diazoalkanes possess a nitrenoid canonical representation (*e.g.* **171**), which is believed to be capable of undergoing intramolecular 1,1-cycloadditions analogous to those of nitrile ylides.

When the *cis* triene-conjugated diazoalkane **171** was generated a mechanistic balance was observed and carbene-derived cyclopropa[*a*]naphthalene **175**, from intramolecular reaction between the carbene moiety and the ε,ζ olefin (scheme **60**), was recovered as the major product.



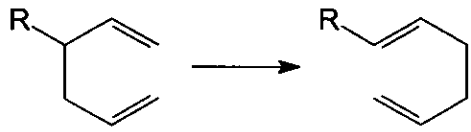
Scheme 60

The rationalisations for this observation were that either N_2 loss from the *cis* triene-conjugated diazoalkane **171** is sterically accelerated, or that the 1,1-cycloaddition of the diazoalkane does occur but the intermediate (**173**) cycloreverts back to the dipole before it can rearrange to a stable product or intermediate. This cycle could repeat indefinitely in theory, but gradual loss of N_2 from the diazoalkane would cause irreversible leakage into the carbene mechanism, which would yield the observed major product.

5 Mechanistic Points

5.1 Cope, Hetero-Cope and Diels-Alder Rearrangements

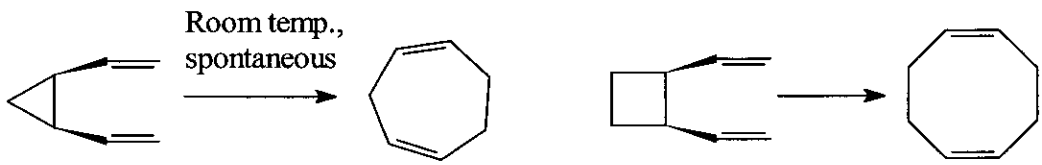
Cope rearrangements occur in 1,5-dienes *via* [3,3] sigmatropic shifts (scheme **61**).



176 **177**

Scheme 61

This reaction can occur in all 1,5-dienes, but is only observable where there is unsymmetrical substitution about the diene (*i.e.* R in **176** and **177** ? H, ∴**176** ? **177**). The 1,5-diene can also form part of a ring-system [100] (scheme **62**), with impetus for the reaction being provided by alleviation of the strain in the small rings of the reactants **178** and **179**.



178 **179**

Scheme 62

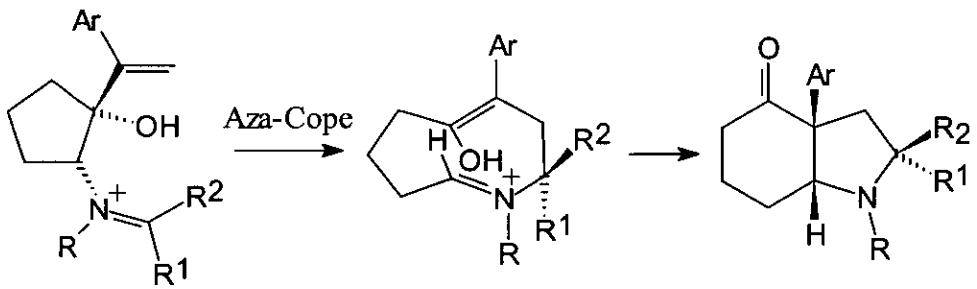
The double bonds which participate in Cope rearrangements need not be olefinic; imino bonds have also been shown to undergo hetero-Cope rearrangements when included in suitable precursor skeletons[101,102] (scheme **63**).

X = N, CH
X = N

X = N, CH
X = N

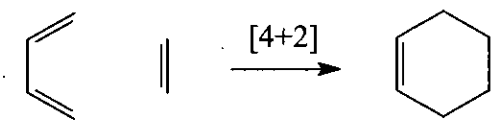
Scheme 63

The example illustrated in scheme **64** shows the complexity which can be conferred on products by utilising this type of reaction, with the well-defined stereochemistry being a useful consequence when the reactions are well planned[103].



Scheme 64

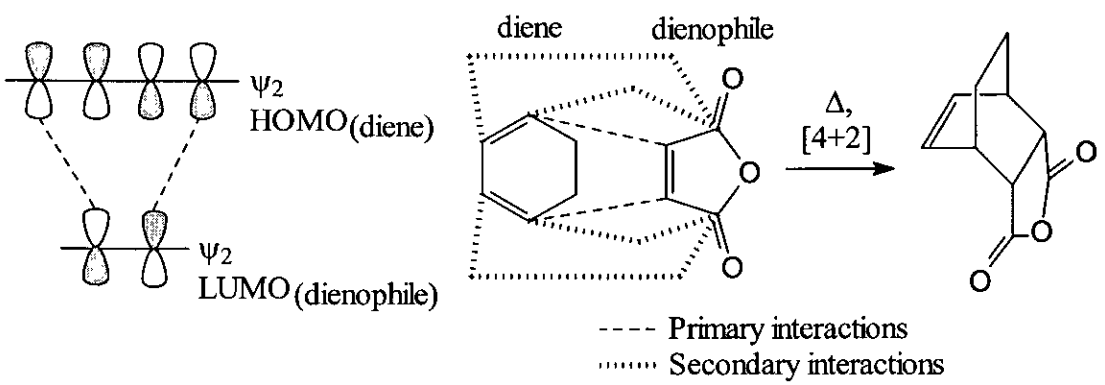
The Diels-Alder reaction is a type of cycloaddition, where a diene (**180**) and a dienophile (**181**) combine in a concerted manner to yield cyclic products (scheme **65**).



180 **181**

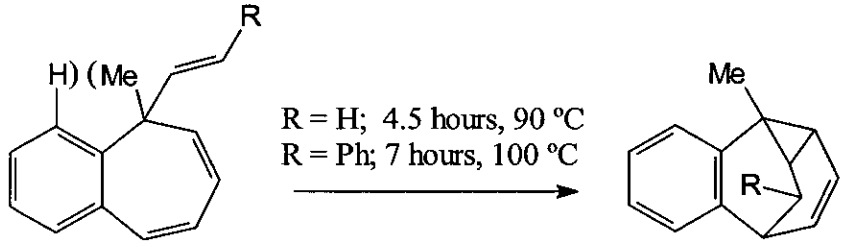
Scheme 65

These reactions are thermally promoted, depending upon orbital symmetry requirements (scheme **66**) and the diene must be able to adopt the *cis*-conformation in order that the termini may both react with the dienophile. The preference for formation of the *endo*-adduct is ascribed to secondary interactions between molecular orbitals of both of the participants, but which are not directly involved in the reaction. These are less important than the primary interactions which lead to the formation of bonds, but significant enough to influence the favoured isomer.



Scheme 66

Battye and Jones[104] reported intramolecular Diels-Alder reactions in systems of the type **182**, where the diene forms part of the cycloheptatriene ring (and so is necessarily in the required *cis*-conformation) and the dienophile was vinyl (**182**) or 2-phenylethenyl (**184**).



R = H; **182**
R = Ph; **184**

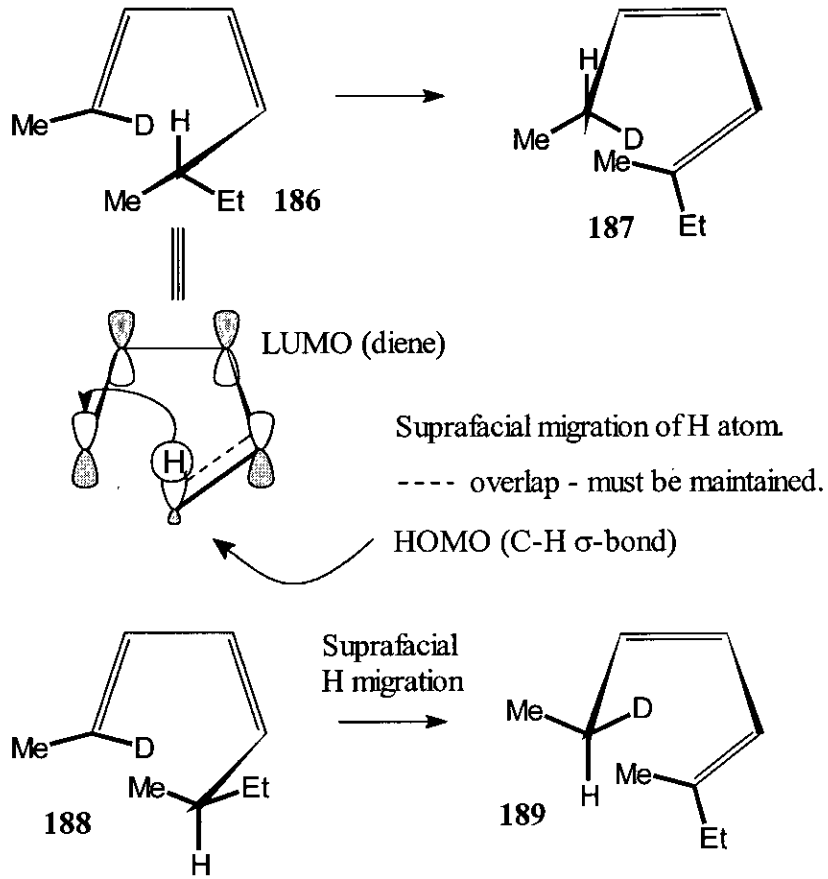
R = H; **183**
R = Ph; **185**

Scheme 67

The relative ease with which this reaction proceeded was attributed to destabilisation of the compounds **182** and **184** by a peri-interaction between the methyl group and the proximate hydrogen atom on the adjacent benzene ring. The effects of this interaction are lessened in the products **183** and **185**, which must be lower in energy than the reactants, even though a strained cyclopropyl ring has been formed in the course of the reaction.

5.2 Sigmatropic Shifts

A sigmatropic rearrangement is a process whereby a σ-bond (*i.e.* a substituent) shifts across a conjugated system to adopt a new position on the π-framework of a molecule[105]. Scheme **68** illustrates a simple example.

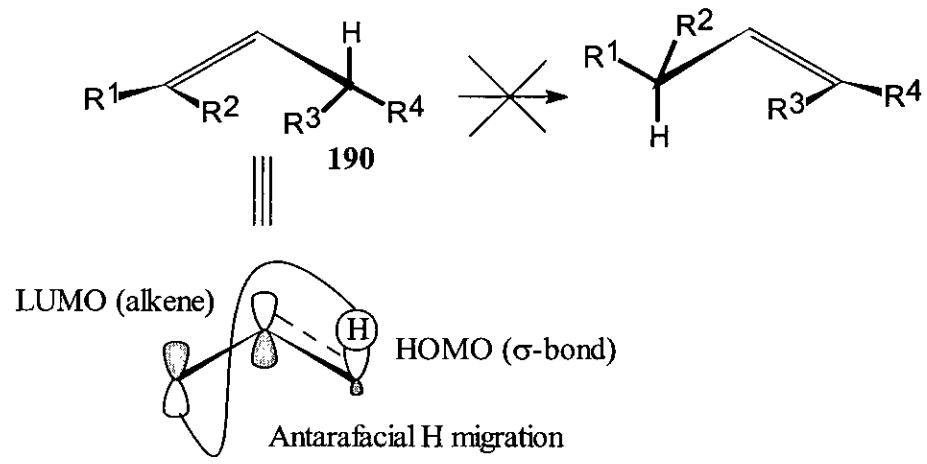


Scheme 68

These processes can be rationalised by consideration of orbital symmetry[106], with a [1,5] sigmatropic shift of H in the diene **186** occurring in a suprafacial manner to give **187** stereoselectively. This is because the HOMO of the C-H bond and the diene LUMO lobe at the destination carbon atom are in phase and thus on the same face of the molecule. In a similar manner, the pentadiene **188** undergoes sigmatropic [1,5] H shift to yield the pentadiene **189**, again stereospecifically.

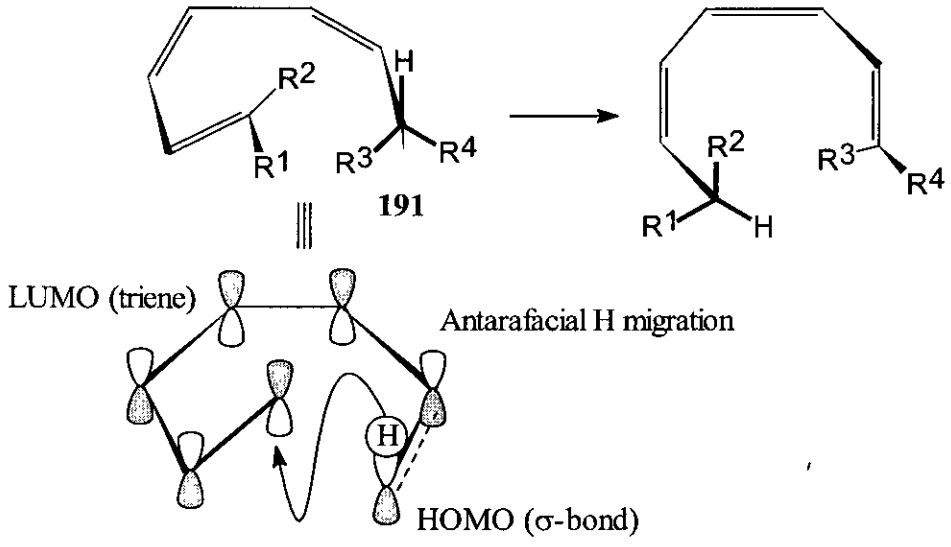
Where there is a propenyl system (*i.e.* **190**), rather than pentadienyl, the [1,3] sigmatropic shift is allowed but will not occur as the origination and destination atoms of the migrating H atom are out of phase. An antarafacial migration of the hydrogen atom, to the opposite face of the molecule is thus required. The propenyl system has limited scope for contortion and cannot arrange itself to maintain the

alkene overlap as well as to form the new overlap and the reaction is unable to proceed.



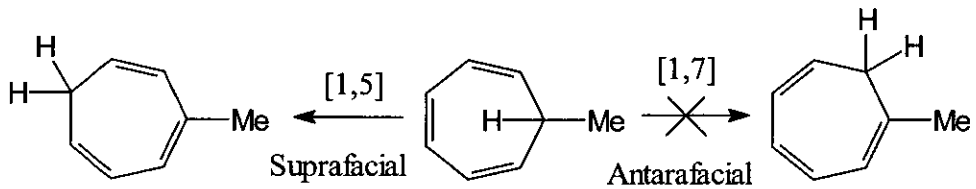
Scheme 69

In the heptatrienyl system **191**, however, the skeleton has sufficient flexibility to allow both overlaps to be made simultaneously. The hydrogen atom can thus undergo antarafacial migration across the molecule and the [1,7] sigmatropic migration is allowed and feasible (scheme **70**). This is a similar situation to that illustrated in figure **11**, the proposed helical transition state implicated in the [1,7] electrocyclisations of conjugated diazoalkanes.



Scheme 70

Evidence for antarafacial migrations in heptatrienyl systems is provided by the behaviour of the cycloheptatrienyl systems (**192**), where the closed ring is unable to adopt the helical configuration required for antarafacial migrations. Accordingly, it does not undergo [1,7] sigmatropic shifts (*i.e.* **193** is not formed), but rather [1,5] sigmatropic shifts occur, suprafacially, to yield **194**.



194 **192** **193**

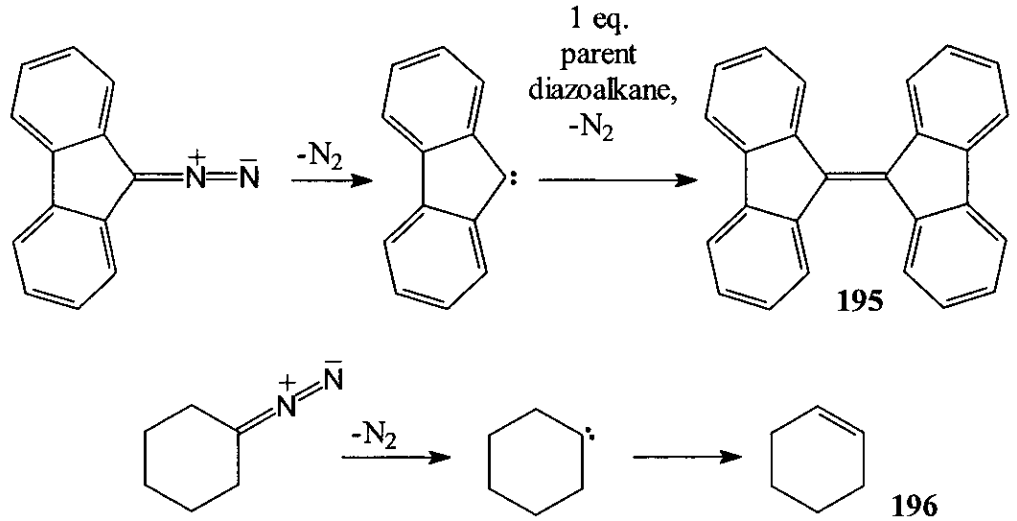
Scheme 71

5.3 Carbenes

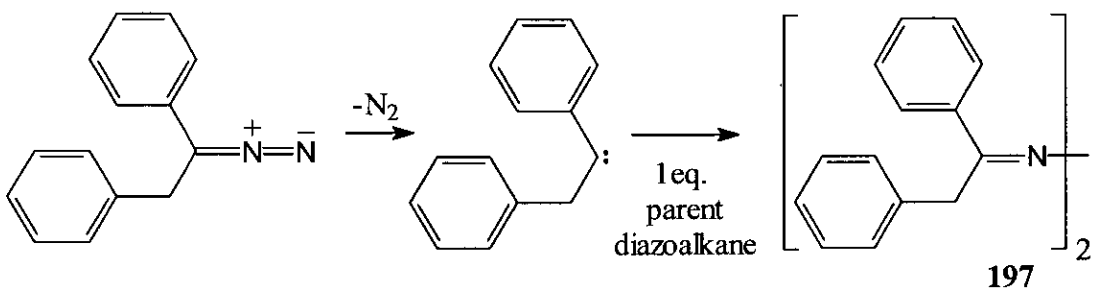
Carbenes are neutral, divalent carbon species with two non-bonding electrons, making them a highly reactive and short-lived species[107]. They are commonly encountered in diazoalkane chemistry where decomposition of the dipole by loss of nitrogen will generate a singlet carbene, so-called because the non-bonding electrons occupy the same molecular orbital and are thus spin-paired.

Carbenes have been shown to undergo a wide variety of reactions, with their high reactivity allowing them to take part in unusual processes such as insertion into carbon-hydrogen bonds, hydrogen abstraction, addition to alkenes and internal structural rearrangements.

A large proportion of the products obtained from the first decompositions of sodium salts of tosylhydrazones reported by Bamford and Stevens[65] were derived from carbenes (schemes **72** and **73**). Both olefins (*e.g.* **195** and **196**) and azines (*e.g.* **197**) were obtained, olefins forming from reaction of one equivalent of the carbenoid species either intramolecularly (to give *e.g.* **196**) or with an equivalent of the parent diazoalkane. Azines form by combination of the carbene with one equivalent of the undecomposed diazoalkane.



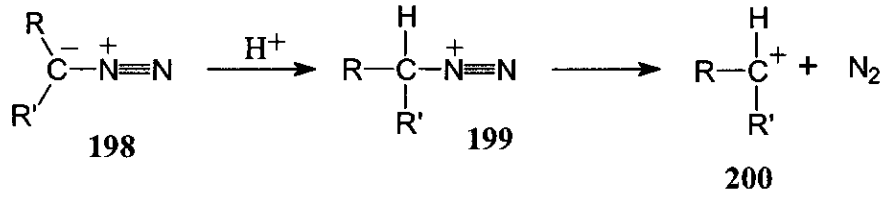
Scheme 72



Scheme 73

In the work to be described here the formation of carbenes from the diazoalkanes was undesirable and the only interest to be gained from these processes was as confirmation that cycloaddition processes involving the diazoalkane had become uncompetitive.

An alternative decomposition process of diazoalkanes occurs if the diazoalkane (**198**) becomes protonated at the carbon atom. In this case, the diazonium species (**199**) is formed, which loses nitrogen to leave the carbocation (**200**) and opens up another branch of possibilities for the outcome of these reactions. As all of the salt decompositions in this work were carried out in aprotic conditions this process will not be discussed further here.

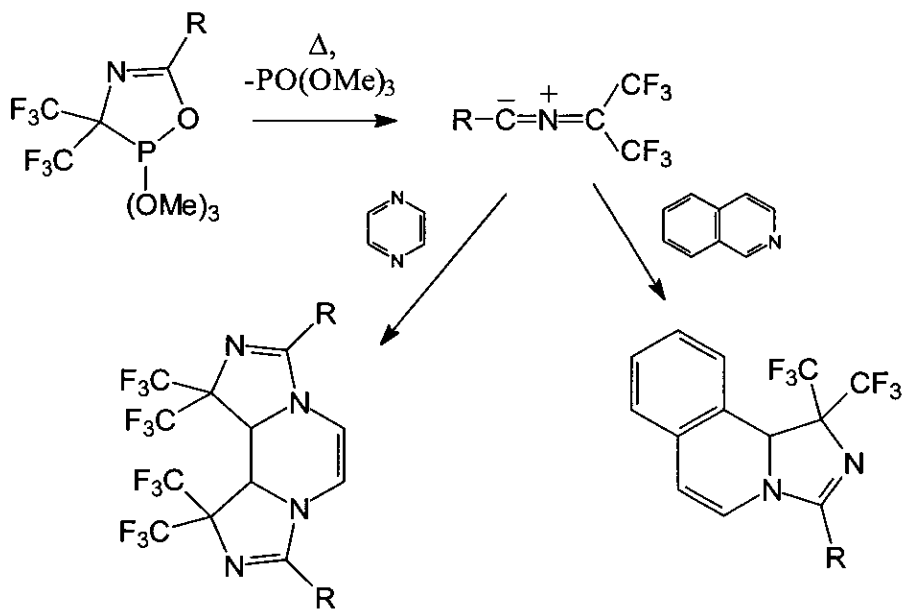


198 199 200

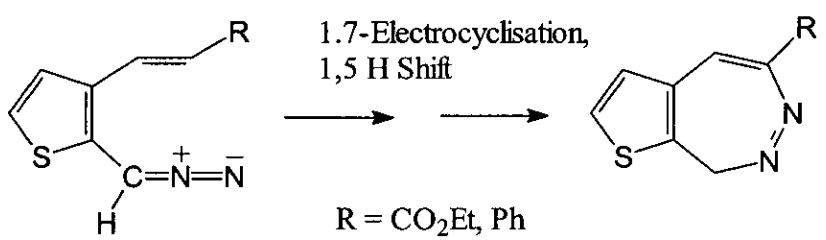
Scheme 74

5.4 Heterocycles in 1,3-Dipolar Cycloadditions

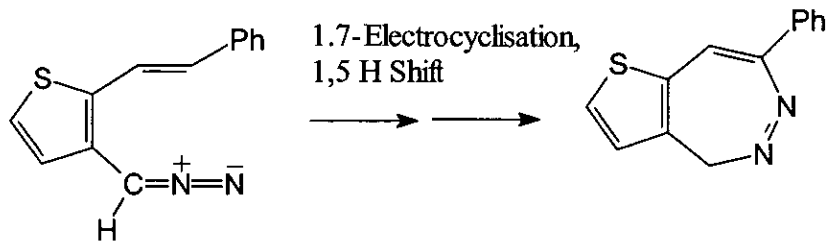
Numerous studies into the effect of incorporating heterocyclic rings into either the dipole or the dipolarophile in intermolecular cycloadditions have been undertaken. The cycloadditions can be either inter[108]- or intramolecular[109,110,111] in nature (schemes 75 - 78)



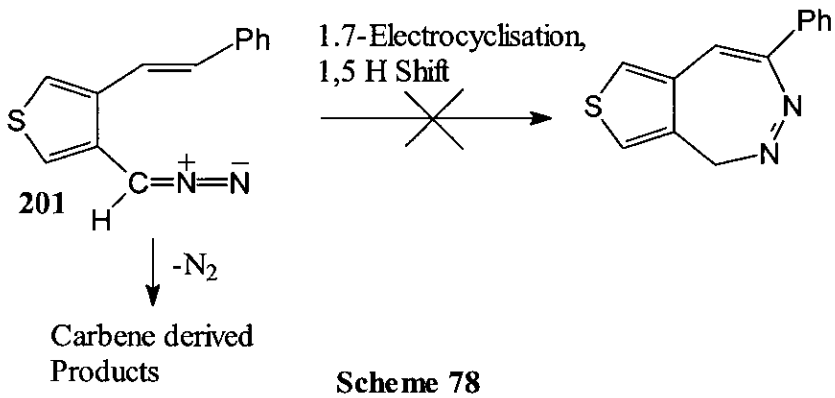
Scheme 75



Scheme 76



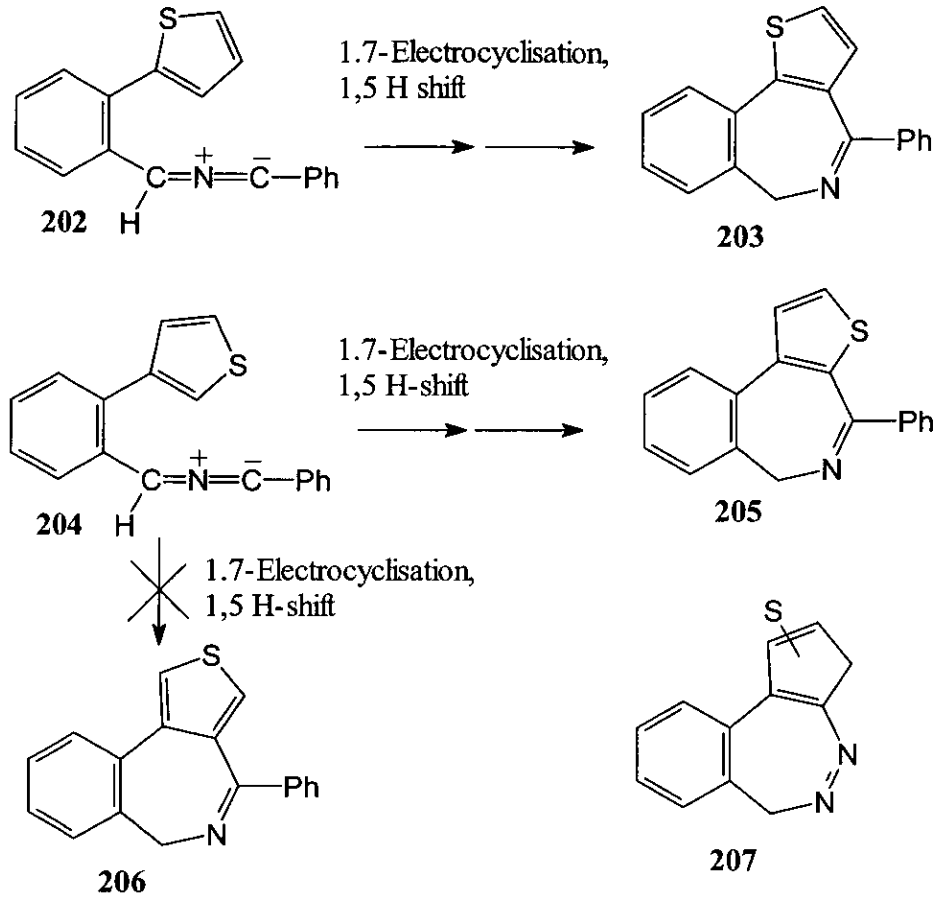
Scheme 77



Scheme 78

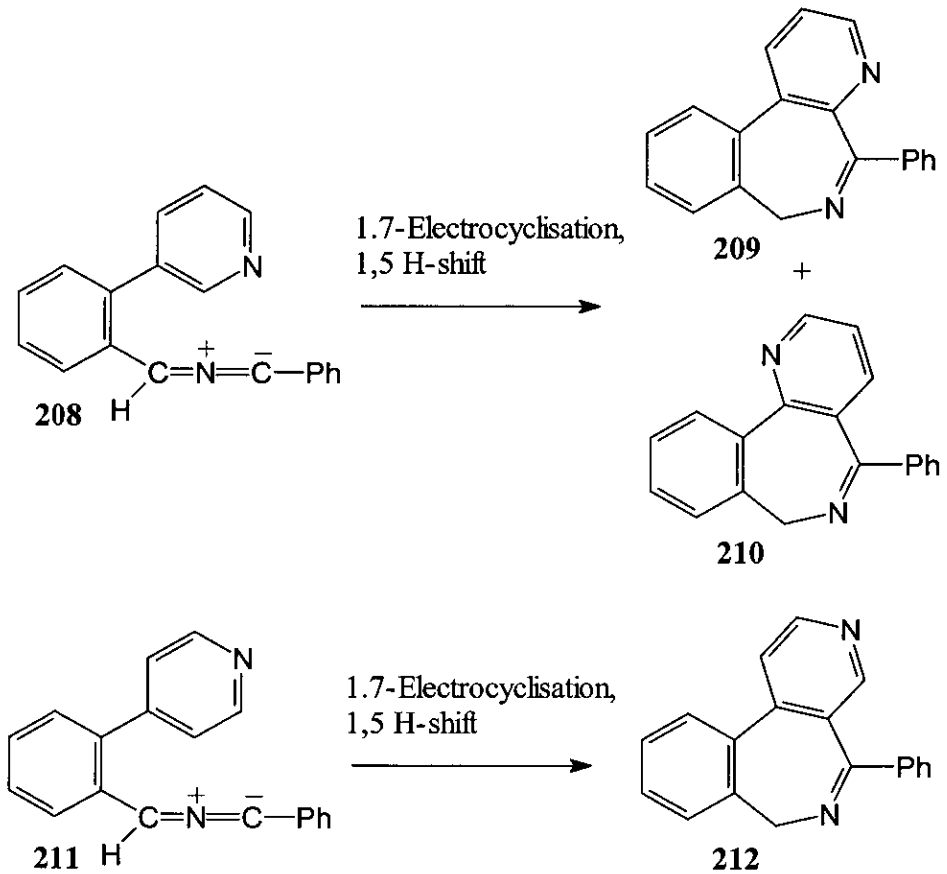
The failure of diazoalkane **201** (scheme **78**) to undergo a cycloaddition process was ascribed to the reduced alkenicity of the thiophene 3,4-bond relative to the 2,3- and 4,5-bonds in diazoalkane **201**. This would disrupt the conjugation between the dipole and the dipolarophile, disfavouring 1.7-electrocyclisation. It could also destabilise the diazoalkane with respect to nitrogen loss.

Benzene rings and heterocycles can also be incorporated into dipolar compounds to act as intramolecular dipolarophiles. When a thiophene ring was incorporated as the γ,δ-unsaturation of isomeric diene-conjugated nitrile ylides (**202** and **204**) then a 1.7-electrocyclisation occurred, yielding the fused azepines **203** and **205**. This was also the case with the analogous diazoalkanes, which yielded the corresponding thiophene-fused 1*H*-2,3-diazepines (*e.g.* **207**). In the case of **204** it is likely that the reduced alkene character of the thiophene 3,4 bond (alluded to earlier) contributed to the lack of cyclisation across these 3,4 positions, rationalising the fact that azepine **206** was not formed.



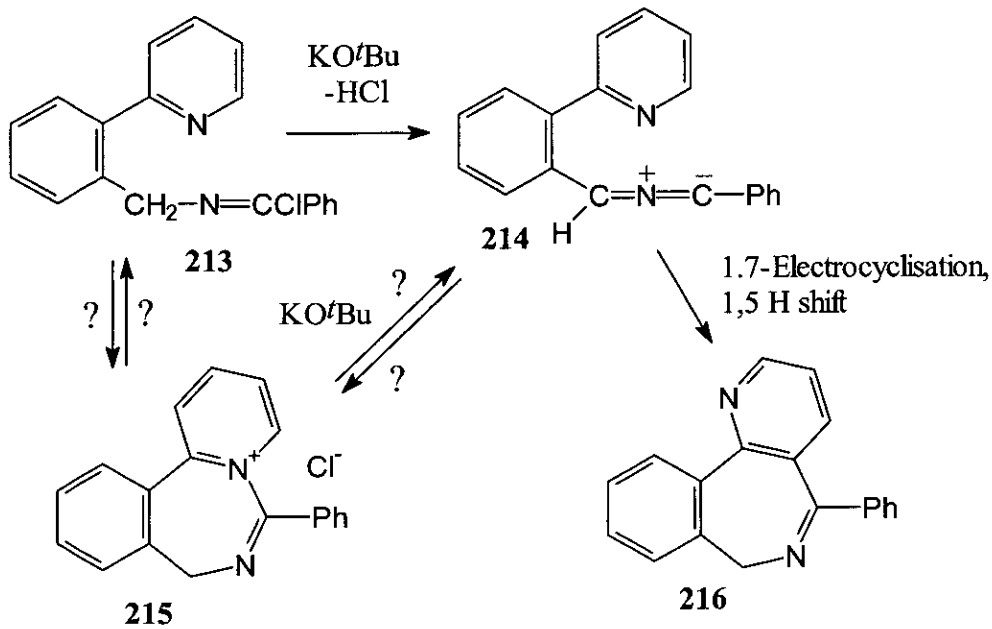
Scheme 79

Reactions using the three isomeric pyridine-containing nitrile ylides **208**, **211** and **214** were also carried out. These gave similar results to those from the thiophene work, with 1.7-electrocyclisations yielding fused azepines **209**, **210**, **212** and **216**.



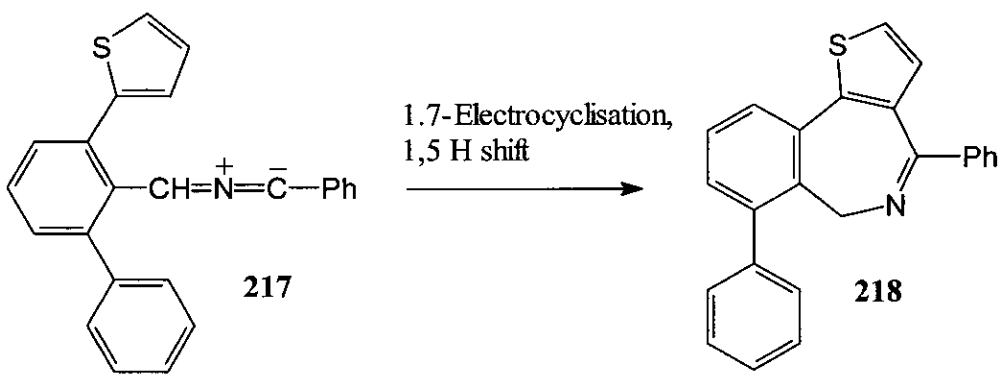
Scheme 80

In the case of **214**, where the pyridyl nitrogen atom is in an *ortho*-position, the only product obtained derived from cyclisation onto the other, free, *ortho*-position. It was thought that the imidoyl chloride could reversibly cyclise onto the nitrogen atom to give the azepinium chloride **215**, and ^{1}H NMR data consistent with the presence of this intermediate were obtained. Regardless of which dipole precursor was obtained from chlorination of the corresponding amide (**213**, **215** or an equilibrium mixture of both), the final product obtained by adding base to the reaction mixture was the pyrido-1*H*-2-benzazepine **216**.



Scheme 81

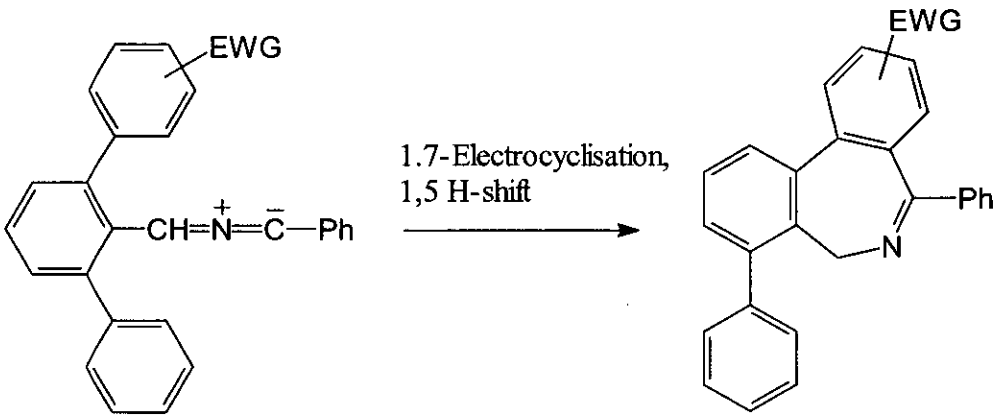
Competition reactions where the nitrile ylide has two possible internal dipolarophiles within reaction range have been carried out (scheme **82**). Where a thiophene ring was included as the alternative dipolarophile to the phenyl ring (nitrile ylide **217**), the product (**218**) derived from 1.7-electrocyclisation onto the thiophene ring was 100-fold more predominant than that from cyclisation of the dipole onto the phenyl ring.



Scheme 82

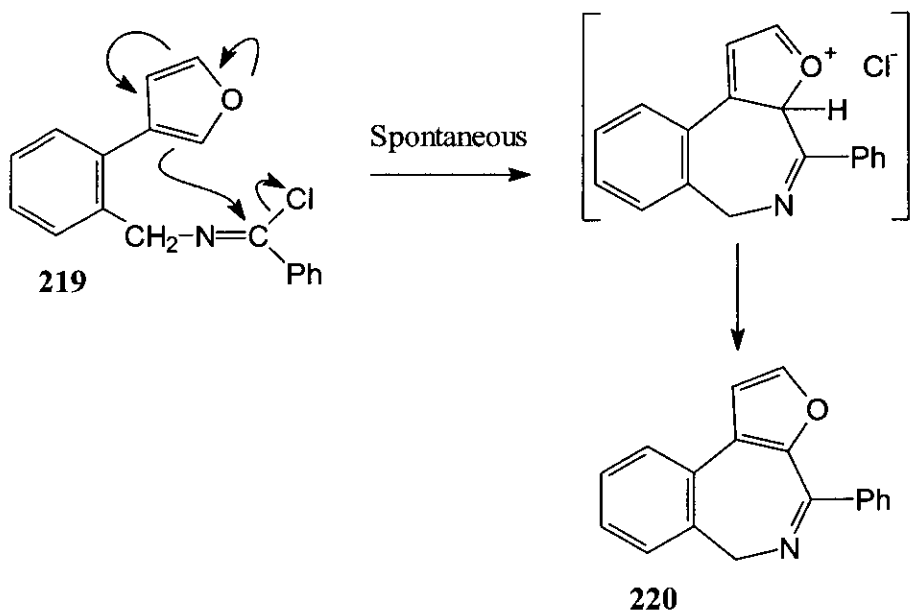
This shows that thiophene rings are strongly activated to electrocyclic reaction with dipoles relative to benzene. Other work in this series of competition reactions showed that the inclusion of strongly electron-withdrawing groups on one of the possible dipolarophilic rings strongly favoured cyclisation onto that ring (scheme

83). Electron donors had a less marked effect in the opposite direction, *i.e.* favouring cyclisation onto the unsubstituted ring.



Scheme 83

When this work was extended to using a furan ring as the dipolarophile it was found that the imidoyl chloride **219** (the usual precursor to nitrile ylides) underwent cyclisation without requiring dehydrohalogenation, yielding the azepine **220** (scheme **84**). This was explained by the high reactivity of furan, with formylation and trifluoroacetylation of furan proceeding two orders of magnitude faster than the same reactions of thiophene[112].



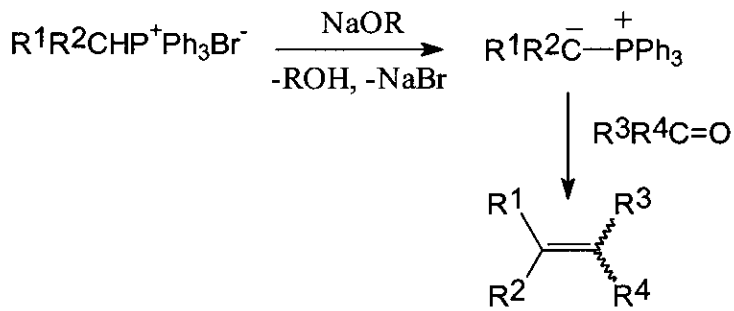
219 **220**

Scheme 84

6. Synthetic Points

6.1 Wittig and Wadsworth-Emmons Olefinations

The Wittig reaction (scheme **85**) is a well-known technique for the generation of olefins[113]. It was first reported in 1954 by Georg Wittig, who received the Nobel Prize in 1979 for his work in this field. The reagents involved are generally a ketone or aldehyde and either an alkyl phosphonium halide or an alkyl phosphonate (in the Wadsworth-Emmons adaptation[114, 115], scheme **86**).

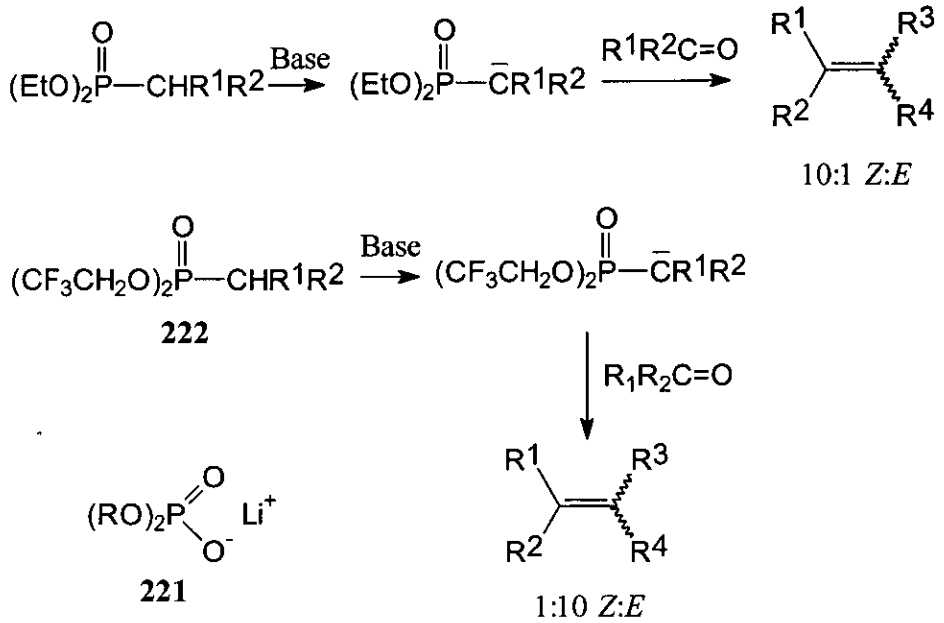


Scheme 85

A multitude of refinements have been reported, with greater stereochemical control generally being the aim of adjustments made to the classical methodology[116]. As a rule of thumb, aldehydes are more reactive than ketones in reactions of this type[117]. The bases used to effect ylide generation are generally alkoxides or organolithium reagents, although bases as mild as *e.g.* barium hydroxide may be used in some cases.

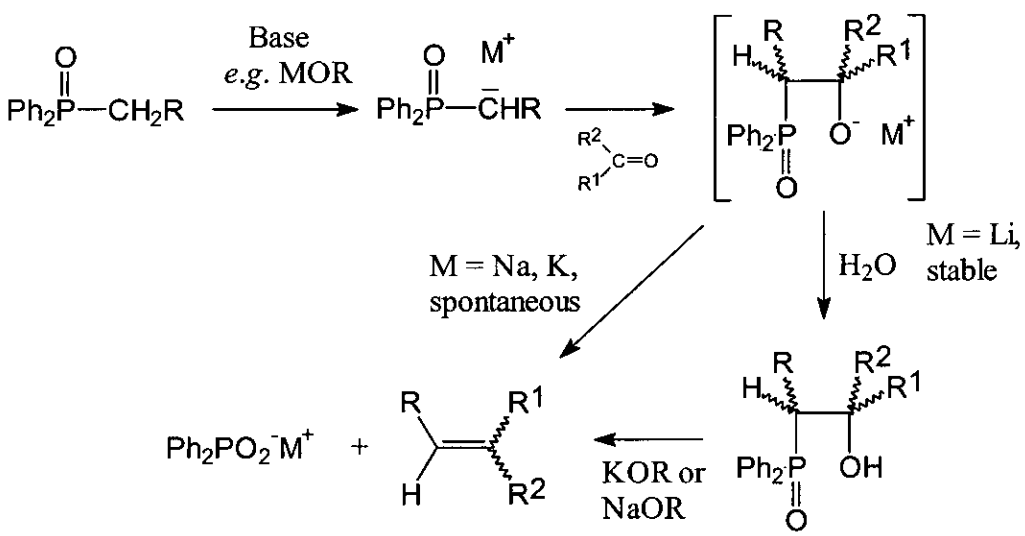
An advantage of the Wadsworth-Emmons reaction over the Wittig is that the side-product **221** is water soluble and thus easily removed, while isolation of a Wittig product from triphenylphosphine oxide generally requires recourse to chromatography.

Greater stereochemical control of the Wadsworth-Emmons reaction can be asserted by use of a phosphonate of the type **222** [118].



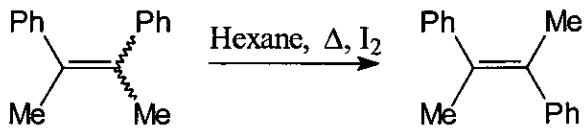
Scheme 86

A similar adaptation of the Wittig olefination – known as the Horner reaction[119] (scheme **87**) – is available to allow access to the opposite isomer to that obtained from the unadapted Wittig reaction.



Scheme 87

Of special importance to this work is the fact that the thermodynamically favoured *E*-isomers of olefins (**223**) are obtainable from the *Z*-isomers (**224**) by heating them in inert solvents in the presence of catalytic amounts of iodine.

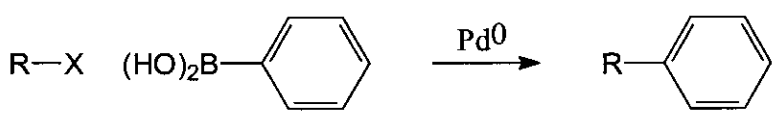


224 **223**

Scheme 88

6.2 Palladium-Mediated Coupling Reactions

H. C. Brown was awarded a Nobel Prize in the same year as Georg Wittig, for Brown's work on the use of boron in carbon-carbon bond forming reactions[120]. A number of hugely important reactions have sprung from this work, including the Suzuki reaction[121,122,123]. This involves coupling a boronic acid (**225**) with an organohalide, the process being catalysed by palladium complexes.

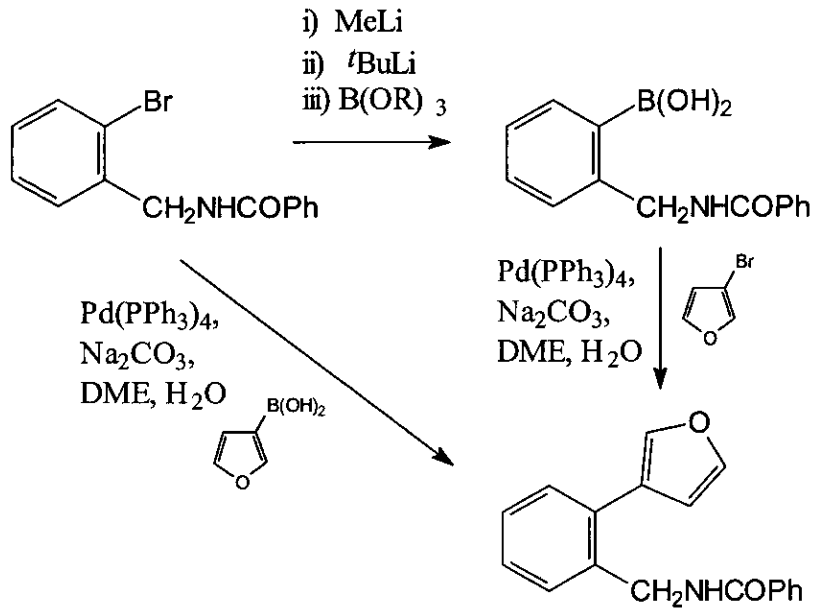


225

Scheme 89

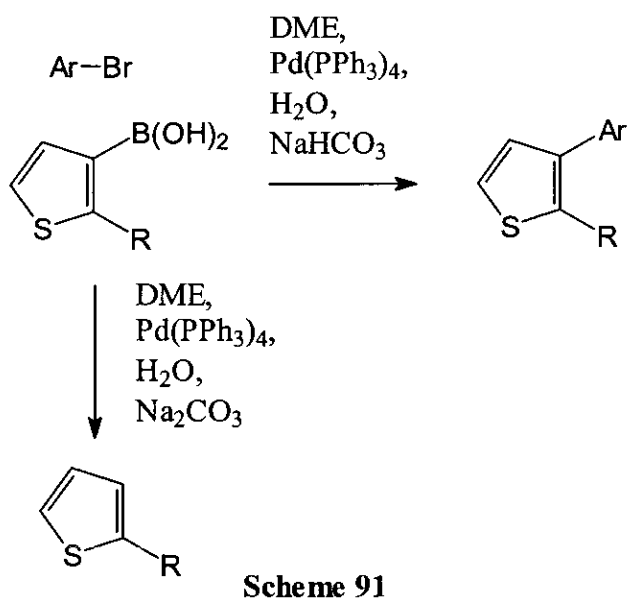
These reactions have been used extensively in organic synthesis since their discovery, owing to the easy synthesis of precursors, their regio- and stereo-specificity and their tolerance of functionality in the substrates.

The boronic acids are readily prepared by reaction of a lithiated aryl ring with a borate ester, commonly triisopropyl borate. The acids are then coupled with the organohalide in the presence of a palladium (0) catalyst.



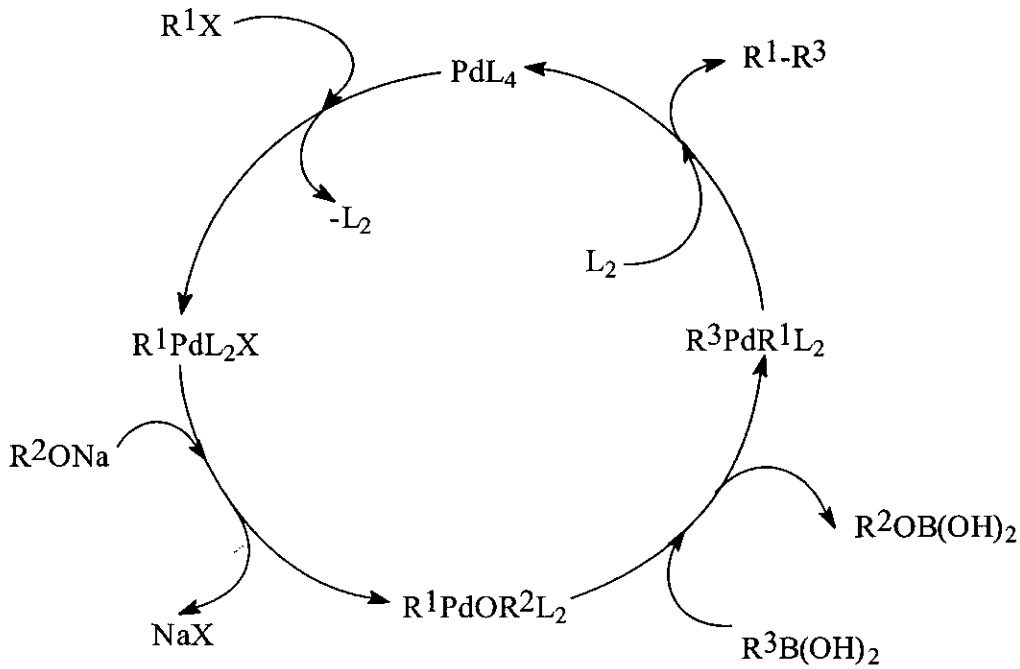
Scheme 90

The Gronowitz modifications[124] of this reaction are utilised in the work described here, using DME as solvent, sodium carbonate as the base and tetrakis(triphenylphosphine) palladium(0) as the catalyst, present as *ca.* 5 mol% of the substrates. These conditions have been found to be optimal for the types of substrates used herein, although reports have been made of thiophene boronic acids being deboronated with no subsequent coupling occurring (scheme **91**). This particular problem was solved by substituting sodium bicarbonate for sodium carbonate.



Scheme 91

The proposed catalytic scheme for palladium(0)-mediated coupling reactions of this type is shown in scheme **92**.



Scheme 92

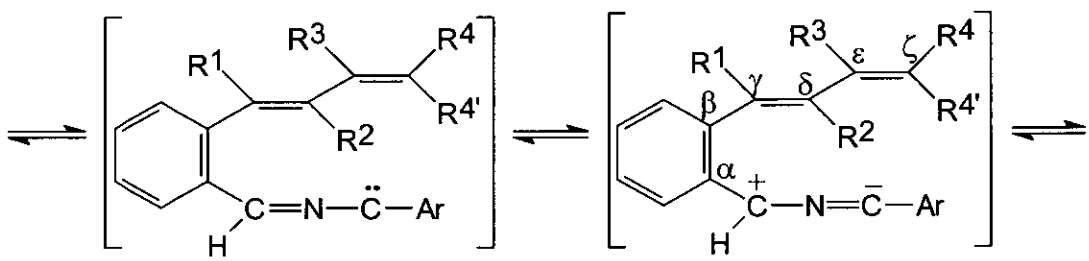
Results and Discussion

Part Two

1. Generation and Reaction of Nitrile Ylides Derived from Substituted (*E,E*)-*N*-[2-(Buta-1,3-dienyl)benzyl]benzamides

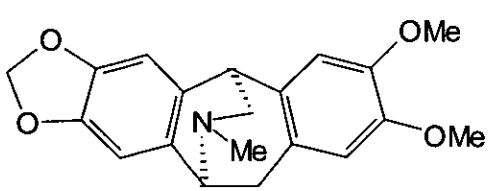
Programme of Research

This section of this thesis is concerned with the reactions of triene-conjugated nitrile ylides of the type **226**, where the α,β unsaturation is aromatic and the γ,δ and ε,ζ unsaturations are both olefinic.

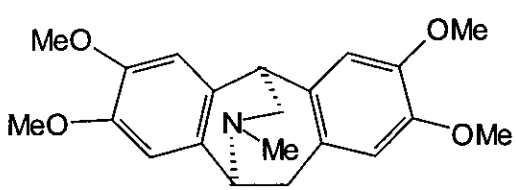


226

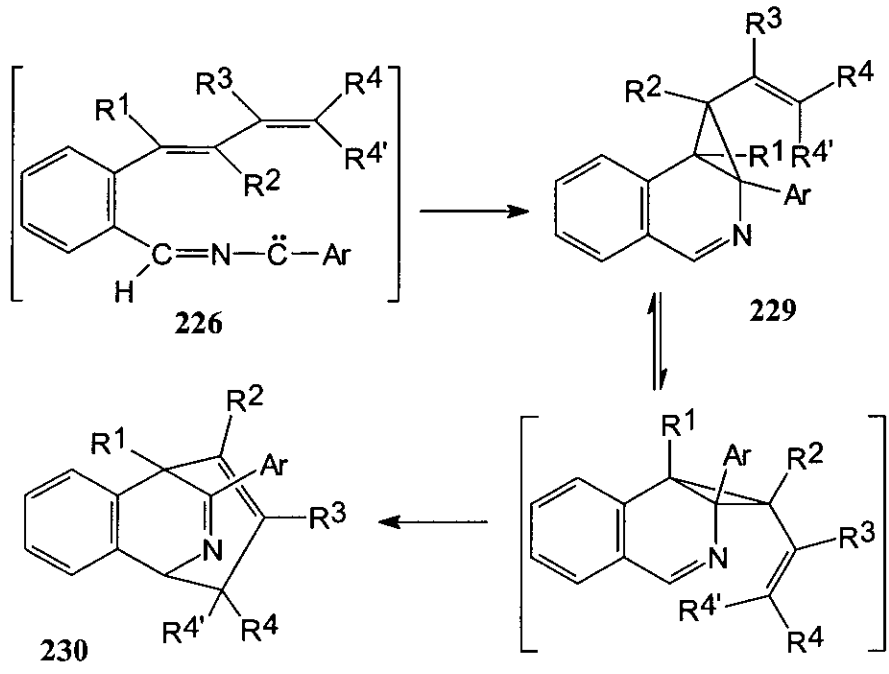
Previous work [94] has shown these compounds to undergo 1,1-cycloadditions to give the 1-alkenyl *exo*-cyclopropa[*c*]isoquinolines **229**, which are stable enough to be isolated. The latter rearrange upon heating *via* two major reaction paths, one of which leads to the bridged isoquinolines **230**, *via* an intramolecular aza-Cope rearrangement (scheme **93**). The bridged isoquinolines are potentially interesting due to their structural similarity to naturally occurring isopavine alkaloids[125] such as amurensine **227** and (-)-*O*-methylthalisopavine **228**, which possess neurological activity and have been found to be useful in treatment of cerebral ischaemia.



(-)-Amurensine **227**

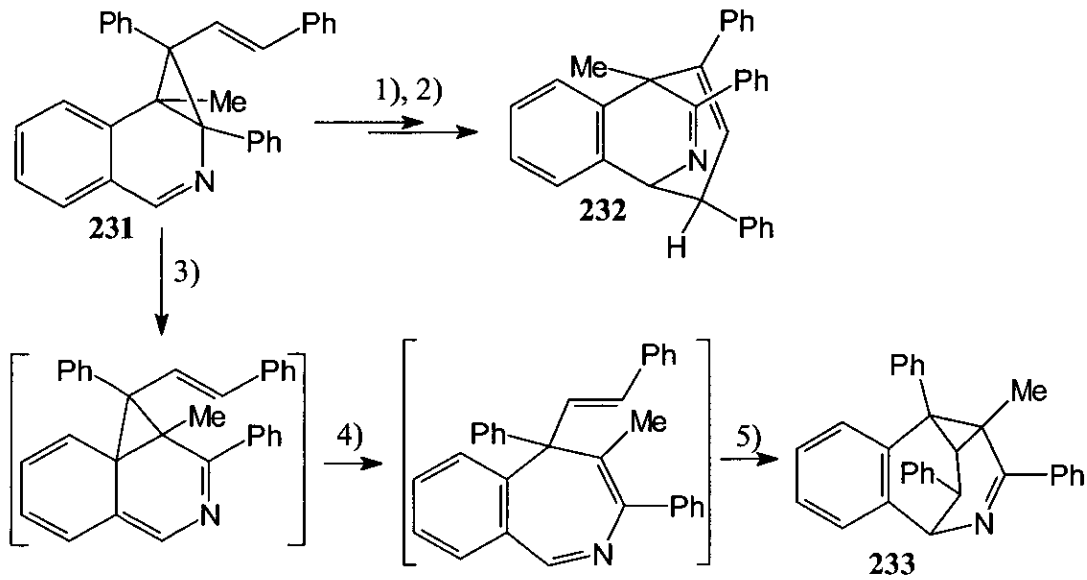


(-)-*O*-Methylthalisopavine **228**



Scheme 93

The most recent work in this area has shown that the reaction path shown in scheme **93** is totally dominant in the case where R^1, R^2, R^3 and $R^{4'}$ = H and R^4 = Ph. However, in previous examples, *e.g.* **231** (scheme **94**) the cyclopropa[*c*]isoquinoline also reacted *via* another pathway to give the azabenzobabaralane derivative **233**, as well as the bridged isoquinoline **232**.



1) Ring-inversion 2) Aza-Cope rearrangement 3) [1.5] Cyclopropyl walk
4) Electrocyclic ring-expansion 5) Diels-Alder

Scheme 94

In general, earlier results indicated that the nature and pattern of substituents on the terminal diene system had a strong effect on the partitioning between the two routes.

The programme of research was designed overall to explore and rationalise substituent effects in this system. In particular, it was intended to find out if the presence of a single substituent at the terminal position, as in **265** (*i.e.* R^1-R^3, $R^{4'}$ = H), would always result in the dominance of the route to the bridged isoquinolines **230**. The first requirement would be to repeat and hopefully confirm this unexpected result, and then to extend the reaction by varying the nature of R^4.

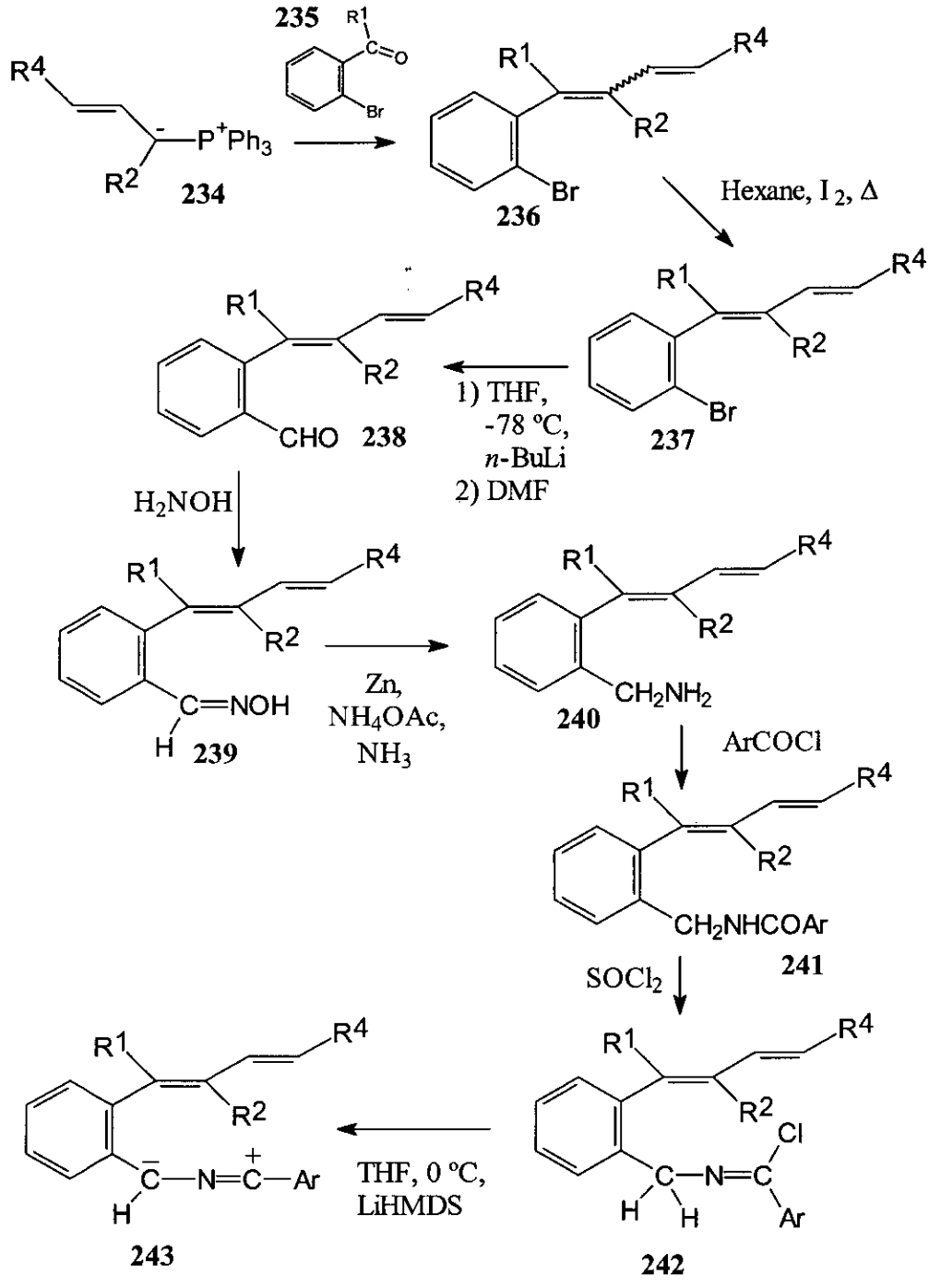
The investigation would then be extended to the effects of substituents in various positions on the triene upon the reactions of the nitrile ylides and the subsequent thermal rearrangements of the cyclisation products.

General Synthetic Strategy for Substituted (*E*,*E*)-*N*-[2-(Buta-1,3-dienyl)benzyl]benzamides

Synthesis of the amides (**241**) was based on the general route shown in scheme **95**. This involved firstly fabrication of the bromotriene system **237** using the appropriate olefination chemistry and then conversion of the bromine atom into the aminomethyl group **240**, *via* the aldehyde **238** and the oxime **239**.

The triene systems were to be constructed using standard olefination techniques with the most suitable methodology to be determined as the work was carried out. Broadly, the initial step was to be a Wittig or Wadsworth-Emmons olefination between the carbonyl compounds **235** and the ylide of the appropriate phosphonate or phosphonium salt (**234**). It was expected that these reactions would yield the desired substituted *o*-(buta-1,3-dienyl)bromobenzenes **236** as mixtures of isomers.

The problem of attaining the desired (*E*,*E*) stereochemistry in the diene moiety was to be solved by utilising radical-initiated isomerisation to provide only the thermodynamically favoured (*E*,*E*) isomer **237**. This is normally achieved by heating the mixture in a suitable inert solvent in the presence of iodine. Problems were expected here, bearing in mind the propensity of conjugated double bonds to polymerise.



Scheme 95

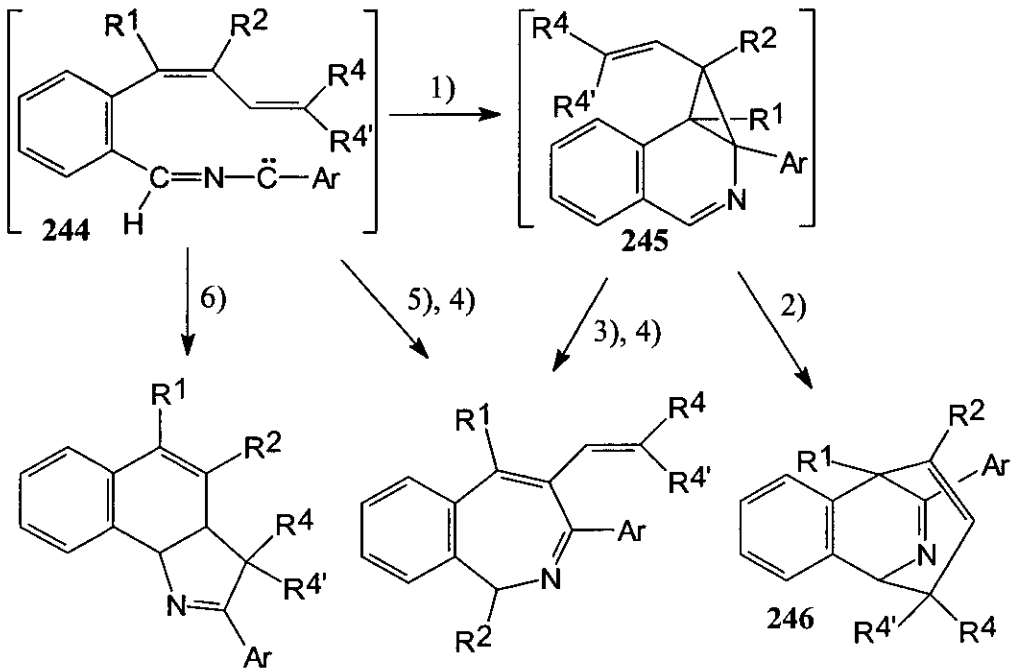
The aldehydes **238** were to be obtained by effecting a bromine-lithium exchange by reacting the bromocompounds **237** with butyllithium and quenching the lithiated intermediates with *N,N*-dimethylformamide (DMF). The aldehydes would then be condensed with hydroxylamine to give the oximes **239**, which would be reduced to

primary amines **240** using zinc and ammonia. Aroylation of the amines would provide the amides **241**, the stable precursors of the labile imidoyl chlorides **242**. The chlorination can be achieved in a number of ways, but thionyl chloride is generally the reagent of choice due to the ease of removal of side products. The imidoyl chlorides were to be dehydrohalogenated using LiHMDS [52] to generate the nitrile ylides (**243**).

1.1 Generation and Reaction of Nitrile Ylides Derived from 4'-Substituted (*E*,*E*)-*N*-[2-(Buta-1',3'-dienyl)benzyl]benzamides

1.1.1 Preamble

Previous closely related work in this area [52] has shown substituent patterns about the triene-conjugated nitrile ylides to be highly influential in the cycloadditions of nitrile ylides and the rearrangements which the cyclisation products undergo (scheme **96**). The geometry about the triene system is also important, with trienes which are *cis* about the γ,δ olefin (**244**) giving rise to 1-alkenyl *endo*-cyclopropa[*c*]isoquinolines **245** *via* 1,1-cycloadditions. These are too reactive to be isolated, as the alkenyl substituent is ideally situated to react with the imino carbon atom (C-13) of the isoquinoline system in an aza-Cope rearrangement, yielding products of the type **246**. This rearrangement can be affected by the characteristics of peripheral substituents. For example, where the ζ position has two non-H substituents (R^4 and $R^{4'} \neq H$) the aza-Cope reaction is blocked.



1) 1,1-Cycloaddition 2) Aza-Cope 3) Electrocyclic ring-opening
4) [1,5] H shift 5) 1.7-Electrocyclisation 6) [3+2] Cycloaddition

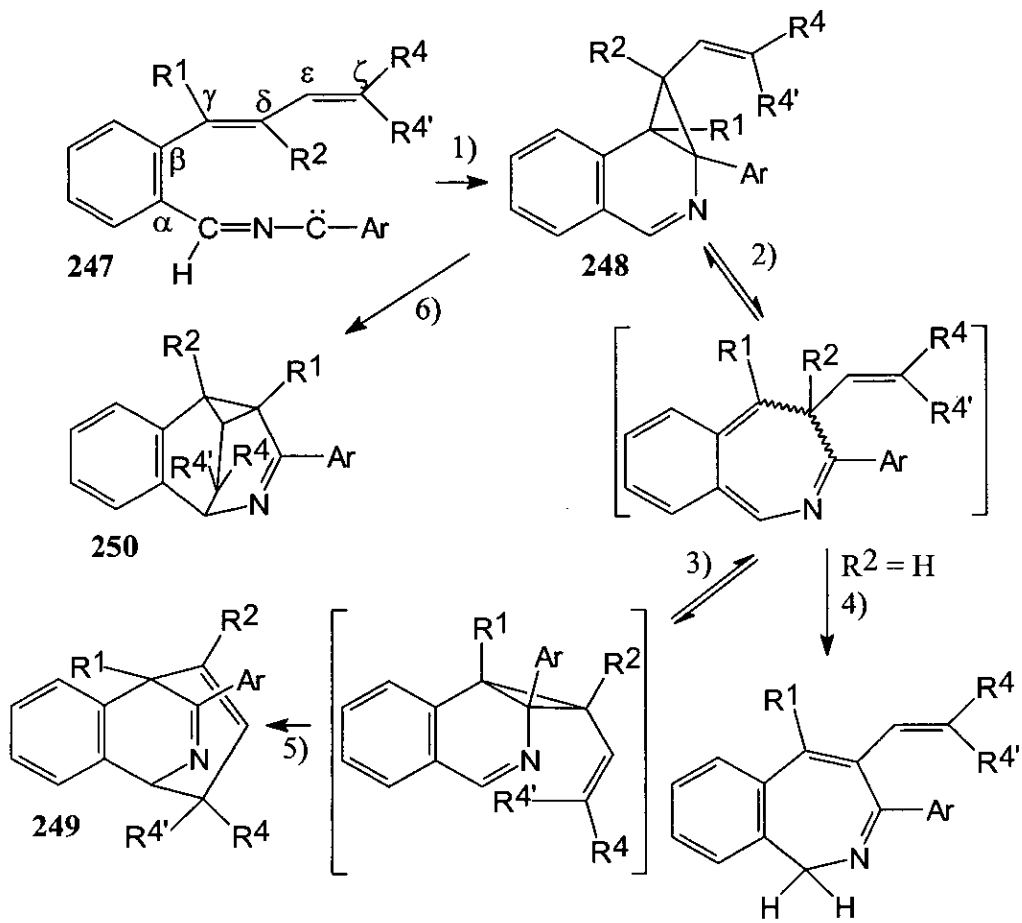
Scheme 96

The *trans* isomers of the triene conjugated nitrile ylides (**247**) also react *via* 1,1-cycloadditions, but yield the 1-alkenyl *exo*-cyclopropa[*c*]isoquinolines **248** which, in contrast to the *endo*-isomers, *are* isolable as they cannot react directly *via* the aza-Cope rearrangement.

The *exo*-isomer can, however, undergo equilibration to the *endo*-isomer when heated (scheme **97**), and so can also yield the bridged isoquinolines **249**. Other rearrangement mechanisms are also possible and the favoured mechanisms are dependent upon the identity of apparently peripheral substituents, *e.g.* those on the triene.

It was hoped that this investigation, by utilising less heavily substituted analogues than in previous work, would allow elucidation of the effects which each individual substituent exerted upon the intramolecular processes involved. Ultimately, it was

hoped that reliable routes to the appealing bridged isoquinoline structures **249** from triene-conjugated nitrile ylides of the type **247** could be established.



1) 1,1-Cycloaddition 2) Electrocyclic ring opening
3) Electrocyclic ring closure 4) [1,5] H Shift 5) Aza-Cope
6) [1.5] Cyclopropyl walk, intramolecular Diels-Alder

Scheme 97

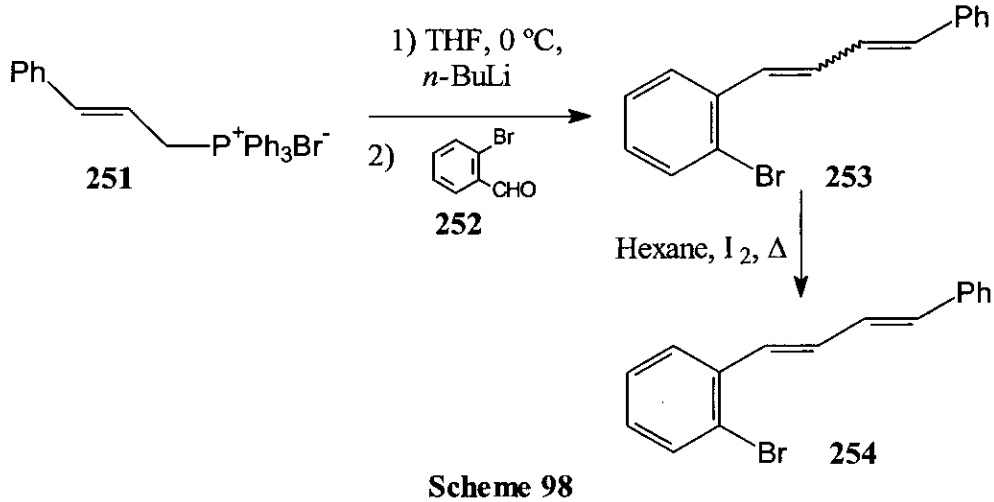
Most examples of compounds of the type **247** generated in previous work rearranged to give both bridged isoquinolines **249** and babaralanes **250**. However, when only the R^4 substituent was a non-H group (**226**, R^1, R^2, $R^{4'}$ = H, R^4 = Ph) then the only product obtained from thermolysis of the cyclopropa[*c*]isoquinoline was the bridged isoquinoline (**230**), *via* an aza-Cope rearrangement. The initial goal of this investigation was to obtain verification that both the 1,1-cycloaddition of the (*E*,*E*) triene-conjugated nitrile ylide **237** (R^1, R^2 and $R^{4'}$ = H, R^4 = Ph) and the subsequent

thermal rearrangement of the resultant 1-alkenyl cyclopropa[*c*]isoquinoline **248** proceeded as expected, *via* the aza-Cope rearrangement to give compound **249**. After this objective had been fulfilled it was then intended to extend the study to other 4-substituted examples.

The synthetic strategy was based on the generation of the required nitrile ylides (**243**, scheme **95**) from appropriately substituted (*E,E*)-*N*-[2-(buta-1,3-dienyl)benzyl]benzamides **241**. This methodology requires the conversion of the amides into imidoyl chlorides (**242**) and the subsequent dehydrochlorination of the latter using a strong base at 0 °C.

1.1.2 (*E,E*)-*N*-[2-(4-Phenylbuta-1,3-dienyl)benzyl]benzamide (262)

The synthesis of the (*E,E*) diene-conjugated *o*-bromobenzene **254** was the first step. This was achieved straightforwardly *via* the Wittig reaction of (*E*)-cinnamyltriphenylphosphonium bromide with *o*-bromobenzaldehyde followed by iodine-catalysed thermal isomerisation of the (*E,E*)/(*Z,E*) mixture obtained, to give only the desired thermodynamic product **254** (scheme **98**).

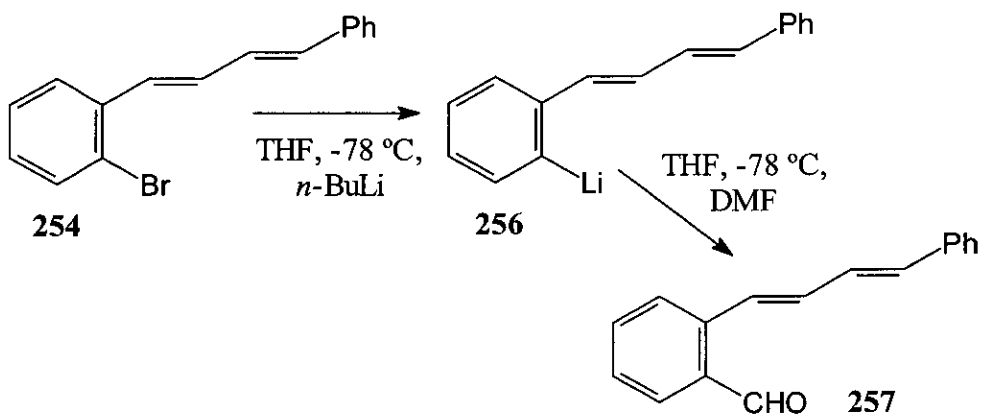


Scheme 98

In this particular case the two isomers in the primary product were distinguishable by TLC and the progress of the isomerisation was easily monitored. After isomerisation, the ^{1}H and ^{13}C NMR spectra showed the presence of only one isomer.

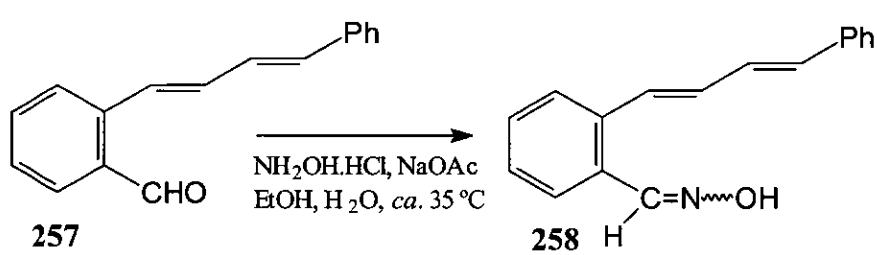
The isomerisation was accompanied by the disappearance of a doublet (*J* 9.2 Hz) at δ 6.60 in the ^{1}H NMR spectrum, which had been due to an olefinic proton of the *cis* isomer. The general strategy worked well in this case and it was hoped that it could be adapted to allow access to a wide variety of analogous bromotrienes through the course of the rest of this investigation.

The desired aldehydic functionality was easily introduced by effecting a metal-halogen exchange between the bromotriene **254** and *n*-butyllithium and reacting the lithiated intermediate **256** with *N,N*-dimethylformamide (DMF) to generate the formyl group. Chromatography allowed isolation of the product from side products, for example hydrocarbon resulting from hydrolysis of the lithiated compound **256** by adventitious moisture prior to reaction with DMF. The yield of aldehyde **257** (68 %) was satisfactory and it was hoped that this methodology could be applied in the synthesis of other analogues.



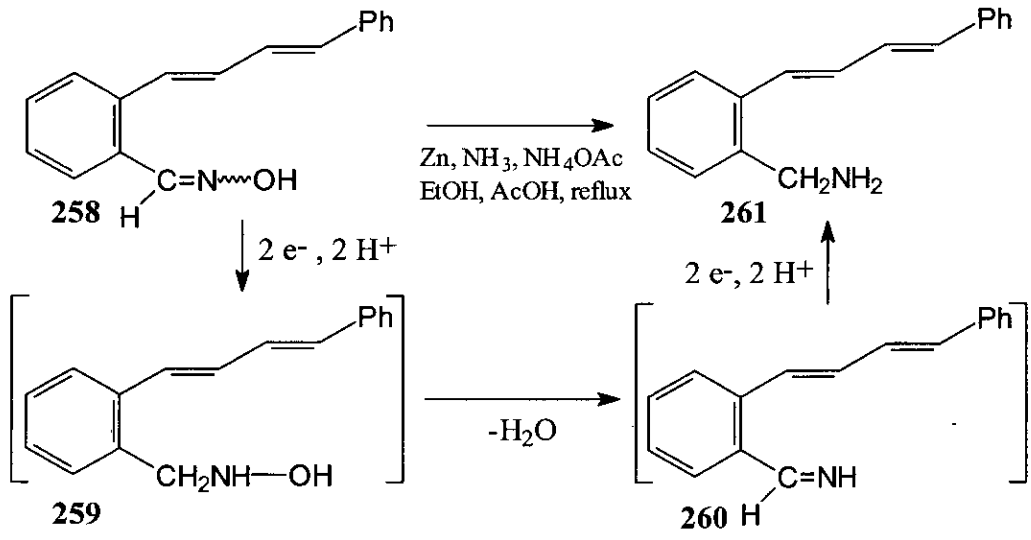
Scheme 99

Condensation of the aldehyde **257** with hydroxylamine hydrochloride gave the oxime **258** (scheme **100**).



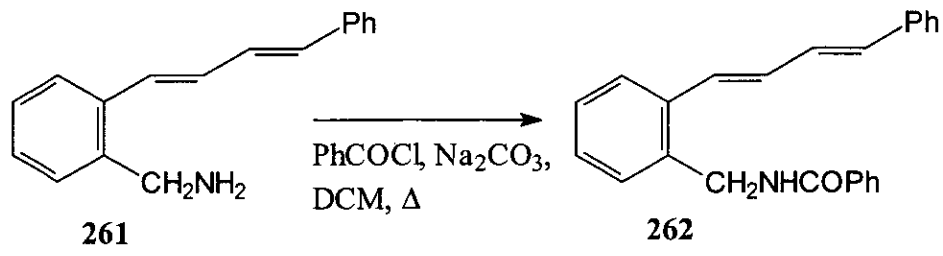
Scheme 100

The oxime **258** was then reduced to the amine **261** with Zn/NH_3. This process is not well understood, but is believed to proceed (scheme **101**) *via* a single electron transfer to the oxime followed by abstraction of protons from the solvent to give the hydroxylamine **259**. This can then dehydrate, regenerating the C-N double bond to give the imine **260**, which is reduced by a similar process. Further single electron transfers to the imine and abstraction of more protons would give the amine **261**, the observed product. These reactions proceeded very quickly with complete consumption of starting material generally observed after *ca.* 30 minutes. This was fortuitous, bearing in mind the expected propensity of the trienes to polymerise and the high reaction temperature.



Scheme 101

The zinc/ammonia reduction fortunately yielded a very pure product after primary workup. It was expected that the amine would be unstable to oxidation and polymerisation and so this crude product was benzoylated without further purification. These aroylations were straightforward (scheme **102**), with the amine, sodium carbonate and benzoyl chloride in DCM being briefly heated at reflux and stirred overnight. The amide **262** was then isolated and purified.



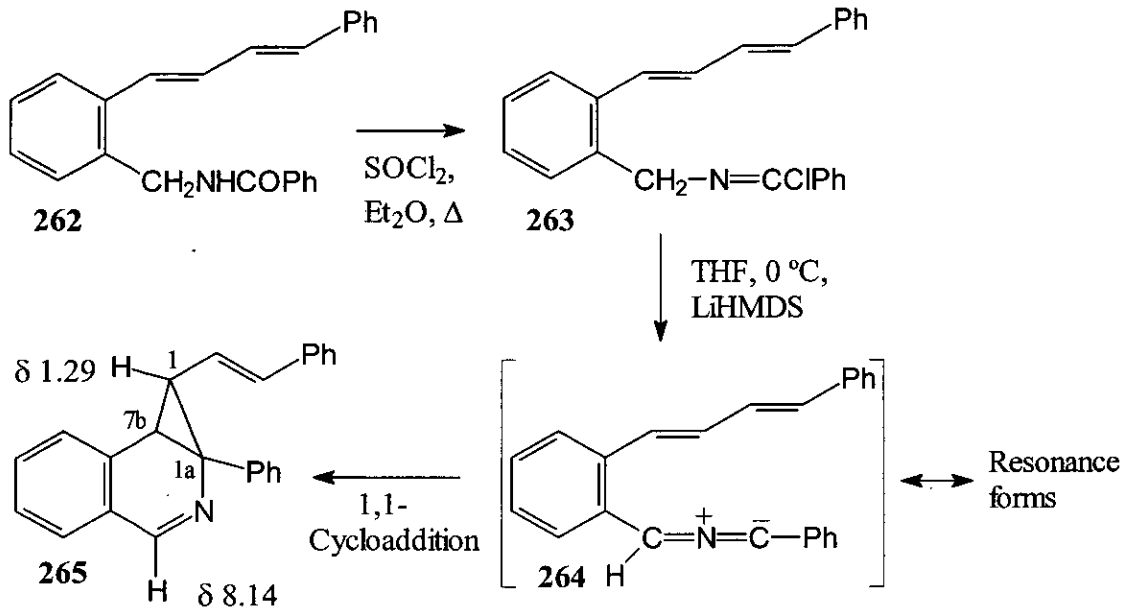
261 **262**

Scheme 102

As mentioned, it was hoped that the series of reactions outlined above and in schemes **98-102** would provide a template for all the subsequent work on synthesis of nitrile ylide precursors. This proved to be broadly true, however problems with construction of the triene system in the first step necessitated optimisation at this stage, depending on the analogue required. Any adaptations made will be outlined and discussed at the relevant points in this section. In contrast to the first step, the subsequent functional group transformations proved applicable for all examples, with yields generally being good to acceptable.

Once the (*E,E*) triene-conjugated amide **262** was in hand it was to be chlorinated to generate the imidoyl chloride **263**. Again, a variety of methods were utilised to effect the chlorinations, some proving more successful than others for particular substitution patterns. The different techniques will be discussed as they arise in this discussion.

In the initial case (chlorination of amide **262**) a straightforward overnight reflux of the amide with an excess of thionyl chloride in dry ether proved adequate for the purpose. After removal of the solvent and excess reagent by evaporation under high vacuum the imidoyl chloride, as a solution in dry THF, was treated with lithium bis(trimethylsilyl)amide at 0 °C. The dehydrohalogenation of the imidoyl chloride **263** to the nitrile ylide **264** (scheme **103**) was monitored by TLC, which showed consumption of the starting amide and appearance of a new, higher running spot. Obviously, the imidoyl chloride is not observed by TLC as it is immediately hydrolysed to the amide on removal from the reaction mixture.

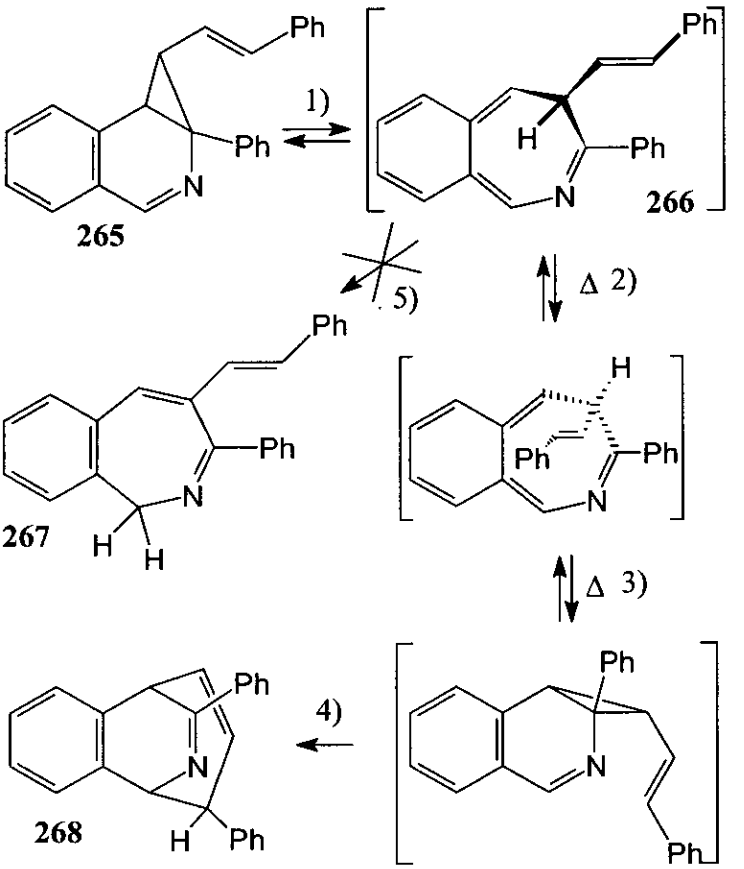


Scheme 103

Isolation of the product by dry-flash chromatography allowed it to be identified as the expected *exo*-isomer of the cyclopropa[*c*]isoquinoline **265**. This was readily identified by a signal in the ^{1}H NMR spectrum at δ 1.29 from the highly shielded cyclopropyl hydrogen on C-1 and a peak due to the deshielded imine proton at δ 8.14.

Thermolysis of the product **265** at 54 °C in $CDCl_3$ solution, with periodic ^{1}H NMR monitoring, caused smooth, quantitative conversion to the bridged isoquinoline **268**, *via* the expected aza-Cope rearrangement (scheme **104**). Complete consumption of the cyclopropa[*c*]isoquinoline occurred after 8 hours at the temperature used.

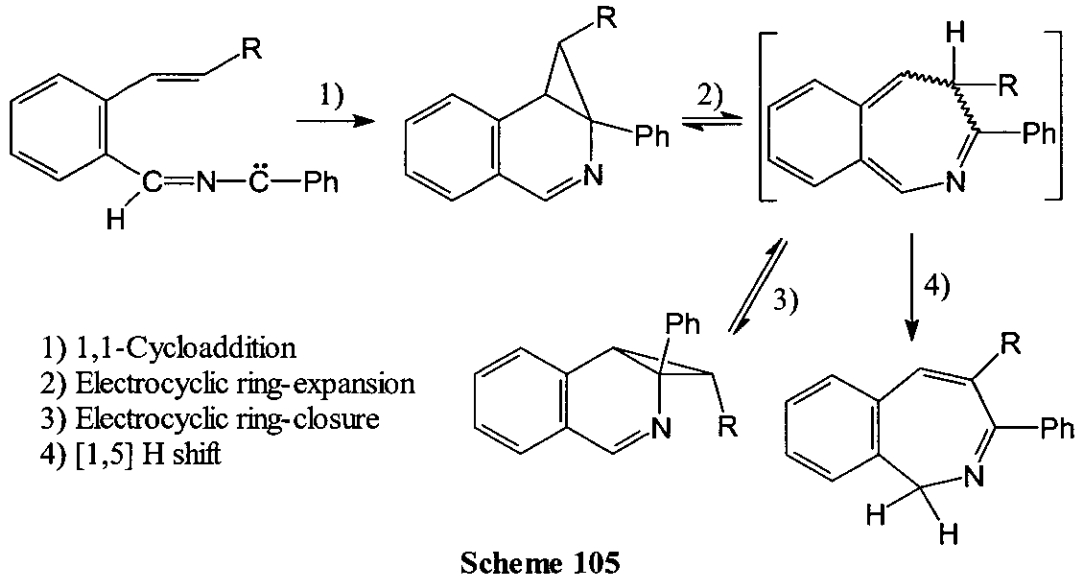
This result confirmed that the bridged isoquinoline **268** is indeed the only ultimate product of the reaction of the triene-conjugated nitrile ylide **264**.



1) Ring-expansion 2) Ring-inversion
3) Ring- closure 4) Aza-Cope 5) [1,5] H shift

Scheme 104

What is particularly interesting in this case is that the intermediate **266** did not react *via* a [1,5] H shift to give the 1*H*-2-benzazepine **267**. This is the standard reaction path for analogues with alkyl or aryl (*i.e.* not olefinic) substituents at the 1-position of the cyclopropa[*c*]isoquinoline (R in scheme **105**). This indicates that steps 3 and 4 in scheme **104** are fast compared to the rate of the [1,5] H shift (step 5).



1) 1,1-Cycloaddition
2) Electrocyclic ring-expansion
3) Electrocyclic ring-closure
4) [1,5] H shift

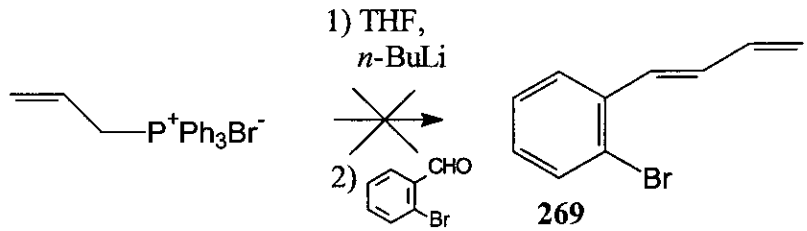
Scheme 105

1.1.3 (*E*)-*N*-[2-(Buta-1,3-dienyl)benzyl]benzamide

Having verified that the route to the bridged isoquinolines was the only reaction path followed for reaction of **265**, the next step was to investigate the effect of changing the terminal substituent on the olefinic diene system (*i.e.* at the ζ-position of the triene).

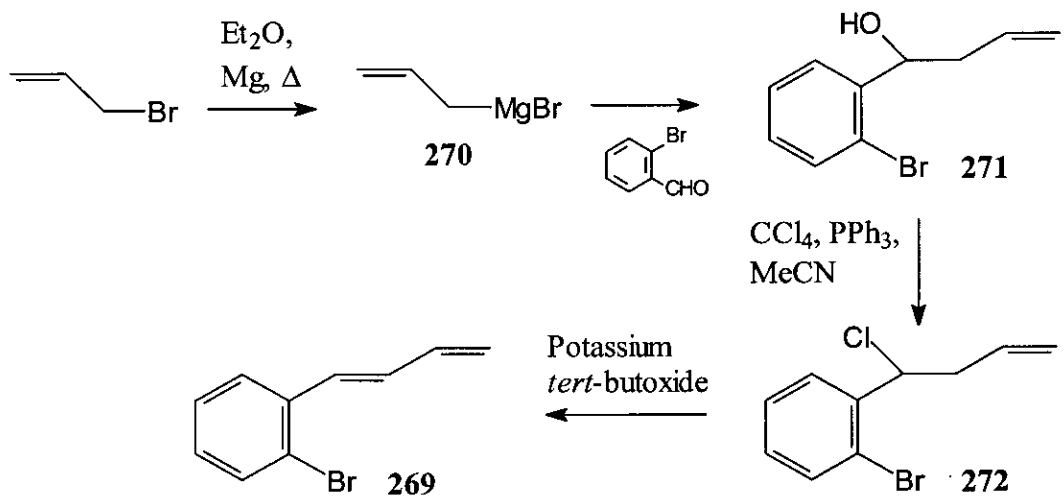
It was decided to start by looking at the triene-conjugated nitrile ylide with no substituents at all, *i.e.* where the ζ substituent = H. It was thought that this would provide an insight into the "default" modes of cyclisation and thermal rearrangement in the triene-conjugated nitrile ylides, without complications caused by the steric or electronic effects of non-H substituents.

Attempts to repeat the initial step of the previous synthesis using allyltriphenylphosphonium bromide instead of cinnamyltriphenylphosphonium bromide failed completely, yielding only the starting aldehyde on workup (scheme **106**). Experiments in which the time allowed for deprotonation of the phosphonium salt was increased and where higher temperatures were used in the ylid generation and/or olefination steps all proved unsuccessful.



Scheme 106

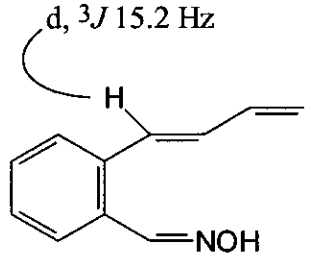
An alternative strategy was obviously required. A search of the literature uncovered a route[126] to the desired compound **269** *via* a Grignard reaction (scheme **107**).



Scheme 107

The first step in this route was generation of allylmagnesium bromide **270** followed by reaction with *o*-bromobenzaldehyde, giving the alcohol **271** cleanly and in good yield (86 %). This was then chlorinated in a Mitsunobu-type reaction with CCl_4 and triphenylphosphine to give **272**, which was dehydrohalogenated with base to generate the *o*-butadienylbromobenzene **269**. As a precaution, the purified product was subjected to the standard isomerisation conditions (hexane/iodine/reflux), but no changes were observed, suggesting that only the (*E*) isomer had formed at the γ,δ olefin during the dehydrochlorination.

The geometry about the γ,δ bond was properly ascertained upon synthesis of the oxime **273**, where the olefinic H-1 (γ-position) signal in the ^{1}H NMR spectrum became unobscured to show itself as a doublet of *J* 15.2 Hz, consistent with a *trans* coupling across the γ,δ olefin.



273

This result should be expected of an E2-type elimination of HCl from **272**, as the departing proton and chlorine atom would be anti-periplanar to each other for elimination to occur (fig **12**). It would also be expected that the most stable rotamer of the chloride would have the bulky bromobenzene group as far removed from the alkene as possible (*i.e.* **272** *anti*, figure **12**), favouring formation of the *trans* olefin. The remainder of the synthetic scheme leading to the amide **274** progressed as expected, with good yields obtained at each stage.

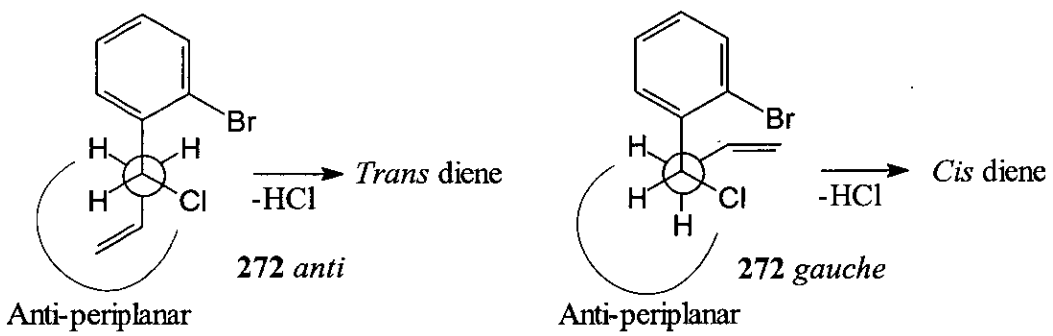
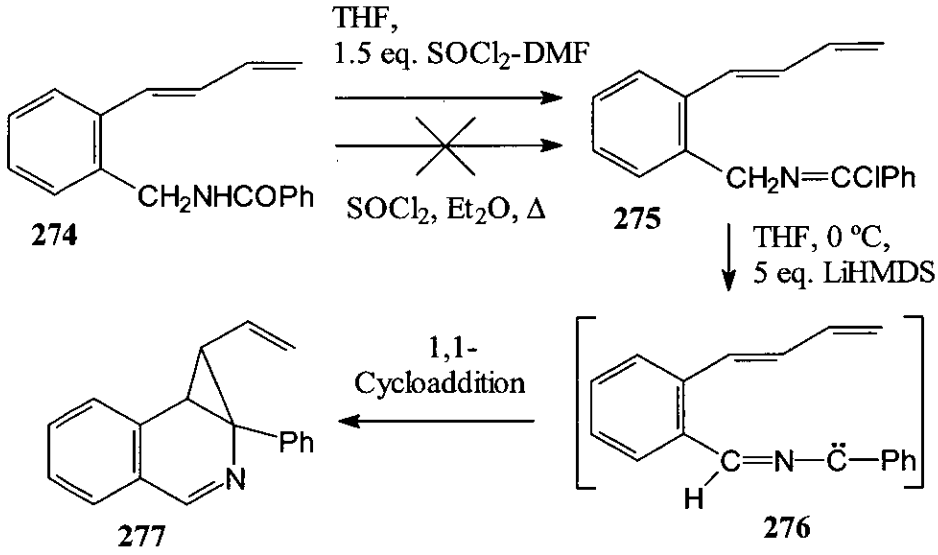


Figure 12

Generation of the imidoyl chloride from the amide proved difficult in this case, however. The methodology that proved successful in the first example failed with this analogue and an alternative method was sought. The strong chlorinating agent *N,N*-dimethylchloroformiminium chloride, generated by reaction of thionyl chloride with dry DMF was used and found to be highly effective. In practice this involved preparation of the chlorinating agent by addition of thionyl chloride to dry DMF,

under scrupulously dry conditions and an inert nitrogen atmosphere. Addition of an aliquot of this to a solution of the amide in dry THF caused rapid precipitation of a fine white solid.

This mixture was allowed to stand at room temperature before being cooled to 0 °C, after which a large excess of lithium bis(trimethylsilyl)amide (LiHMDS) was added, sufficient to react with both the imidoyl chloride **275** and the acidic side products. This base was chosen following an extensive investigation into the most suitable reagent for this purpose within Sharp's group[52].

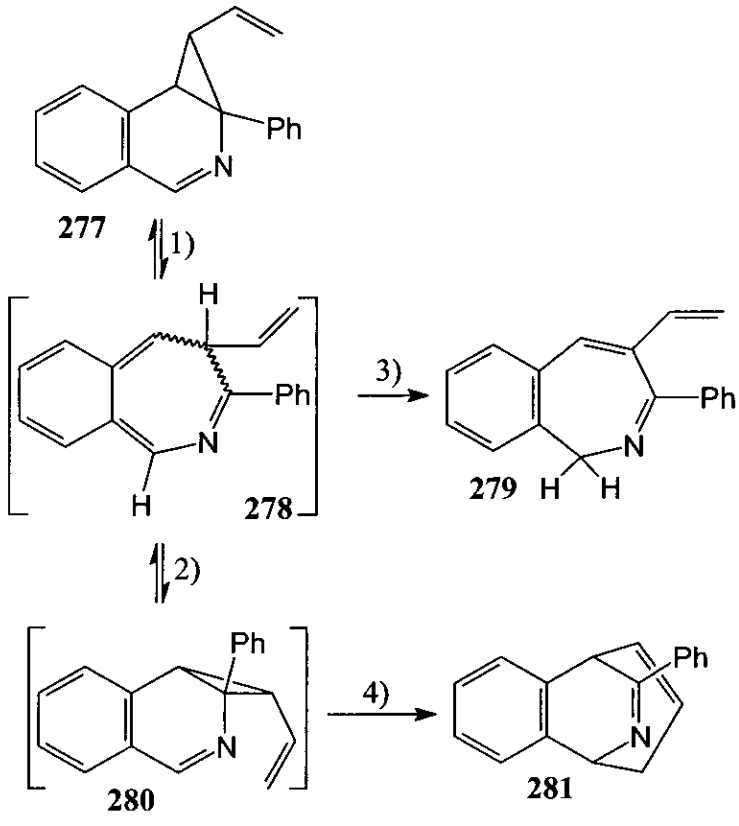


Scheme 108

The advantage of the above technique, which could account for its success, is that the highly reactive and labile imidoyl chloride is generated and reacted *in situ* without being isolated, lessening the possibility of hydrolysis by adventitious moisture. A disadvantage is that it is difficult to gauge the amount of acidic side-products left after chlorination has occurred, and so how much base will be required to react completely with the imidoyl chloride as well as with these unquantified residues. Also, a relatively large amount of involatile DMF is left in the crude product mixture after workup and this can be difficult to remove from thermolabile products such as cyclopropa[*c*]isoquinolines.

The expected product **277** was obtained from the cyclisation of nitrile ylide **276** in acceptable yield when a 50 % excess of chlorinating agent over amide and a 230 % excess of base over chlorinating agent were used, with some starting amide also being recovered. It is not known whether the recovered starting material originated from unchlorinated amide (which would indicate premature addition of base or insufficient chlorinating agent having been used) or from hydrolysis of the imidoyl chloride by adventitious moisture. The product exhibited the spectroscopic properties expected from comparison with the primary example **265** and other earlier examples of the cyclopropa[*c*]isoquinoline system [99].

As before, an NMR sample of the cyclopropa[*c*]isoquinoline was prepared in $CDCl_3$ and heated at 54 °C, with ^1H NMR spectra being obtained at measured intervals. The progress of the thermal rearrangement was found to be much slower than expected, with **277** taking around twice as long as **265** to completely rearrange under the same reaction conditions. This seemed to suggest that electronic effects, rather than steric, were the dominant factor controlling the rate of the rearrangement of the cyclopropa[c]isoquinolines. This observation was unexpected and provided impetus for further investigation. Complete consumption of the cyclopropa[*c*]isoquinoline **277** was observed after 17 hours of heating at 54 °C.



1) Electrocyclic ring-opening 2) Electrocyclic ring-closure
3) [1,5] H shift 4) Aza-Cope

Scheme 109

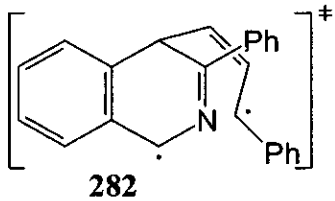
Examination of the ^{1}H NMR spectrum of the product and comparison with that of **268** suggested that there was a mixture of products in this case, rather than only the bridged isoquinoline as obtained upon thermolysis of **265**. This was borne out by TLC analysis which showed two close-running spots, neither of which was due to starting material. Dry-flash column chromatography allowed isolation of each compound and identification of the bridged isoquinoline **281** as the minor (40 %) component and 4-ethenyl-3-phenyl-1*H*-2-benzazepine **279** as the major (60 %) product of the thermolysis.

This surprising result shows that the identity of the seemingly remote terminal substituent had a profound effect on the rates of the possible rearrangement processes.

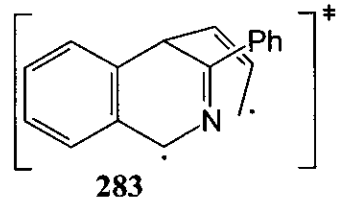
Both reaction products **279** and **281** would be formed *via* the same intermediate (**278**), produced by an electrocyclic ring-opening of **277**. In one reaction path **278** reacts *via* a [1,5] sigmatropic hydrogen shift to give the 4-ethenyl-1*H*-2-benzazepine **279**, and in the other path *via* a ring inversion followed by an aza-Cope rearrangement to give the bridged isoquinoline **281**. In the first example where R^4 = Ph then the first path, surprisingly, was not observed at all but in this case the replacement of the terminal Ph with H has so changed the relative rates that it is now the favoured path.

The change of substituent must therefore either be enhancing the rate of the [1,5] H shift or slowing down the rate of ring-inversion of **278**, or slowing down the rate of the aza-Cope reaction. It is not easy to explain any of these effects on steric grounds in terms of the reduction of the bulk of the terminal substituent on going from Ph to H.

It may be that the transition state for the aza-Cope process has some radical character, as indicated in **282**, and is stabilised by delocalisation into the terminal phenyl group. Where this group is absent, as in the case of compound **277**, the stabilisation of the transition state **283** would be lessened. This would have the effect of making the aza-Cope rearrangement less favourable, as observed.



282



283

At no time was the theoretically stable *endo* isomer of the cyclopropa[*c*]isoquinoline (**280**) observed by ^{1}H NMR, confirming that this isomer is very transient and either reacts *via* the aza-Cope rearrangement or reverts back towards the *exo*-isomer very quickly. It is also possible that the rate of the [1,5] hydrogen shift is somehow changed by the nature of the ζ-substituent in **278**, but this is unlikely as the substituent is a long way from the reaction site.

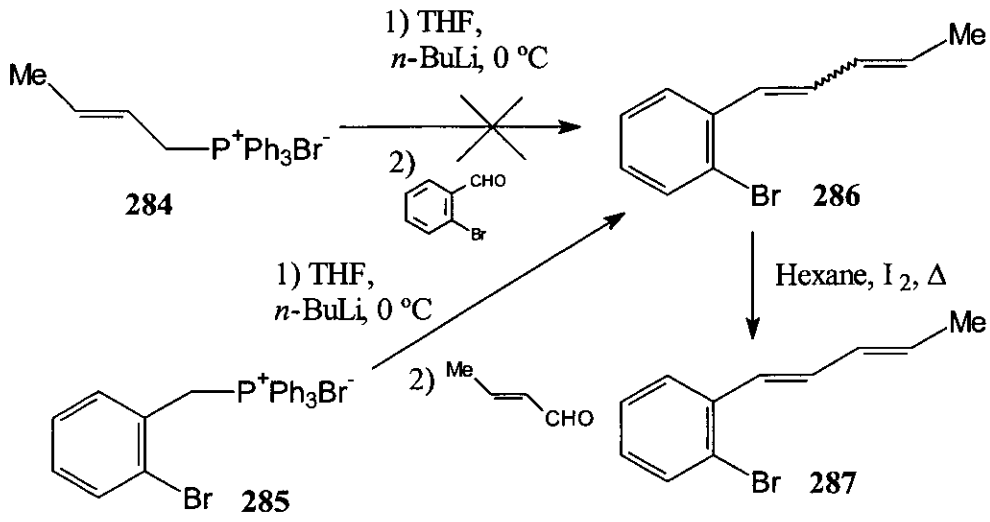
Another possible explanation is that the isomerisation to the theoretically reactive *endo* form (**280**) of the cyclopropa[*c*]isoquinoline is retarded in some way where R^4 = H, which would again have the effect of disfavouring the aza-Cope rearrangement. Further investigation was clearly required.

1.1.4 (*E,E*)-*N*-[2-(Penta-1,3-dienyl)benzyl]benzamide (289)

The next example investigated was the analogue with a methyl group at the terminal position. It was initially hoped that a uniform approach to synthesis of the *o*-dienylbromobenzenes could be developed, so that these starting materials could be constructed by simply choosing suitably substituted, readily available building blocks from two families, *e.g.* an aldehyde and a phosphonium halide. These reagent pairs could then be mixed and matched to obtain efficiently a large number of analogues.

An attempted Wittig reaction between crotyltriphenylphosphonium bromide (**284**) and *o*-bromobenzaldehyde proved unsuccessful, with only the starting aldehyde being recovered on workup (scheme **110**). Using the complementary pair (*i.e. o*-bromobenzyltriphenylphosphonium bromide (**285**) and crotonaldehyde, however, proved highly successful, giving a good yield of the (*E,E*) and (*Z,E*) isomers of the desired product **286**.

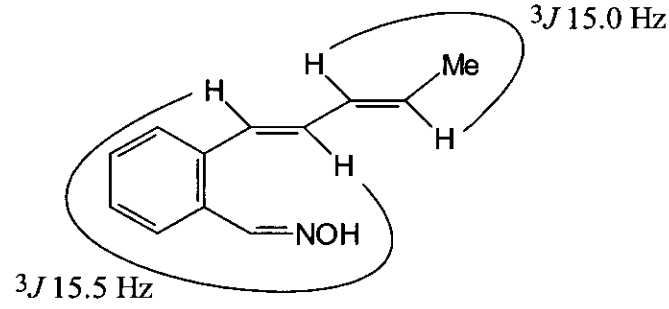
The unwanted isomer was converted to the desired (*E,E*) isomer **287** under the usual conditions, although TLC analysis was not helpful as the two spots were superimposed. Treatment of **286** in refluxing hexane for extended periods was found to cause some polymerisation, the products of which were removed by passing the crude extract from the isomerisation through a short pad of silica as a solution in 9:1 hexane-ether. The geometry about the γ,δ olefin again was not obvious in the ^{1}H NMR spectrum of **287** as the signals from H-1 and H-2 were superimposed, but the ^{13}C spectrum showed only the number of peaks expected of a single isomer.



Scheme 110

This protocol (incorporating the prospective ε,ζ olefin *via* the aldehyde) proved in the event to be the best general method, and further batches of the preceding examples of *o*-dienylbromobenzenes (R^4 = Ph, H; **254** and **269** respectively) were subsequently synthesised *via* this route, using acrolein or cinnamaldehyde in place of crotonaldehyde.

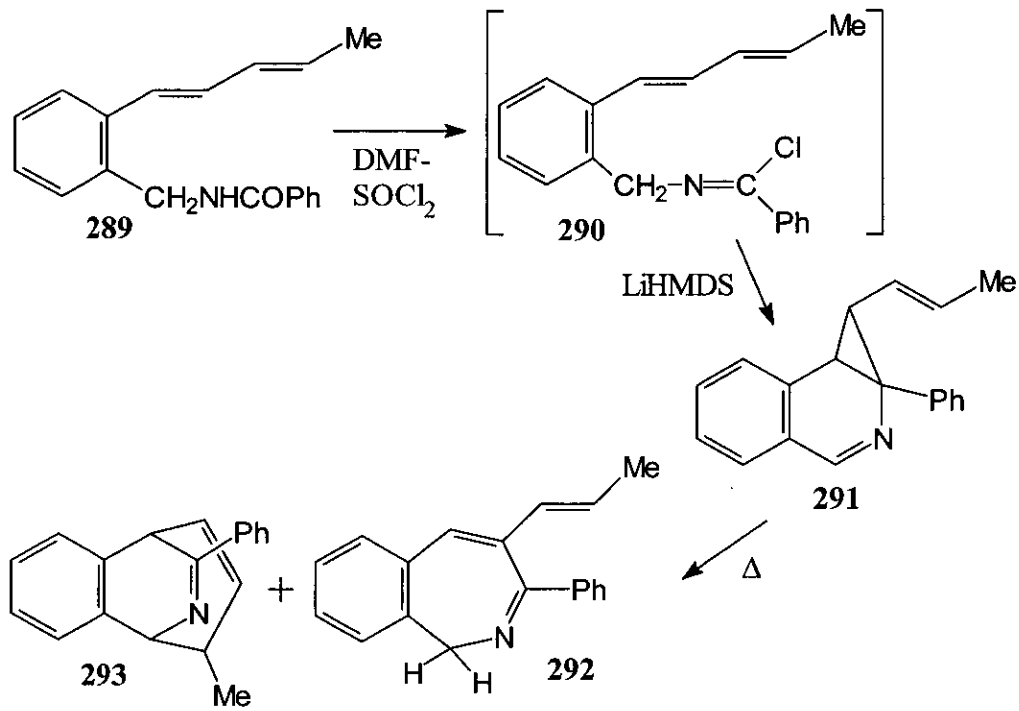
The functional group transformation steps again proceeded as expected, in good yields. The ^{1}H NMR spectra of the aldehyde and oxime allowed assignment of each olefinic proton signal, with $^3J_{HCCH}$ values of 15.5 Hz observed for the splitting about γ,δ double bond and 15.0 Hz about the ε,ζ unsaturation, confirming that the trienyl system was indeed in the (*E*,*E*) configuration.



288

The imidoyl chloride **290** was generated from amide **289** using the DMF/$SOCl_2$ method and **290** was reacted by treatment with LiHMDS, as in the previous example.

Chromatography of the products allowed isolation of some unreacted starting material, and the (*E*)-2-propenyl substituted *exo*-cyclopropa[*c*]isoquinoline **291**, which had the expected spectroscopic properties. Thermolysis of this new product in $CDCl_3$ was again found to proceed slowly, with total consumption of starting material observed to occur after 16 hours of heating at 64 °C.



Scheme 111

The ^{1}H NMR spectrum of the new product again showed that a mixture of the bridged isoquinoline and the 1*H*-2-benzazepine had been obtained. In this case the two components **292** and **293** proved to be inseparable by all chromatographic techniques available, including MPLC, and were completely indistinguishable by TLC under all solvent systems used. The mass spectrum of the mixture showed the molecular ion to be *m/z* 259.1361, the mass required of both products shown to be present by ^{1}H NMR.

This result was broadly in line with expectations following the thermolysis of **277**. The product ratio (3:1 azepine:bridged isoquinoline) had been moved even further in favour of the azepine by placing a methyl group at the ζ position of the triene. If the behaviour of the cyclopropa[*c*]isoquinoline **277**, which was derived from the

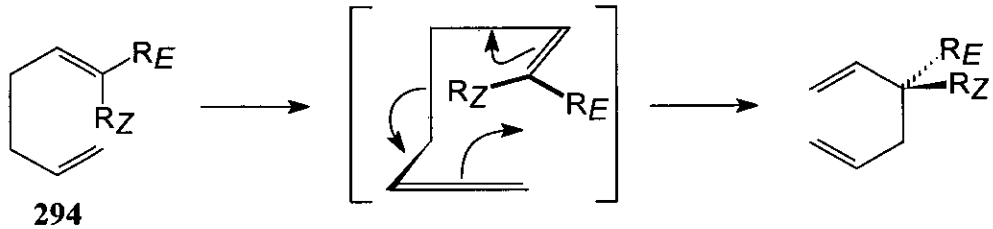
unsubstituted amide **274**, is taken as the default behaviour of 1-alkenyl cyclopropa[*c*]isoquinolines then it appears that adding the methyl group at the terminus of the olefinic system (*i.e.* in **291**) has had little effect. The rearrangement time was significantly longer than that for the ζ-Ph analogue **265**, which again seems to suggest that no one rearrangement mechanism is particularly favoured by making this change at the ζ-position, and that the aza-Cope has been disfavoured in some way.

From these three results (thermolyses of **265**, **277** and **291**) a pattern begins to emerge concerning the effects that the ζ-substituent on the conjugated (*E,E*) triene exerts on the direction taken in the thermal rearrangements of 1-alkenyl-*exo*-cyclopropa[*c*]isoquinolines. If the methyl group can be classified as electron donating by its inductive effect, hydrogen is taken, by definition, as electronically neutral and the phenyl group has an electron-withdrawing effect, then these results could be partially explained by consideration of the electron density at the ζ position.

If this argument holds, the initial example (R^4 = Ph) has the lowest electron density at this position and reacts entirely *via* the aza-Cope rearrangement. The example with R^4 = Me would have the highest electron density at the ζ terminus of the olefinic system and is observed to react predominantly *via* the [1,5] hydrogen shift to give the azepine. The analogue **277** with H in the ζ-position would be expected to have intermediate electron density at this position, and the product distribution is indeed pitched between those obtained from the two substituted analogues **265** and **291**.

The classification of the electronic behaviour of the three ζ-substituents is supported by the chemical shifts of the ζ-protons in the ^{1}H NMR spectra of the precursors, with the expected doublet from this proton being obscured by the aromatic multiplet in the phenyl case. When the ζ-substituent is alkyl the signals from the ζ-proton are clearly observed at a lower shift, suggesting a greater degree of electronic shielding for these protons.

The results of *ab initio* calculations on the effects of geminal bond participation on the rate of Cope rearrangements of 1,5-hexadienes carried out by Inagaka and co-workers[127] are also in agreement with the results observed here. They concluded that electron-accepting σ-bonds at the *trans* position of the olefin **294** (R_E, scheme **112**) should facilitate this reaction. This is analogous to the situation where R^4 = Ph, and an acceleration of the aza-Cope was indeed observed experimentally, with the analogues **277** and **291** (R^4 = Me and H respectively) being less able to undergo this rearrangement.

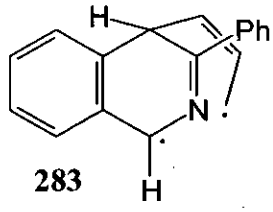


294

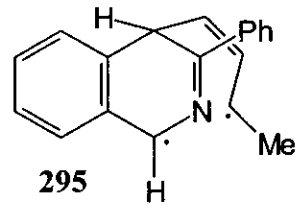
Scheme 112

Inagaki and co-workers also noted that the Cope rearrangement should be accelerated by an electron-donating group at the *cis*-position (R_Z) of a participating alkene, but no reactions of that type were attempted here.

It is possible that, where R^4 is aromatic, the postulated diradical intermediates in the aza-Cope rearrangements are stabilised by greater delocalisation than is possible where R^4 is *e.g.* methyl or hydrogen. This extra stability would have the effect of favouring the aza-Cope process more where R^4 is aromatic than where it is alkyl, as has been observed here. It would be expected that where R^4 = Me the associated radical in transition state **295** would be more stabilised than the case where R^4 = H (*i.e.* **283**) as secondary radicals are more stable than primary ones. The fact that more aza-Cope product was obtained where R^4 = H is ascribed to the smaller steric bulk of that group compared with the methyl group.



283



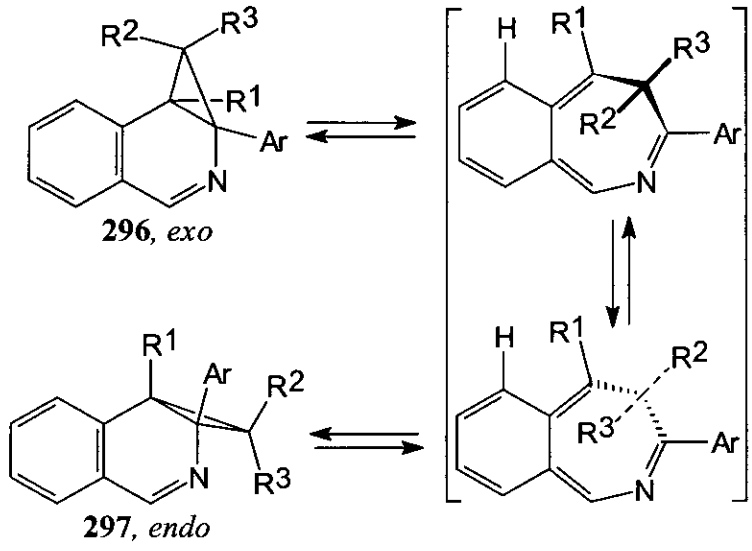
295

The mechanism (or balance of mechanisms) by which the effect of the ζ-substituent operates is unclear at this point. The slower rates of rearrangement of **277** and **291** (R^4 = H and Me respectively) suggests that the isomerisation of the *exo* to the *endo* isomer of the cyclopropa[*c*]isoquinolines is retarded in some way to favour the *exo* isomer (which cannot react *via* the aza-Cope rearrangement). It could also be inferred that the aza-Cope has become less facile and the *endo* isomers of **277** and **291** are initially formed, but do not react with the imine before reverting back to the *exo* form or undergoing a [1,5] H shift. Although a solid conclusion cannot be drawn from these results, at least a pattern can be recognised.

1.1.5 (*E*,*E*)-*N*-[2-(Penta-1,3-dienyl)benzyl]-*o*-toluamide (299)

The aza-Cope rearrangement can only take place in the *endo*-isomer of the cyclopropa[*c*]isoquinoline, *i.e.* the one in which the alkenyl group is *cis* related to the imine function. The rate of this process could, therefore, depend on the position of the equilibrium between the *exo* and *endo* isomers. The intention was to perturb the position of this equilibrium and find out if this had any effect on the course of the thermal reaction of the 1-alkenyl cyclopropa[*c*]isoquinolines.

Earlier work [99] had shown that in cases where R^3 = Me or Ph the equilibrium favours the *endo* isomer by *ca.* 2-3:1 (scheme **113**). This shows that the R^3 group has a stronger steric interaction with Ar in **296** than with the imino N atom in the *endo*-isomer **297**. Increasing the bulk of the aryl group (Ar) should therefore push the equilibrium further in favour of the *endo* isomer, making the aza-Cope rearrangement more feasible where R is alkenyl in **296**.



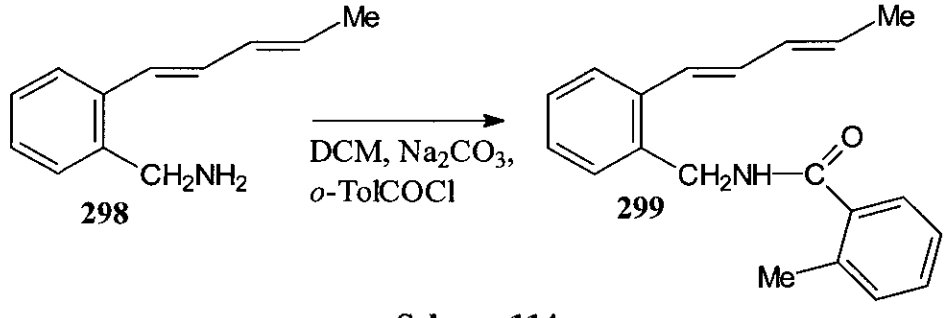
296, *exo*

297, *endo*

R^1, R^2 = Ph, Me or H
R^3 = alkenyl

Scheme 113

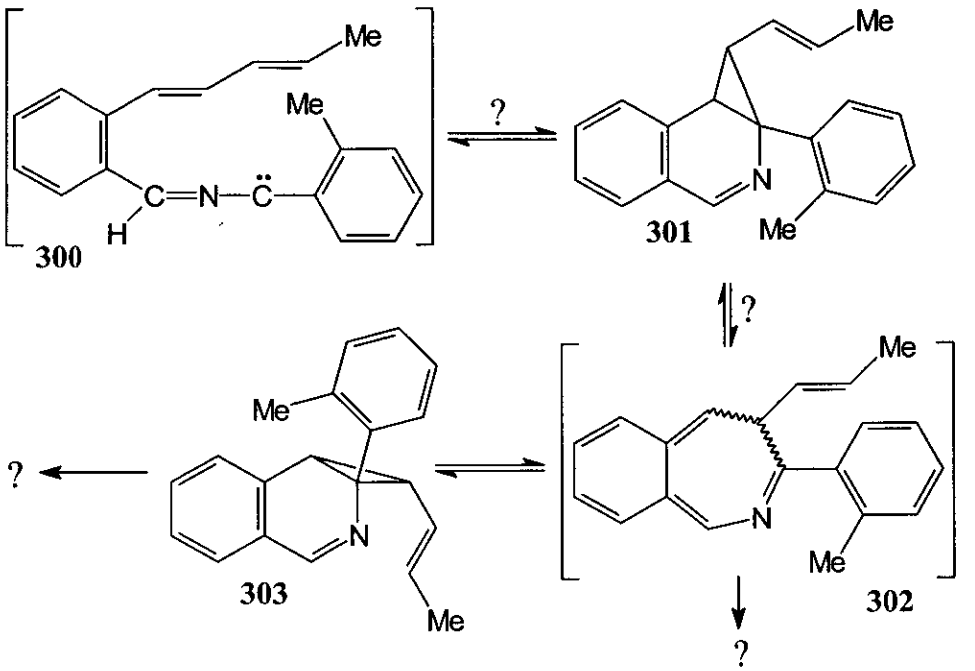
It was therefore decided to resynthesise the amine **298** (ζ = Me), but instead of reacting this with benzoyl chloride to obtain the benzamide **289**, *o*-toluoyl chloride would be used to generate the *o*-toluamide **299**.



298 **299**

Scheme 114

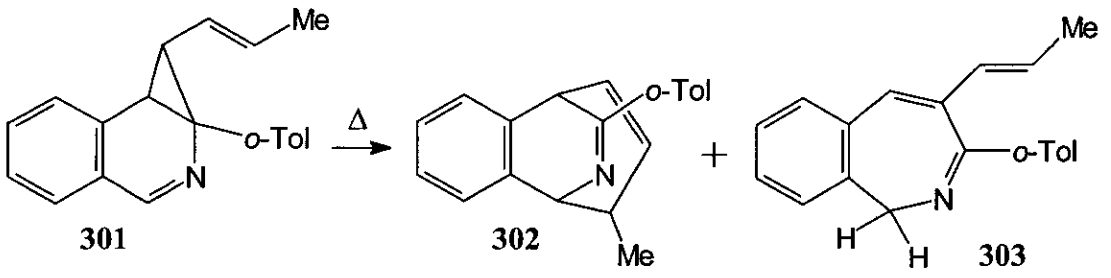
The intention here was to increase steric bulk at the cyclopropyl ring in the cyclopropa[*c*]isoquinoline **301**, relative to the examples synthesised thus far (**265**, **277** and **291**) by incorporation of the *ortho*-methyl group on the aryl ring of the amide, while incorporating a trienyl system which had already been used in this type of reaction and whose basic behaviour was known.



Scheme 115

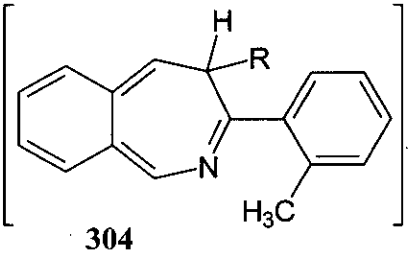
As stated, the synthesis of the amide **299** was simply a matter of using *o*-toluoyl chloride in the aroylation of the previously synthesised amine **298**. This step was achieved in good yield, with the product **299** exhibiting the expected spectroscopic properties. Chlorination of the amide by the established DMF-$SOCl_2$ methodology and subsequent dehydrochlorination of the imidoyl chloride with LiHMDS in the usual manner allowed generation of the nitrile ylide **300**, which reacted as expected. The cyclopropa[*c*]isoquinoline **301** was isolated and thermolysis of this was carried out as usual.

It is interesting to note that complete rearrangement of the cyclopropa[*c*]isoquinoline **301** was found to take substantially longer than was required for the analogue **291** (Ar = Ph). Surprisingly, however, the composition of the product mixture obtained from **301** was found to be nearly identical to that obtained from **291**.



Scheme 116

The greater amount of time required for complete consumption of starting material **301** compared to that taken for reaction of **291** (Ar = Ph) is attributed to lessening of conjugation in the non-aromatic planar azepine structure **304**, which is the transition state for ring-inversion. Where Ar = Ph the substituent ring can adopt the correct geometry with the azepine ring to allow conjugation between the two. Where a methyl substituent is added in the *ortho* position of the Ar ring then this ring is twisted out of the plane of the azepine ring and conjugation in this structure, and thus stabilisation of the intermediate **304** is lessened.



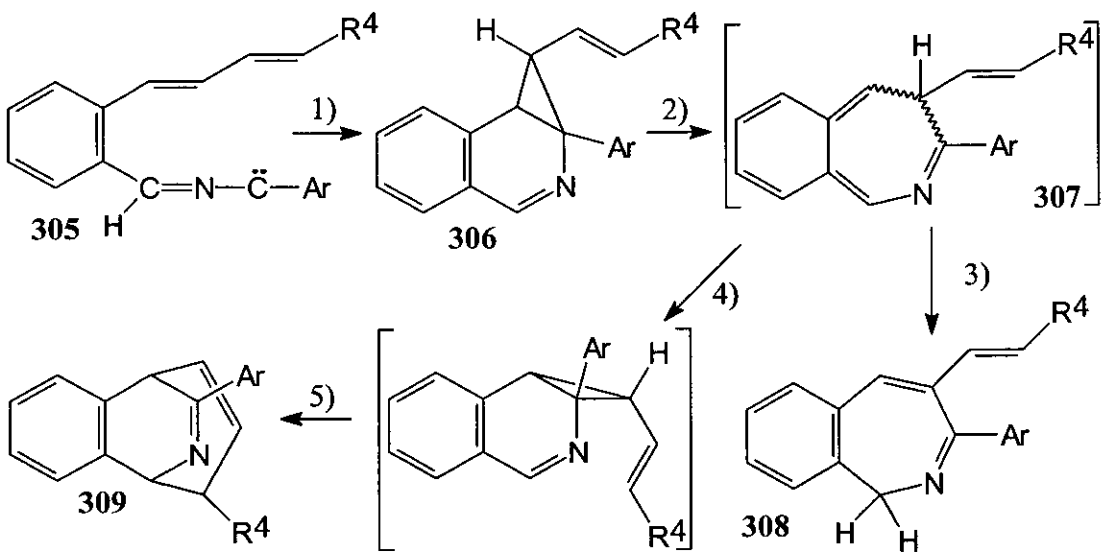
304

It would appear therefore that the bulk of the 1a-substituent of the cyclopropa[*c*]isoquinolines and hence the position of the *exo*/*endo* equilibrium does not have a major effect on the outcome of the thermolyses of these compounds.

1.1.6 Conclusion

Table 1

R^4	Ar	Amide No.	Primary product	Thermolysis product(s)
Ph	Ph	**262**	**306** (74 %)	**309** (Quantitative)
H	Ph	**274**	**306** (47 %)	**308** (60 %) + **309** (40 %)
Me	Ph	**289**	**306** (64 %)	3:1 **308**:**309** (Quantitative)
Me	*o*-Tol	**299**	**306** (56 %)	3:1 **308**:**309** (Quantitative)



1) 1,1-Cycloaddition 2) Electrocyclic ring-expansion 3) [1,5] H Shift
4) Electrocyclic ring-closure 5) Aza-Cope rearrangement

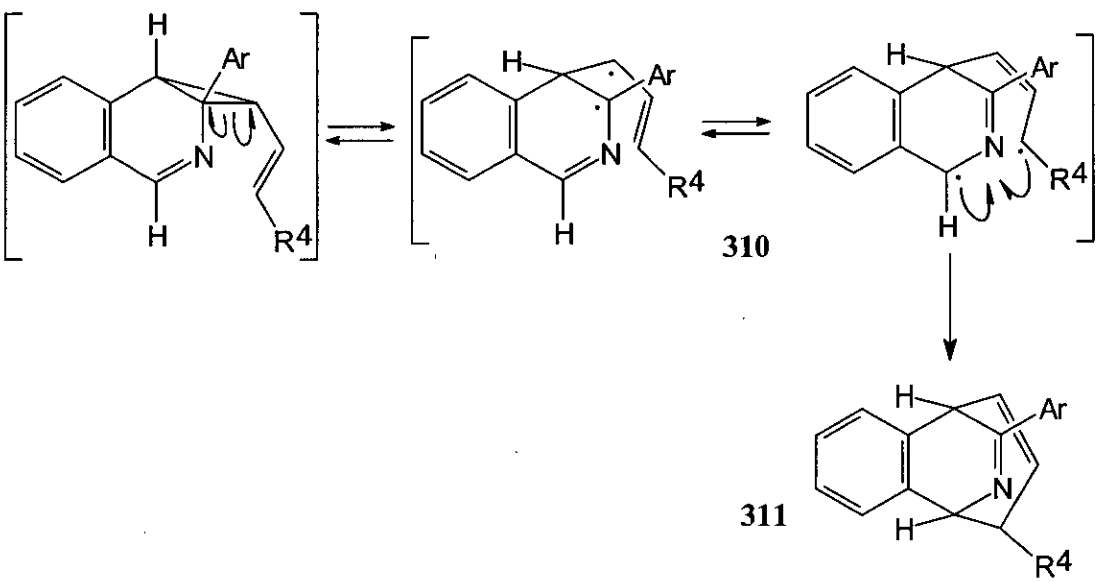
Scheme 117

The results from the reactions detailed in the foregoing sections show that the ζ-substituent of triene-conjugated nitrile ylides of the type **305**, where the γ,δ;ε,ζ unaturations are olefinic, holds a strong influence over the favoured rearrangement processes of the initially-formed 1-alkenyl cyclopropa[*c*]isoquinolines (**306**). The trend that becomes apparent from the results reported here is that aromatic ζ-substituents favour rearrangement of the cyclisation product *via* an aza-Cope rearrangement to yield the bridged isoquinolines **309**. Non-aromatic substituents at

this position appear to disfavour this process and promote rearrangement *via* a sigmatropic [1,5] H shift in **307** to yield the 4-alkenyl 1*H*-2-benzazepines **308**.

The bulk of the substituent at C-1a of the cyclopropa[*c*]isoquinolines **306**, which was increased in example **301** (Ar = *o*-Tol) relative to the other analogues (Ar = Ph), does not appear to hold a decisive role in deciding the favourabilities of the two rearrangement processes observed thus far.

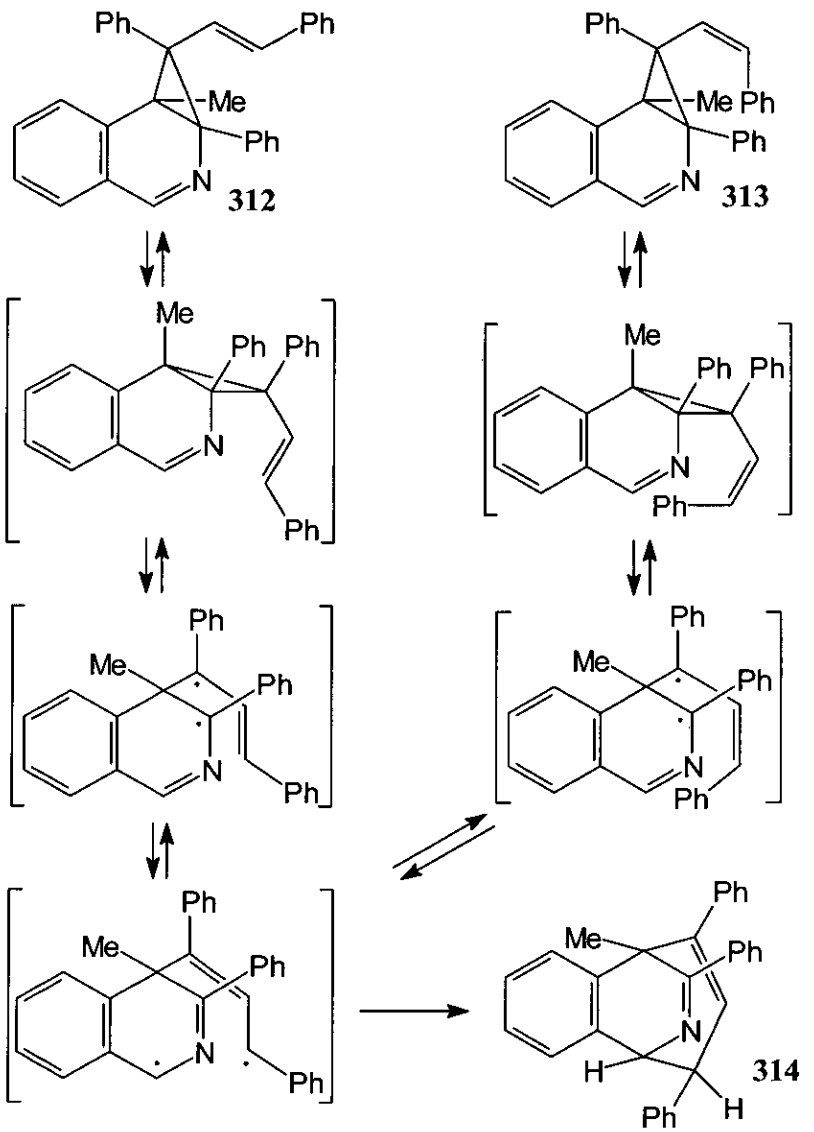
The intermediacy of diradicals of the type **310** in the aza-Cope rearrangement could account for the results obtained in this section, with aromatic groups at R^4 conferring greater stability than in cases where R^4 is alkyl. Accordingly, the example where R^4 = Ph (compound **265**) was observed to rearrange exclusively *via* this pathway, whereas examples where R^4 = Me or H favoured an alternative rearrangement mode, *via* a [1,5] H shift. These facts are consistent with the diradical intermediate **310** being implicated in the aza-Cope reaction.



Scheme 118

Observations which provide support for this theory have been made previously by Sharp. Where the (*Z*)-1-(2-phenylethenyl)cyclopropa[*c*]isoquinoline **313** was thermolysed it was found to yield the same product mixture as that obtained from the (*E*) isomer (**312**). The formation of the (*E*) isomer **312** was also observed while

monitoring the thermolysis of the (*Z*) isomer **313**, suggesting that all steps except the final ring-closure to give **314** in the aza-Cope reaction are reversible. This is consistent with the intermediacy of a diradical species such as **310**.

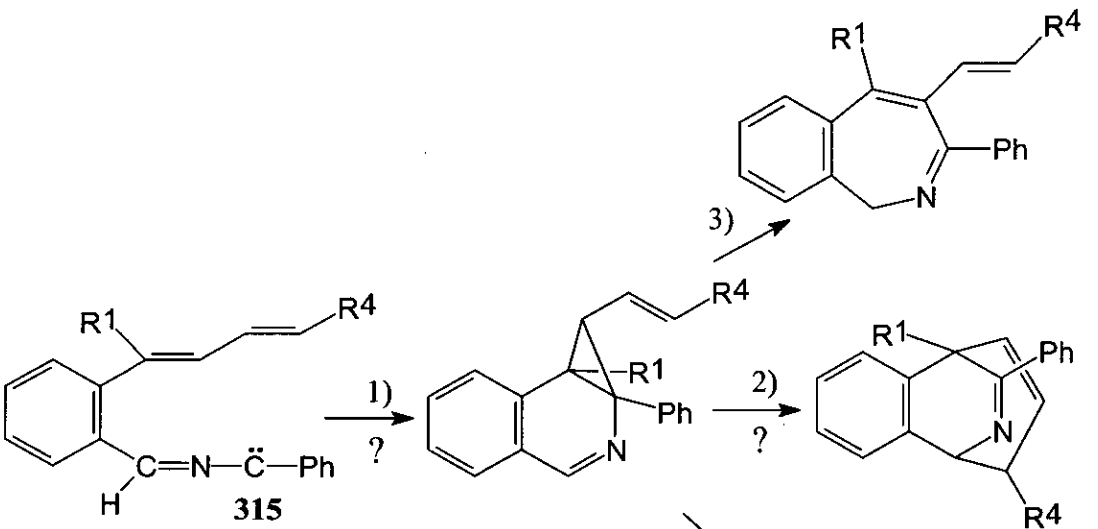


Scheme 119

1.2 Generation and Reaction of Nitrile Ylides Derived from 1',4'-Disubstituted (*E*,*E*)-*N*-[2-(Buta-1',3'-dienyl)benzyl]benzamides

1.2.1 Preamble

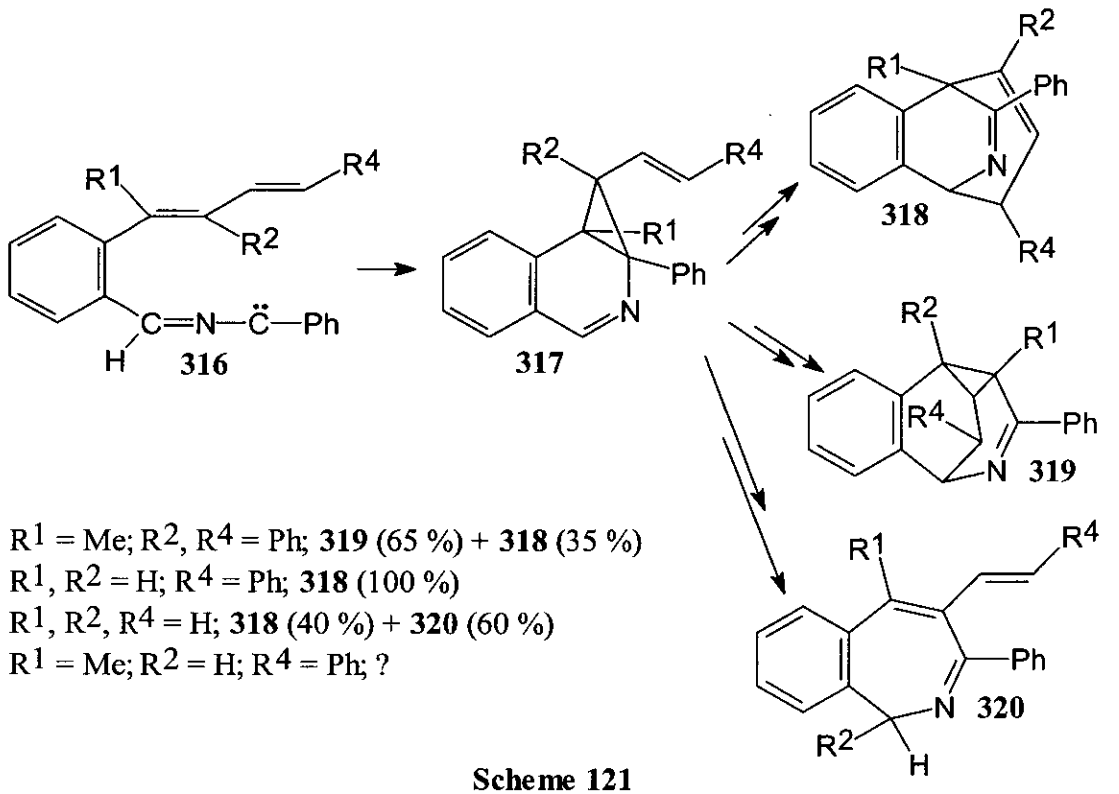
As the previous work made clear, the identity of the substituent at the terminal (ζ) olefinic position in triene-conjugated nitrile ylides has a profound effect on the preferred pathway of thermal rearrangement of the cyclisation products. In order to explore further, it was decided to investigate the effect of placing substituents at the γ position on the trienes **315** (scheme **120**).



Scheme 120

In previous work[94], triene-conjugated nitrile ylides with tri-substitution at the γ-, δ- and ζ-positions of the triene (**316**) have been shown to undergo 1,1-cycloadditions. The cyclopropa[*c*]isoquinolines so derived were found to rearrange to give bridged isoquinolines (**318**) along with azabenzobabaralenes (**319**) in a process which will be discussed later in this discussion (section **1.3.2**). The rearrangement leading to the second product was also discussed in the introduction of this thesis (section **5.1**) and

in the programme of research. It was hoped that the reduction in the bulk of the substituent at the δ-position of the reactant would disfavour azabenzobabaralane formation and favour formation of the bridged isoquinolines.

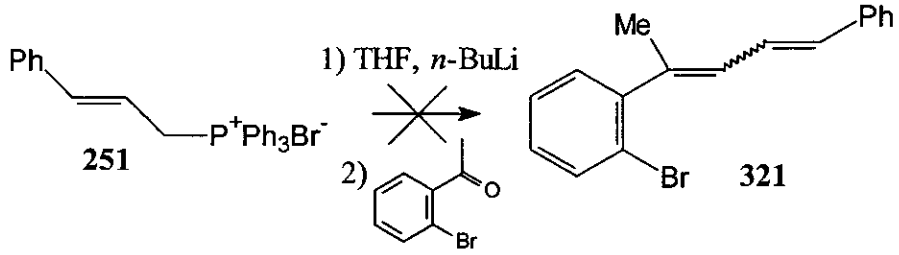


R^1 = Me; R^2, R^4 = Ph; **319** (65 %) + **318** (35 %)
R^1, R^2 = H; R^4 = Ph; **318** (100 %)
R^1, R^2, R^4 = H; **318** (40 %) + **320** (60 %)
R^1 = Me; R^2 = H; R^4 = Ph; ?

Scheme 121

1.2.2 (*E*,*E*)-*N*-[2-(1-Methyl-4-phenylbuta-1,3-dienyl)benzyl]benzamide (326)

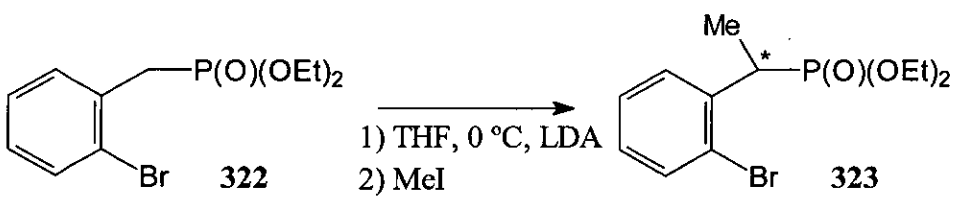
The primary target in this work was the diene-conjugated bromobenzene **321**, with a methyl group at the olefinic γ position and a phenyl ring at the terminal ζ position. Initial attempts at the synthesis of this compound using the protocol developed for the analogous compound **255** proved unsuccessful, with very poor yields (at best) being obtained from the reaction of the ylid of cinnamyltriphenylphosphonium bromide **251** with *o*-bromoacetophenone (scheme **122**). Experimentation with reaction conditions (base used, time allowed for deprotonation, temperatures used) did not improve matters. The starting ketone was the only compound recovered in each case.



Scheme 122

It was decided to move away from Wittig methodology and, rather than resorting to the lengthier Grignard synthesis used to obtain compound **269**, introduce Wadsworth-Emmons type reactions in an attempt to refine the olefination protocol to allow greater flexibility with regard to substituent position.

Initially, this reaction sequence involved methylation of diethyl *o*-bromobenzylphosphonate **322**, itself derived from *o*-bromomethylbromobenzene and triethylphosphite[128]. This new methyl group would be incorporated at the desired γ-position on the triene following the olefination reaction. Generation of the ylid by deprotonation of the phosphonate **322** with LDA or LiHMDS (*not* BuLi, to avoid Li/Br exchange at the bromobenzene ring of **322**) followed by quenching with iodomethane generated the methylated phosphonate **323**. This compound was easily isolated and purified on a large scale prior to its use in olefination reactions.

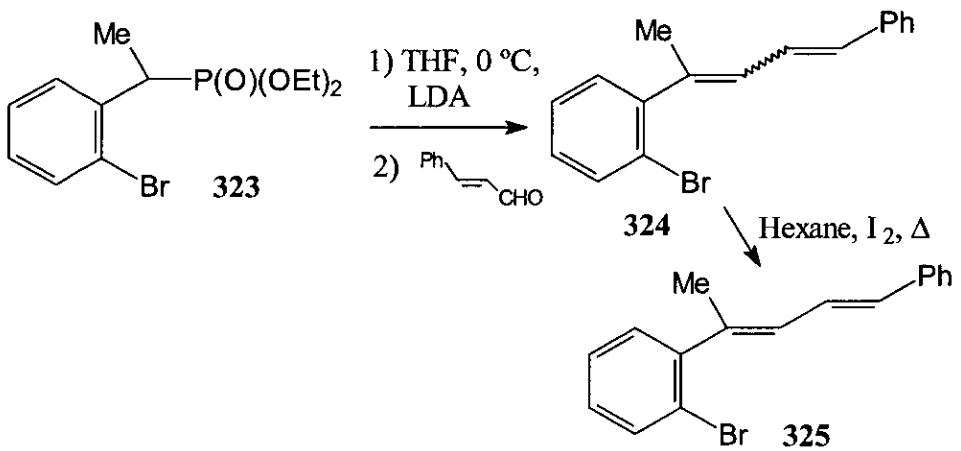


Scheme 123

The fact that a chiral centre (* in **323**) was being generated was irrelevant, as it would be obliterated upon deprotonation in the ensuing Wadsworth-Emmons reaction and the carbon atom concerned was fated to become trigonal in the product.

Once the methylated phosphonate was in hand, it was deprotonated as detailed for the methylation and the ylid was reacted with cinnamaldehyde. Monitoring the

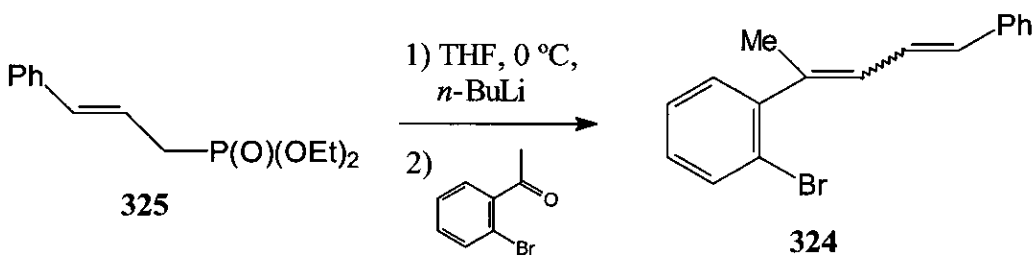
reaction by TLC revealed a new high running spot, which on work up was found to be the desired compound **324**, as a mixture of (*E,E*) and (*Z,E*) isomers. Standard iodine-catalysed isomerisation gave the (*E,E*) isomer **325** and the rest of the synthetic sequence to the amide proceeded well.



Scheme 124

The protocol outlined above, either with or without the methyl group on the phosphonate, proved to be the optimum route to the diene-conjugated bromobenzenes, working excellently for all previous and subsequent syntheses of this type. This was generally a better procedure than the analogous Wittig reaction.

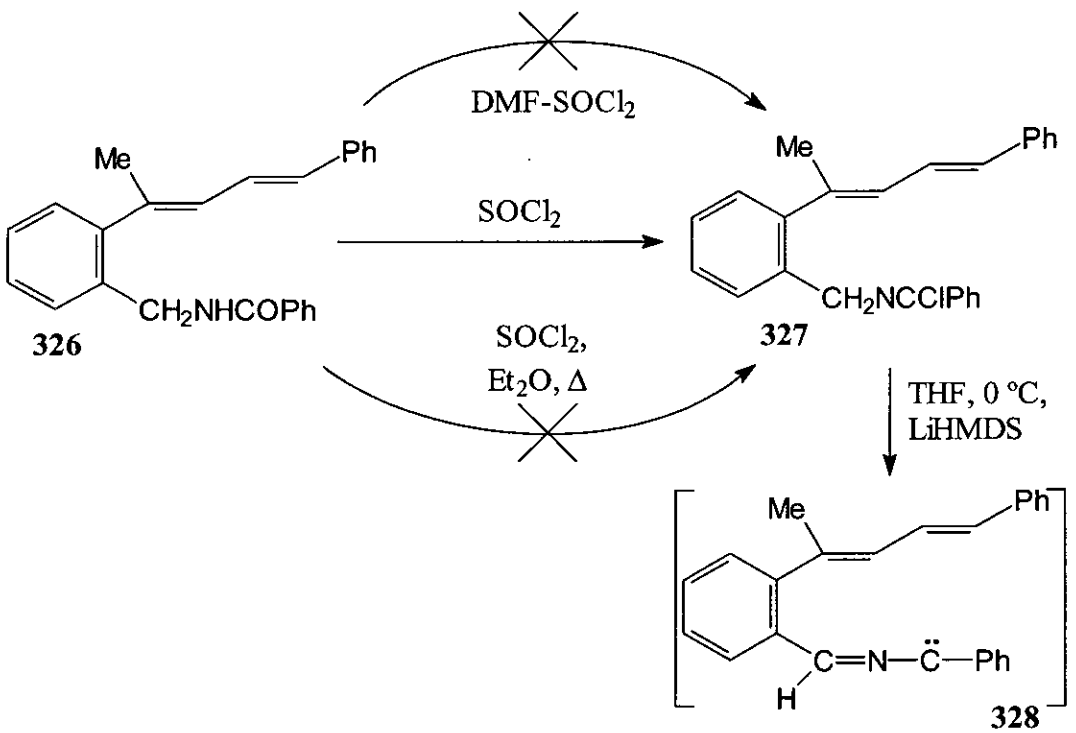
The synthesis of **324** was also achieved *via* a Wadsworth-Emmons reaction between diethyl (*E*)-cinnamylphosphonate and *o*-bromoacetophenone (scheme **125**), although the yield was less good than the method previously described. Analogous Wadsworth-Emmons and Wittig reactions between allyl- and crotyl-triphenylphosphonium bromides and diethylphosphonates and *o*-bromoacetophenone failed completely.



Scheme 125

Generation of the imidoyl chloride **327** from this amide proved even more problematic than for the previous examples. The DMF/$SOCl_2$ chlorination technique and refluxing a solution of the amide and thionyl chloride in ether over prolonged periods both failed to produce any new compounds on treatment of the mixture with base. Even after ensuring the dryness of all reagents no reaction was detected in any attempt.

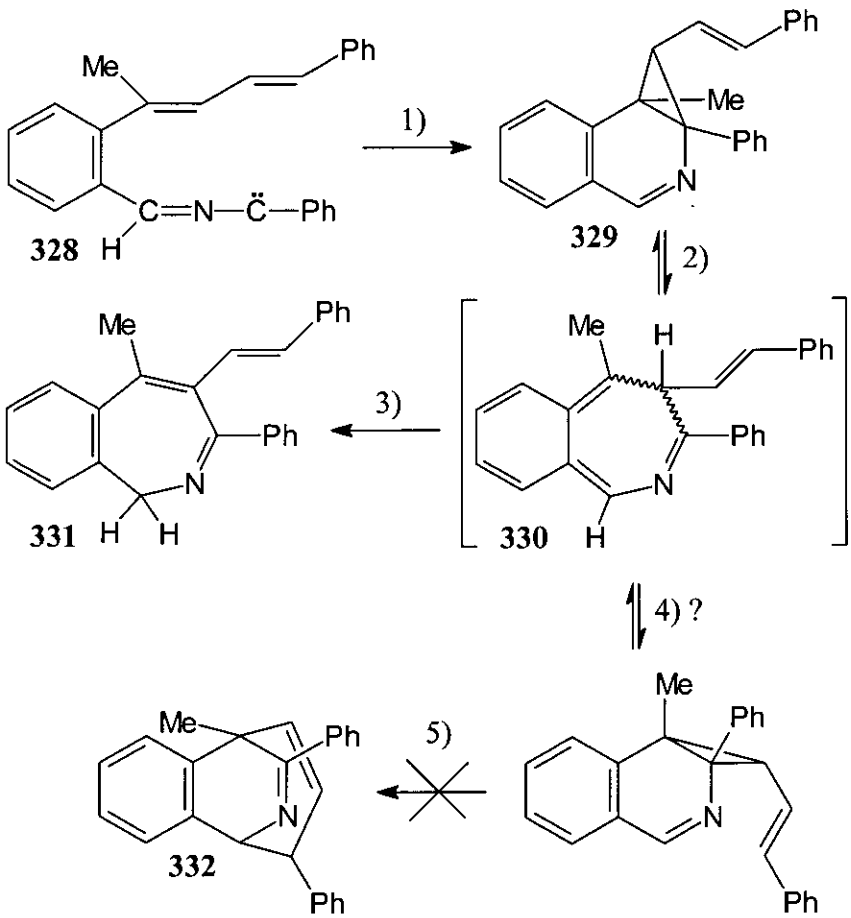
A more direct approach was taken in view of these failures. A portion of the amide **326** (1.7 mmol) was stirred with a large excess of neat thionyl chloride (4.0 cm^3) at room temperature under nitrogen and after 30 minutes the excess chlorinating reagent and volatile side-products were removed from the dark yellow solution *in vacuo*. A sample of the crude gum obtained was dissolved in $CDCl_3$ which had been stored over 4 Å molecular sieves and the solution was transferred to an NMR tube which had been dried at high vacuum over fresh P_2O_5. The ^1H NMR spectrum obtained showed that the sample consisted primarily (> 80 %) of a new compound, the signals from which were consistent with those expected of the imidoyl chloride **327**.



Scheme 126

The most indicative feature of this ^{1}H NMR spectrum was an intense singlet at δ 4.92 with an integral trace corresponding to two protons, arising from the methylene group of the imidoyl halide **327**. This signal is also present in the same region in the ^{1}H NMR spectrum of the amide **326**, but in the amide it appears as a doublet due to splitting by the vicinal NH proton. As the signal now appeared as a singlet it was obvious that the chlorination had been successful and the bulk of the amide **326** had been converted to the imidoyl chloride **327**.

The remainder of the prepared imidoyl chloride was dissolved in dry THF and treated with LiHMDS at 0 °C as usual. Monitoring of the reaction's progress by TLC showed a new spot developing, as well as residual amide, which was expected as the ^{1}H NMR spectrum of the imidoyl chloride had indicated incomplete conversion. Workup of the reaction followed by chromatography allowed isolation of the new product in good yield. The ^{1}H NMR spectrum showed the characteristic peaks of the cyclopropa[*c*]isoquinoline system along with the expected (*E*)-olefinic signals. Heating a solution of this product in $CDCl_3$ caused complete consumption of **329** after 8 hours at 54 °C. The only product observed in the ^{1}H NMR spectrum after thermolysis was easily identified as the 5-methyl-4-alkenyl-3-phenyl-1*H*-2-benzazepine **331**, with the characteristic broad, temperature sensitive doublets arising from the methylene group appearing at δ 3.95 and δ 4.80.



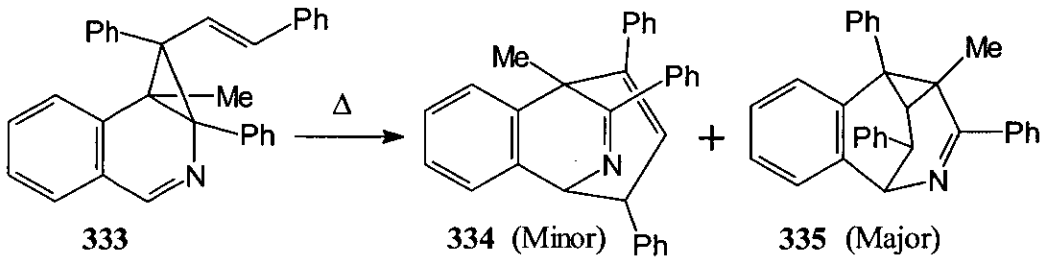
1) 1,1-Cycloaddition 2) Electrocyclic ring-expansion
3) [1,5] H shift 4) Electrocyclic ring-closure 5) Aza-Cope

Scheme 127

This surprising result illustrated the high degree of sensitivity of the thermal behaviour of 1-alkenyl cyclopropa[*c*]isoquinolines to the nature and position of substituents on the olefinic system. In this case the imposition of a substituent at a site apparently remote from the aza-Cope reaction sites has caused a complete switch of mechanism away from the aza-Cope, which occurred exclusively in this group's absence, to the ring-opening / H-shift mechanism, resulting in only the 1*H*-2-benzazepine **331** being obtained.

This switch of mechanism is doubly surprising in view of previous results from Sharp's group[95], where an analogous (*E*)-1-(2-phenylethenyl)-*exo*-cyclopropa[*c*]isoquinoline **333** with a methyl in this position (at C-7b) and also a

phenyl ring at the C-1 position rearranged (over 35 hours in refluxing C_6D_6, scheme **128**) to give, as the minor (35 %) product the bridged isoquinoline **334**, as well as the azabenzobabaralene **335**, which will be discussed later.



333 **334** (Minor) **335** (Major)

Scheme 128

As none of the bridged isoquinoline **332** whatsoever was obtained in the current example it is clear that substituents at the γ and δ positions, as well as at the ζ position, have an important influence on the rearrangement processes. The presence of a substituent at the γ position obviously either disfavours the aza-Cope mechanism and/or favours the [1,5] H shift in **330**. As the example from Strachan's work showed, however, the aza-Cope mechanism can still operate, albeit to a reduced extent, with a substituent at the γ position. In that case the H shift was precluded as a phenyl ring had replaced the migrating hydrogen atom.

In light of the information to hand thus far, then, it appears that the mechanistic selectivity is dictated by relative rates of the competing rearrangements, *i.e.* rearrangement processes which are not observed to occur are not impossible, but are outpaced by more favourable processes.

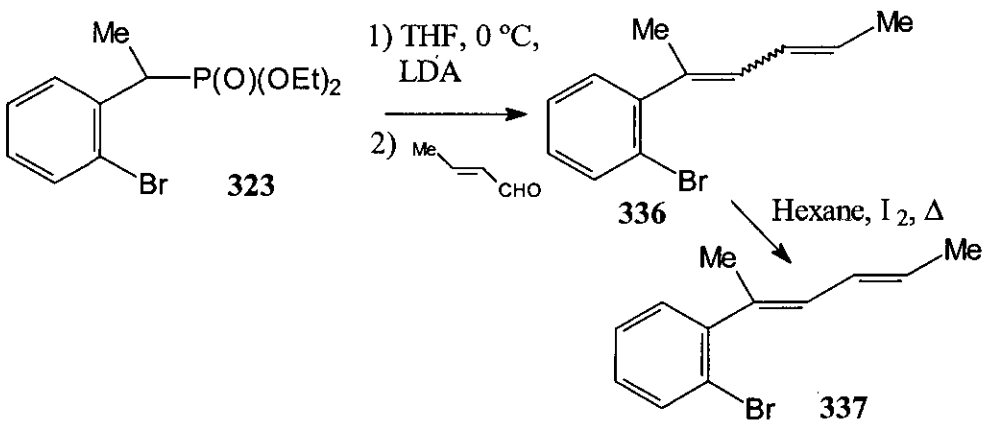
In the absence of non-hydrogen substituents about the triene the aza-Cope rearrangement and [1,5] H shift appear to be closely matched in terms of rate, as shown by the result of thermolysis of **277**. Aromatic ζ-substituents appear to favour the aza-Cope rearrangement, with non-aromatic ζ-substituents retarding the progress of the aza-Cope rearrangement and so allowing significant competition from the [1,5] H shift, as reflected in the compositions of the product mixtures from thermolysis of **265**, **277** and **291**. However, a methyl substituent located at the C–7b

position (*e.g.* in **329**) strongly promotes the [1,5] H shift (at the expense of the aza-Cope mechanism), so making the 1*H*-2-benzazepines **320** the dominant products.

1.2.3 (*E*,*E*)-*N*-[2-(1-Methylpenta-1,3-dienyl)benzyl]benzamide (338)

As the identity of substituents at the terminal ζ position in the previous series had been found to be critical in determining the favoured products of the thermal rearrangements of the cyclopropa[*c*]isoquinolines it was decided to synthesise the precursors which hold a methyl group at the γ position and vary the ζ substituent. To this end, compound **337** was to be the initial target.

This synthesis was achieved straightforwardly and in high yield by Wadsworth-Emmons reaction of crotonaldehyde with the ylid of methylated diethyl *o*-bromobenzylphosphonate **323**, followed by the usual iodine catalysed isomerisation to give only the desired (*E*,*E*) isomer of the diene **337**.

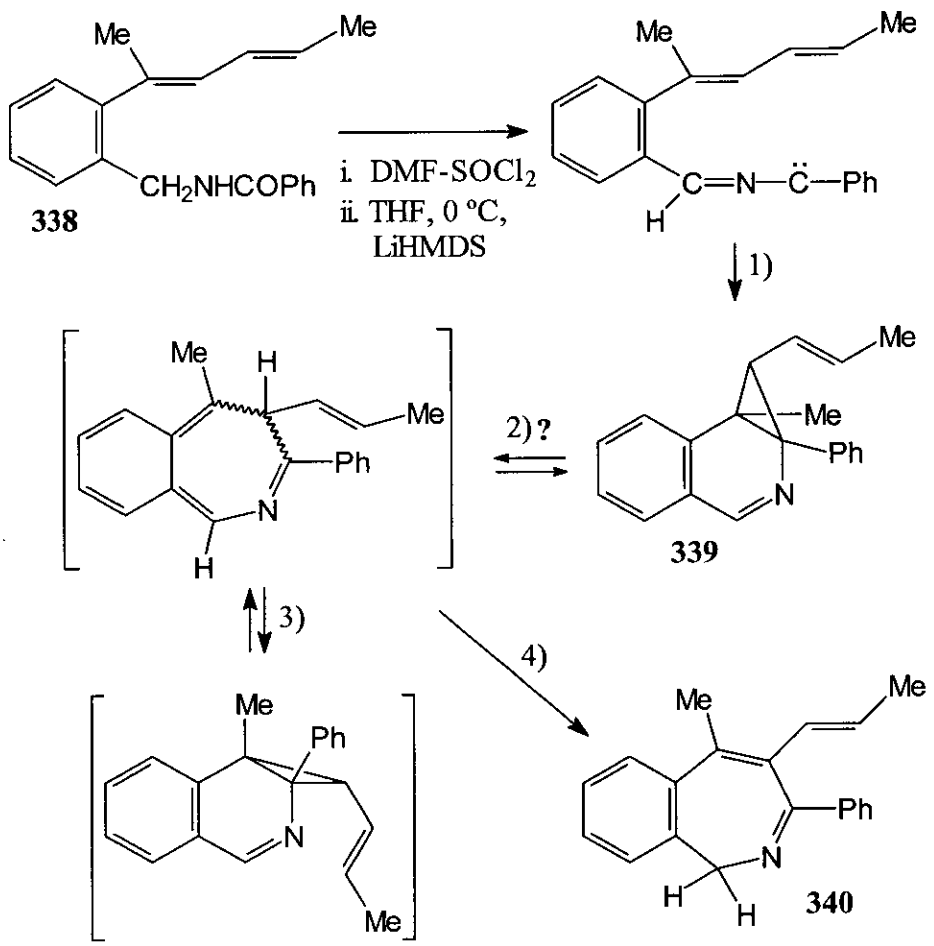


Scheme 129

The subsequent formylation, condensation with hydroxylamine, oxime reduction and benzoylation of the amine all proceeded as expected, in consistently good yields. With the amide in hand the chlorination and dehydrohalogenation steps were undertaken to effect the cycloaddition.

In this case, the DMF/$SOCl_2$ chlorination methodology followed by treatment with LiHMDS proved successful with a good (67 %) yield of the expected 7b-methyl-1-

exo-alkenyl cyclopropa[*c*]isoquinoline **339** being isolated. Thermolysis of a sample of this compound in the usual manner yielded only the 5-methyl-4-alkenyl-1*H*-2-benzazepine **340**, in quantitative yield, with the starting material having been totally consumed after only 4 hours of heating at 54 °C.



1) 1,1-Cycloaddition 2) Electrocyclic ring-expansion
3) Electrocyclic ring-closure 4) [1,5] H Shift

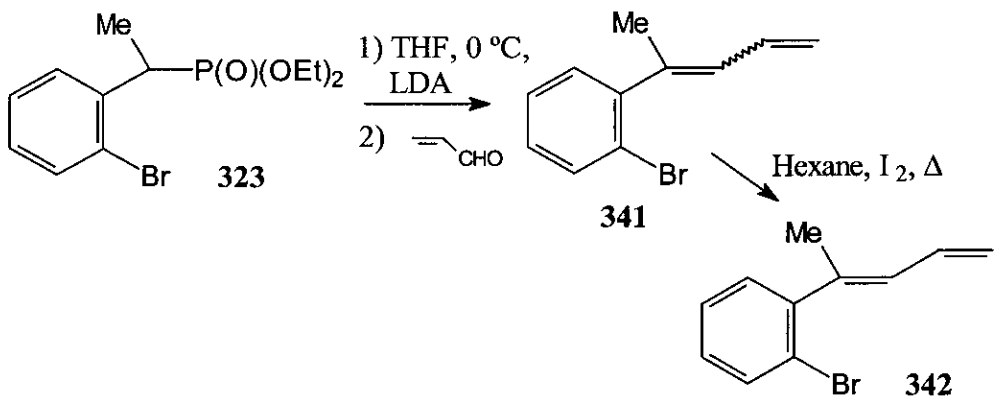
Scheme 130

Again, the [1,5] sigmatropic hydrogen shift has been found to be the entirely dominant mechanism of thermal rearrangement of the 1-alkenyl *exo*-cyclopropa[*c*]isoquinoline. This is not entirely surprising in view of the previous result, and bearing in mind the fact that compound **291**, with a methyl substituent at the terminal olefinic position and hydrogen at the C-7b position also favoured

rearrangement by the [1,5] H shift mechanism. The extra acceleration of this mechanism provided by the γ-position methyl group means that the aza-Cope rearrangement is again so disfavoured as to be unobserved.

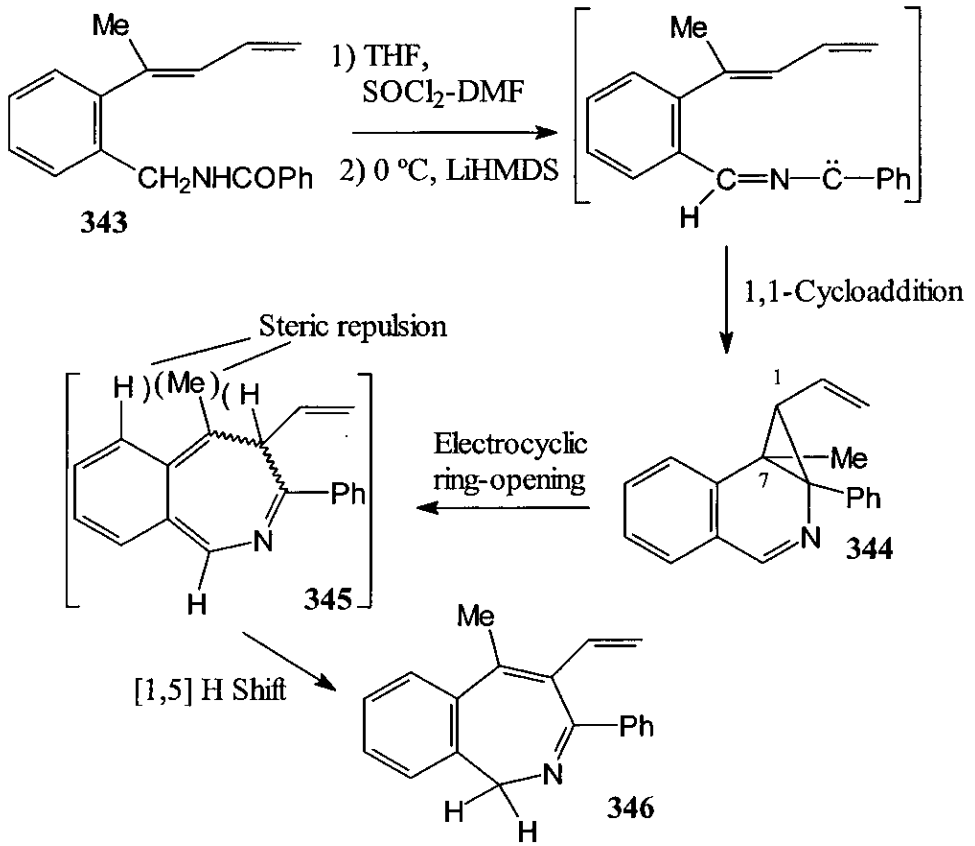
1.2.4 (*E*,*E*)-*N*-[2-(1-Methylbuta-1,3-dienyl)benzyl]benzamide (343)

The next analogue in this series to be studied had a methyl group at the γ position and no other substituent (*i.e.* ζ substituent R^4 = H). The first step in the synthesis of the dipole precursor was again to construct the diene-conjugated *ortho*-bromobenzene, (**342**). This was achieved in an identical manner to the previous two examples, with acrolein being used as the aldehyde in the Wadsworth-Emmons olefination. This methodology proved successful, furnishing the desired compound, which was isomerised to give the required (*E*)-isomer. Again, the ensuing reaction sequence to obtain the amide **326** proceeded as expected and in consistently good yields (70-90 %).



Scheme 131

Chlorination of the amide **343** was achieved by the DMF/$SOCl_2$ method, with the subsequent dehydrochlorination by LiHMDS yielding the 1-alkenyl substituted cyclopropa[*c*]isoquinoline **344** after workup and chromatography. Thermolysis of this product with regular monitoring by ^{1}H NMR showed that the starting material had been consumed after 4 hours at 54 °C and that the rearrangement had proceeded *via* the [1,5] H shift exclusively to yield only the 5-methyl-4-ethenyl-1*H*-2-benzazepine **346**.



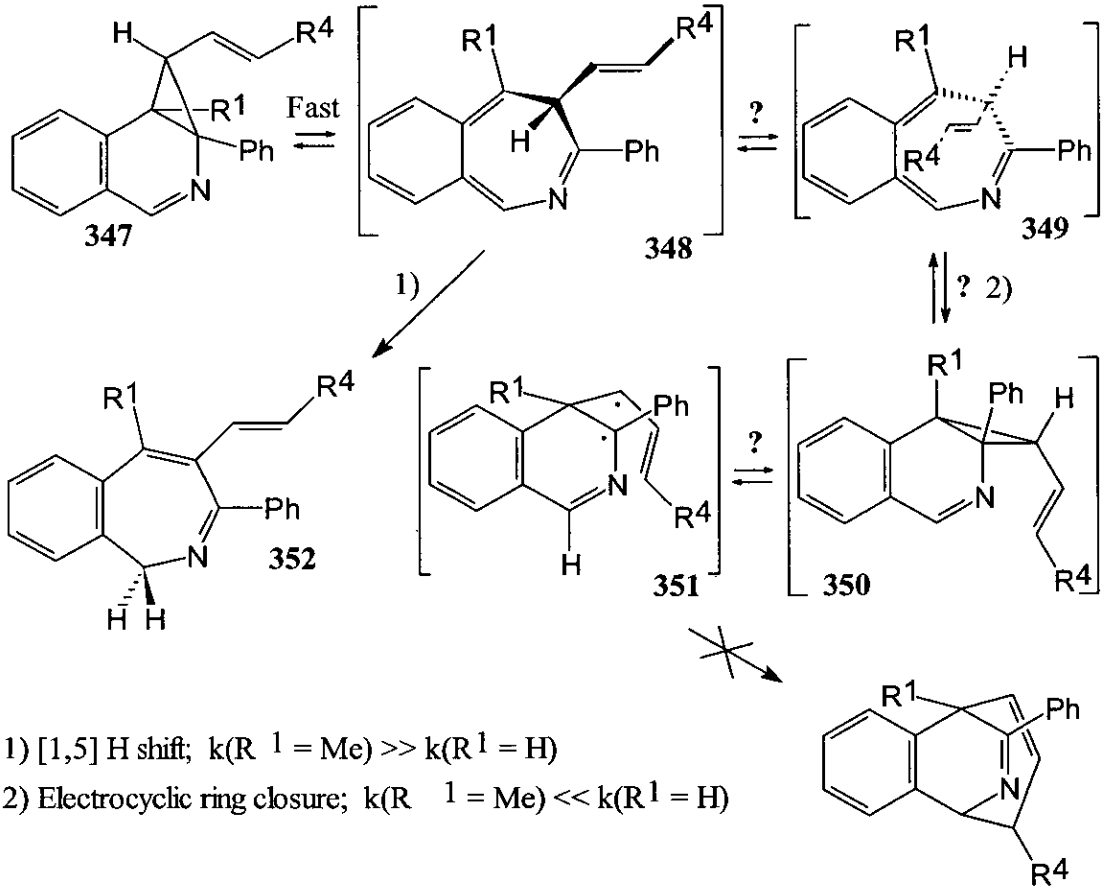
Scheme 132

1.2.5 Conclusion

The consistent results of thermolysis of 1-alkenyl *exo*-cyclopropa[*c*]isoquinolines where the substituents at C-7b = Me and C-1 = H, derived from nitrile ylides of the type **315**, communicate a clear message. In sharp contrast to the analogues where the R^1 = H (at C-7b in the cyclopropa[*c*]isoquinoline structure), the only products obtained from thermolysis of cyclopropa[*c*]isoquinolines **329**, **339** and **344** (R^1 = Me) were the corresponding 4-methyl-5-alkenyl-1*H*-2-benzazepines **331**, **340** and **346**, obtained *via* a sigmatropic [1,5] hydrogen shift in **348** (scheme **133**). The substituent at the ζ-position of the conjugated triene appeared to have no influence on the favoured rearrangement process of the derived cyclopropa[*c*]isoquinoline.

The most likely reason for this observation is that the added methyl group at C-7b provides steric and/or electronic acceleration to the migrating hydrogen atom, simply

through its bulk and proximity to this atom in the non-aromatic intermediate **348**. The steric interaction between the methyl group and another H atom, on the fused benzene ring as indicated in **353** and **345**, could also serve to cause distortion of the intermediate. This distortion could also possibly favour migration of the H atom to yield the azepines **352**. These factors would also have the effect of disfavouring the aza-Cope rearrangement, as the *endo*-isomer of the cyclopropa[*c*]isoquinoline would not be so readily formed due to the effective diversion of the intermediates down the [1,5] H shift pathway.



Scheme 133

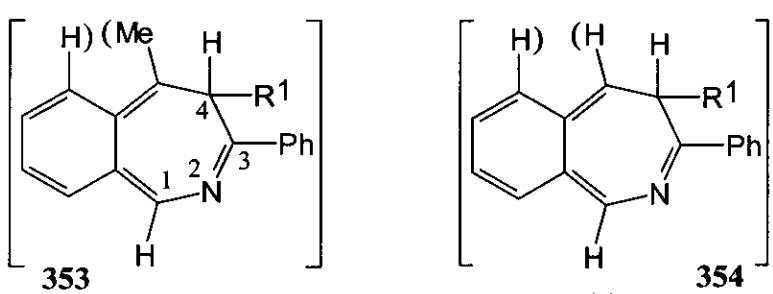
As the C-7b substituent is attached to the cyclopropyl ring it is also possible that the ring inversion and/or closure steps of the isomerisation of **347**→**350** (but not necessarily the electrocyclic ring opening of **347**→**348**) are inhibited.

It is postulated that the methyl (R^1) and phenyl substituents, being *cis*-related on the cyclopropane ring in **347**, could accelerate ring-opening as the repulsion between

them would be alleviated in **348**. Conversely, ring closure of **349** to give the *endo*-cyclopropa[*c*]isoquinoline **350** would be *dis*favoured, as the methyl and phenyl groups would again be *cis*-related across the cyclopropane ring. The methyl group at C-7b in the cyclopropa[c]isoquinoline would serve the dual purpose of accelerating the [1,5] H shift in **348** and simultaneously making ring-opening of **347** more facile and formation of the *endo*-cyclopropa[*c*]isoquinoline **350** less favourable. This would neatly explain the observed result.

The rationalisations put forward above to explain the observations made in this section are compatible with the diradical mechanism proposed to explain the results of the first section. It is most likely that the [1,5] H shift in the intermediate **348** is so facile with the methyl group at C-7, however, that the stability of the diradical intermediate **351** is not an issue. It is likely that, even with a stabilising phenyl ring as R^4, the aza-Cope rearrangement is still swamped by the more rapid [1,5] H shift and only azepines are recovered. It is also possible that the diradical intermediate **351** is not even formed, if the *exo* / *endo* isomerisation step is very slow compared to the H-shift.

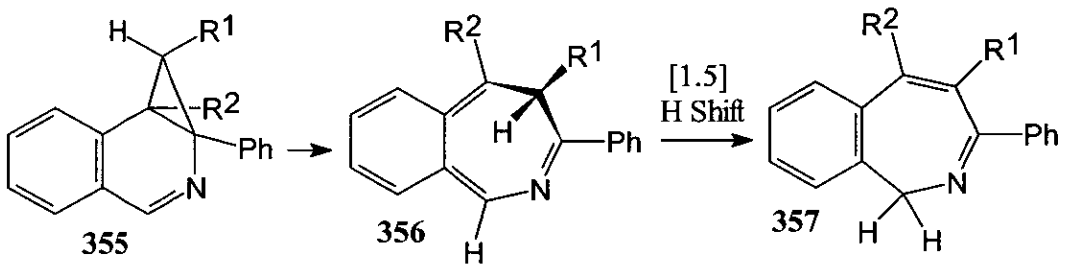
Interestingly, the cyclopropa[*c*]isoquinolines **355** derived from *diene*-conjugated nitrile ylides have been observed to rearrange by the [1,5] H shift mechanism much more slowly than the examples generated in this work. The presence of the methyl group at C-7b was found to have a retarding effect on the rearrangement where R^1 was an alkyl or aryl group. This effect was attributed to destabilisation of the non-aromatic intermediates **353** by a peri-interaction between the methyl group and the hydrogen atom on the fused benzene ring (scheme **134**).



More stable.

Scheme 134

Conversely, in this work all cyclopropa[*c*]isoquinolines which have borne a methyl group at C-7b and where R^1 was olefinic have undergone the [1,5] H shift rapidly, generally within 4 hours at 54 °C, significantly faster than those examples **without** the C-7b substituent. The reason for the acceleration of this rearrangement where R^1 is alkenyl is not clear from the information available.



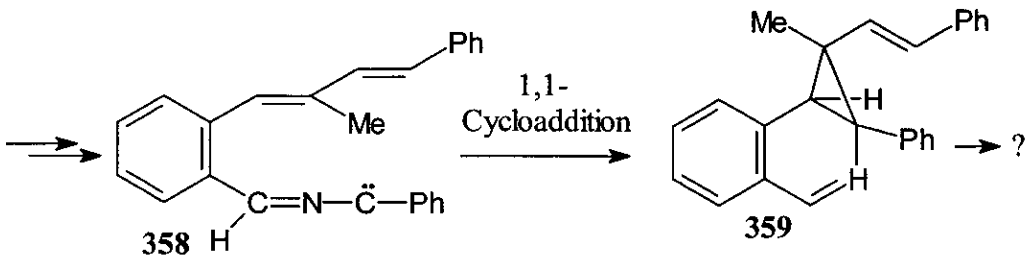
R^1 = H, R^2 = Me; 12 hr, refluxing benzene.
R^1 = Ph, R^2 = Ph; 24 hr, refluxing toluene.
R^1 = *E*-MeCH=CH-, R^2 = Me; 4 hr, 54 °C.

Scheme 135

1.3 Generation and Reactions of Nitrile Ylides Derived from 2',4'-Disubstituted (*E,E*)-*N*-[2-(Buta-1',3'-dienyl)benzyl]benzamides

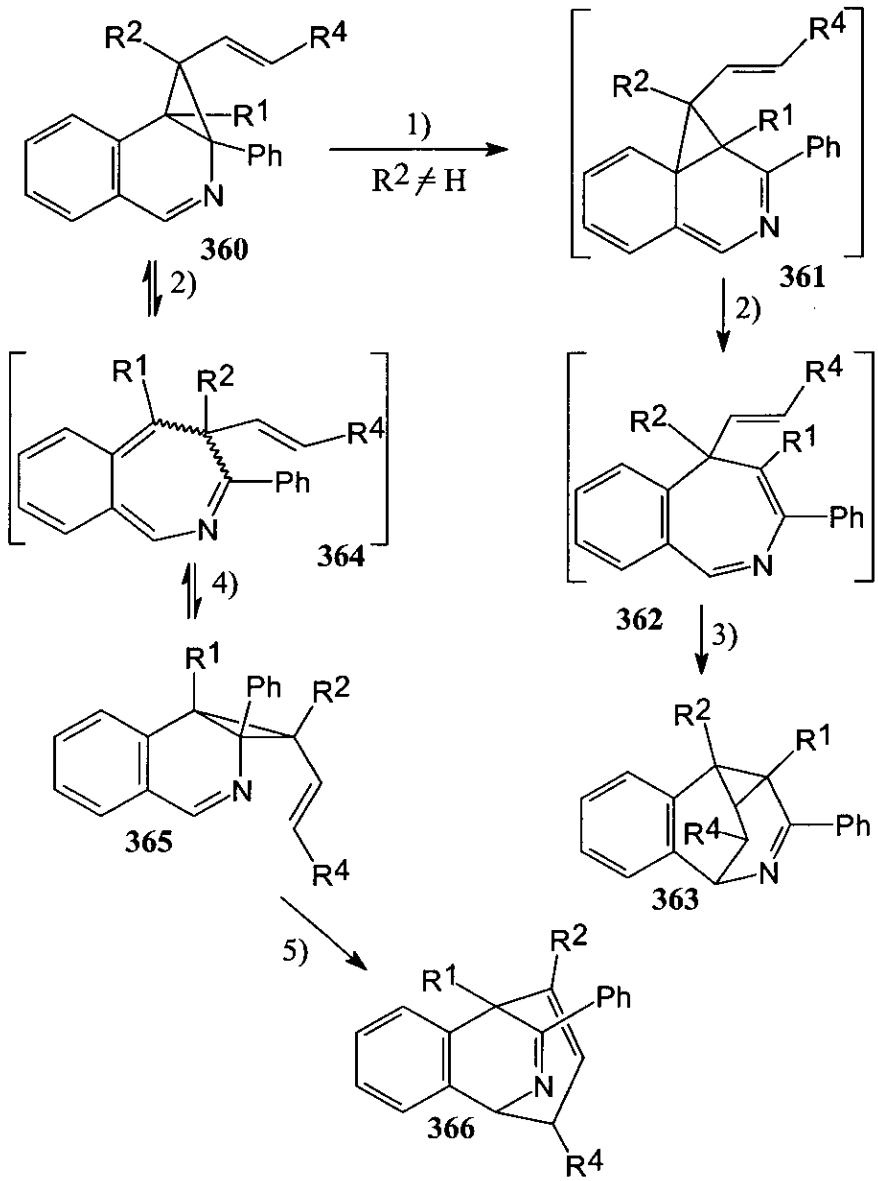
1.3.1 Preamble

In view of the dominant effect caused by adding a substituent at the γ position on the triene systems it was decided to leave this position free (R^1 = H) and synthesise an analogue **358** with a substituent at the δ position (R^2). Strachans analogue **333**, with a substituent at this position as well as at the γ position was observed to yield the interesting bridged isoquinoline system **334** (35 %) as well as the babaralane **335** (65 %) as an unexpected new product. The mechanism for the formation of this product from 1-alkenyl *exo*-cyclopropa[*c*]isoquinolines has been discussed in section **5.1** of the introduction section of this thesis, and a brief outline will be given here.



Scheme 136

In a case where the aza-Cope rearrangement and [1,5] H shift are disfavoured by some factor an alternative pathway can become competitive (scheme **137**). The *exo*-cyclopropa[*c*]isoquinoline **360** undergoes a de-aromatising [1,5] walk of the cyclopropane ring to give **361**, which re-aromatises *via* an electrocyclic ring-expansion to give **362**. This intermediate 5*H*-2-benzazepine is then able to undergo an intramolecular Diels-Alder reaction, yielding the stable, observed product **363**. In the work described here thus far the [1,5] H shift and aza-Cope mechanisms have been so facile as to preclude rearrangement of any analogue by the [1,5] cyclopropyl walk mechanism.



1) [1.5] Cyclopropyl walk 2) Electrocyclic ring expansion
3) Intramolecular Diels-Alder 4) Electrocyclic ring-closure
5) Aza-Cope

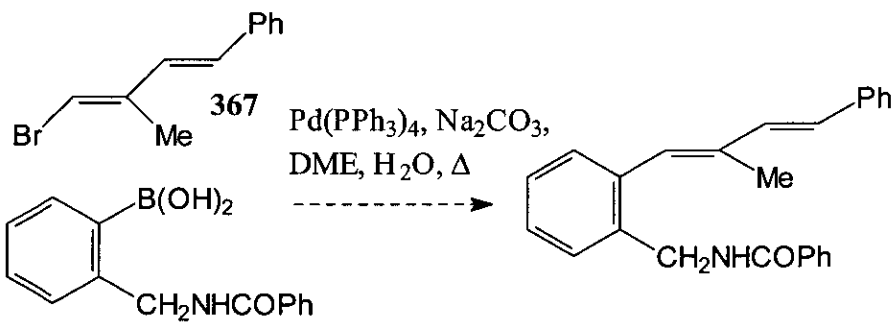
Scheme 137

It was hoped that removing the γ methyl substituent (R^1) that was present in the example from Strachans work (*i.e.* R^1 = H in structure **360**) would further favour the aza-Cope rearrangement and allow access to the bridged isoquinolines with substitution at C-9 (R^2 in **366**). In any case, it was felt that further elucidation of the roles of substituents at each site of the triene in the thermal rearrangements was

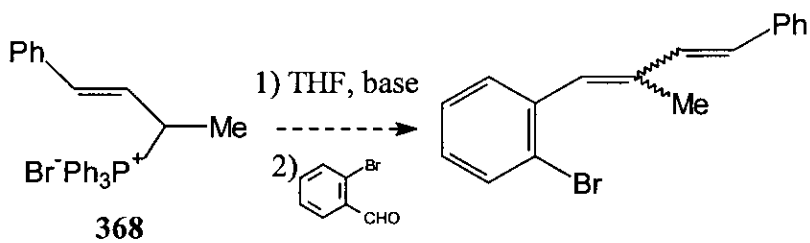
required. Altering each site individually would give more easily interpreted information to this end.

1.3.2 (*E,E*)-*N*-[2-(2-Methyl-4-phenylbuta-1,3-dienyl)benzyl]benzamide (372)

There were several approaches to the synthesis of the dipole precursor which could have been adopted. The Suzuki reaction depicted in scheme **138** was feasible but it was felt that the bromodiene **367** would be unstable and difficult to synthesise in the required (*E,E*) form. Another possible route is *via* the Wittig reaction depicted in scheme **139**, where the δ substituent is incorporated from the olefinic phosphonium salt **368**, a route that has been shown to be successful in the past[129].

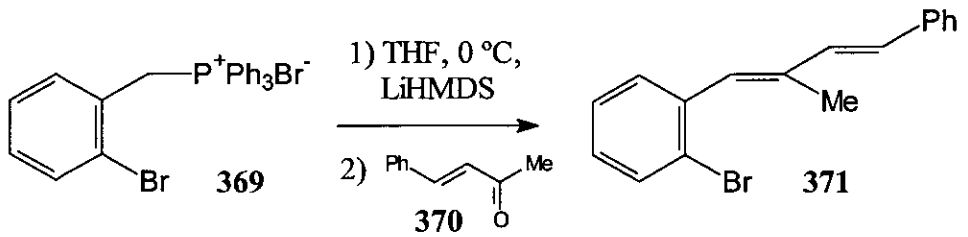


Scheme 138



Scheme 139

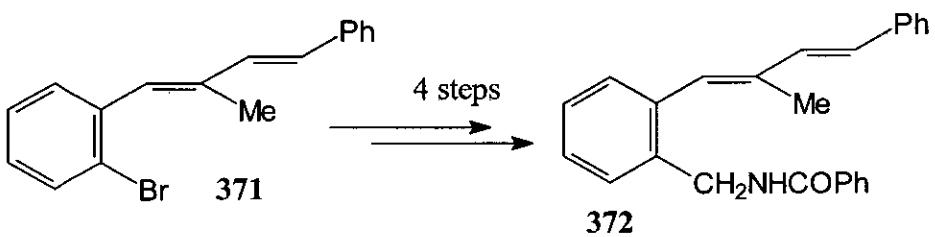
It was decided, however, to remain faithful to the protocol established in this work, by utilising the Wittig reaction between the ylid of *o*-bromobenzyltriphenylphosphonium bromide **369** and benzylideneacetone **370**, both of which being cheap and readily available starting materials.



Scheme 140

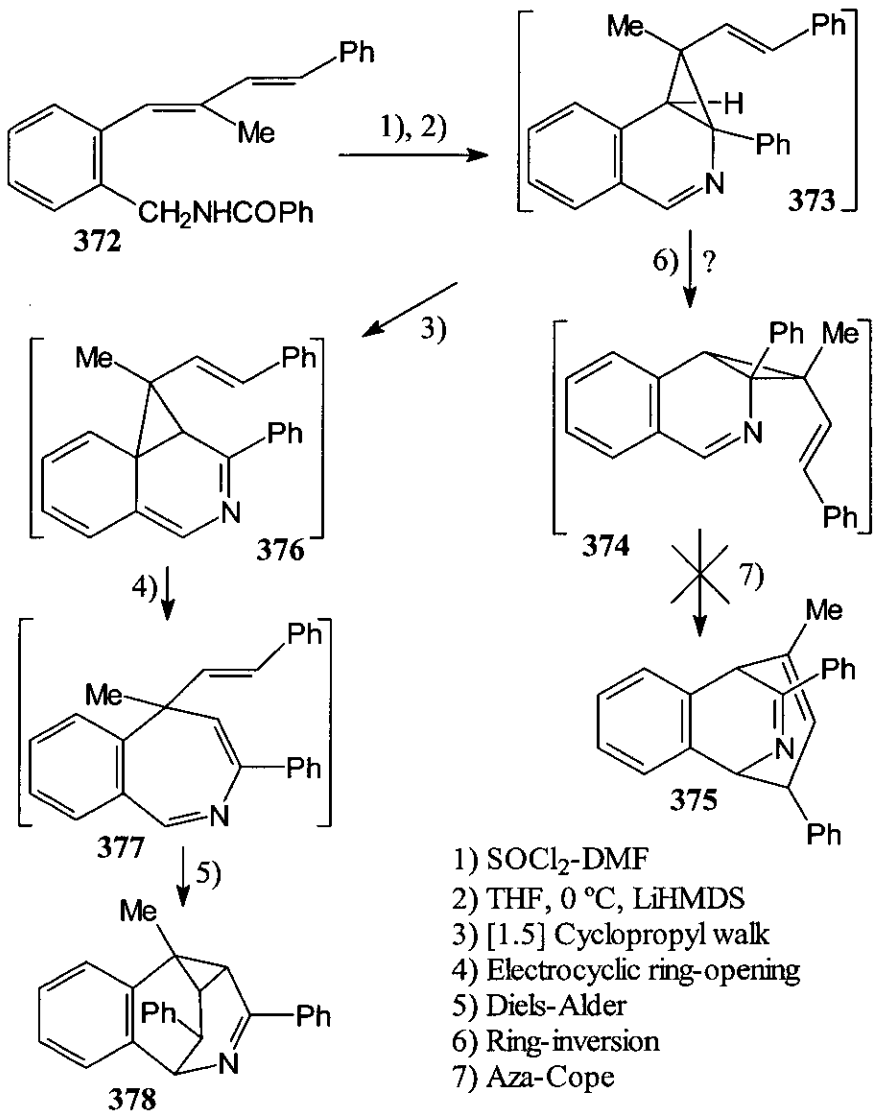
The Wittig reaction (scheme **140**) was undertaken in the usual way, but with gentle heating of the reaction mixture after addition of the ketone, as it was felt that the more hindered carbonyl compound **370** would be less reactive than the simple aldehydes utilised thus far. Monitoring the reaction by TLC revealed the presence of a new, non-polar product, which was found on isolation and purification to be the desired compound **371**, obtained in modest but acceptable yield (45 %). The usual iodine-catalysed isomerisation gave the desired (*E*,*E*) configuration.

The formylation – hydroxylamine condensation – reduction – benzoylation sequence again proceeded as expected in good yields (60-85 %).



Scheme 141

Chlorination of the amide **372** by the DMF/$SOCl_2$ method and dehydrochlorination in the usual manner gave a reaction mixture which upon TLC analysis was shown to contain one new compound. Quenching of the reaction followed by chromatography allowed isolation of this product. Inspection of its ^1H NMR spectrum revealed it to be not the expected 1-alkenyl cyclopropa[*c*]isoquinoline **373** but the babaralane **378**, which would be a product of thermal rearrangement of **373**.



Scheme 142

This was a remarkable and unexpected result. It would appear that the substitution pattern of **372** has resulted in the formation of a primary product, the cyclopropa[*c*]isoquinoline **373**, of unprecedented lability which has rearranged rapidly *via* a route thought to be the least favoured of all the available options

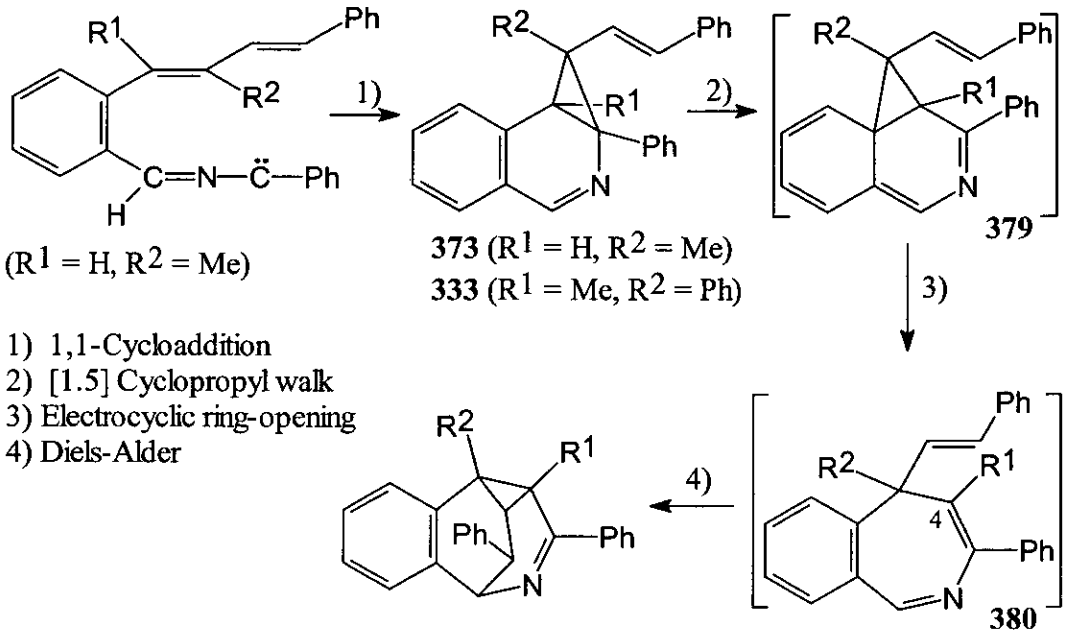
The reason for the unprecedentedly rapid thermal rearrangement of the assumed intermediate 1-alkenyl cyclopropa[*c*]isoquinoline **373** is not fully understood, nor is the reason for the complete switch in mechanism from aza-Cope rearrangement to favour the sequence culminating in the intramolecular Diels-Alder reaction. There

seems to be no obvious reason why the alternative path (scheme **142**), yielding **375** *via* the aza-Cope process, should be particularly disfavoured for this pattern of substituents.

Comparison of the expected cyclopropa[*c*]isoquinoline structure **373** with those which held a methyl group at the C-7b position (**329**, **339** and **344**) hints at a possible explanation. In the expected *exo*-cyclopropa[*c*]isoquinoline **373** the methyl and the phenyl groups on the cyclopropyl ring would be *trans*-related, and thus well separated from each other. In the *endo*-isomer **374**, however, these substituents would be *cis* to one another, and thus likely to interact sterically. This effect would disfavour formation of the *endo* isomer and so the aza-Cope would be less able to occur.

As the 1-position of the cyclopropa[*c*]isoquinoline **373** does not bear a migratable H atom the [1,5] H shift mechanism is inoperative. The only option open for rearrangement of the compound in this case, assuming that the formation of **374** was strongly disfavoured, would then be the pathway in which the first stage is the [1,5] cyclopropyl walk yielding **376**, and ultimately giving the azabenzobabaralane **378**.

The γ-substituent of the triene-conjugated nitrile ylides (R^1 in scheme **143**) would be situated at the 4-position of the putative azepine intermediate **381**, in-between the phenylethenyl Diels-Alder dieneophile and the diene. Larger groups at this position could feasibly increase steric hindrance and interfere with the progress of the Diels-Alder reaction in **381**, explaining the longer reaction time for an example generated by Strachan (**333**) to convert to the analogous azabenzobabaralane **335**. It is possible that the current example (cyclopropa[*c*]isoquinoline **373**), where the γ-substituent (R^1) = H, could form the intermediate **376** more easily or undergo the Diels-Alder rearrangement with less hindrance presented by the small 4-substituent, and would thus react by this route preferentially.



R^1 = H, R^2 = Me, **378**; steps 2-4 spontaneous, room temp.
R^1 = Me, R^2 = Ph, **335**; steps 2-4 35 hr, 80 °C.

Scheme 143

The sequence culminating in the intramolecular Diels-Alder rearrangement of **380** to yield **378**, therefore, appears to have become highly favourable, swamping all other rearrangement processes.

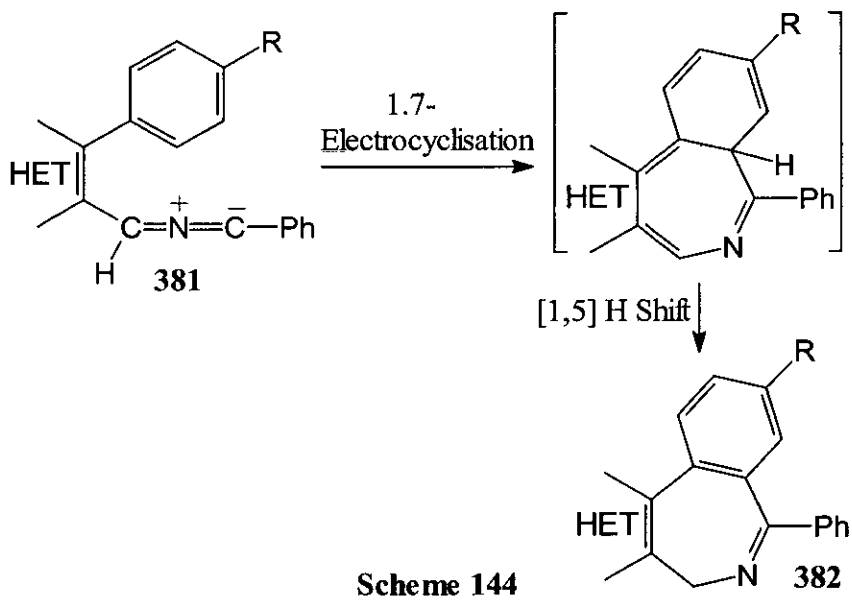
The rationalisations put forward are that the *exo/endo* isomerisation step for the cyclopropa[*c*]isoquinoline **373** is effectively inoperative, as it would involve changing the relation of the methyl and phenyl groups across the cyclopropyl ring from *trans* to *cis*. This would strongly disfavour the aza-Cope rearrangement. The [1,5] cyclopropyl walk occurs in the absence of the ring-flipping step, as has been observed previously[94]. The intramolecular Diels-Alder reaction of the inferred azepine **380** can occur easily, as there is little hindrance from R^1 (H, in this case). The R^2 group could also provide acceleration for this reaction by its destabilising peri-interaction with the hydrogen atom on the fused benzene ring, an interaction which would be alleviated in the product **378**.

1.4 Generation and Reaction of the Nitrile Ylides Derived from 4'-Substituted (*E,E*)-*N*-Benzoyl-2-aminomethyl-3-(buta-1',3'-dienyl)thiophenes

1.4.1 Preamble

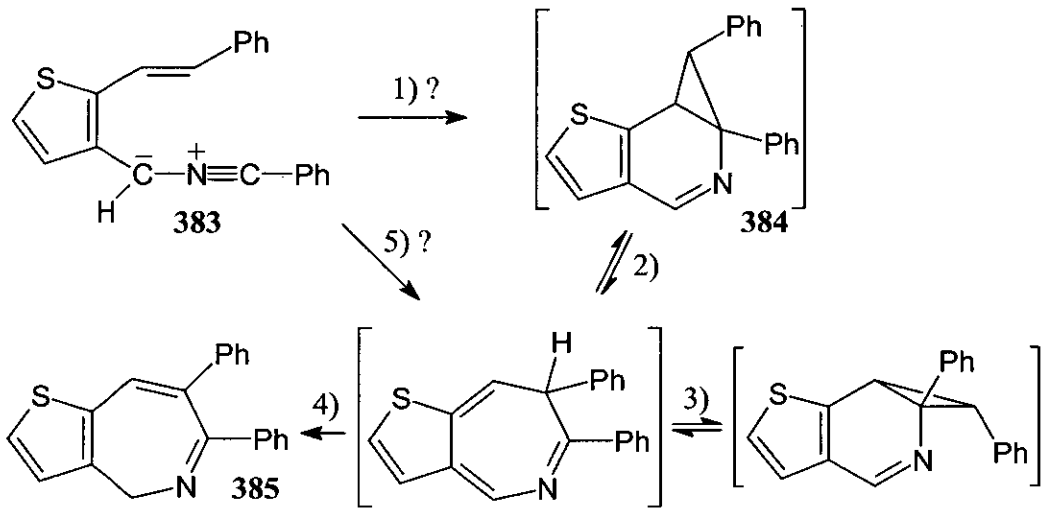
An aspect of the triene system which has not been varied in this work thus far is the α,β unsaturation which has been incorporated as part of a benzene ring in all of the previous examples. It was decided to investigate the effect of altering the nature of this unsaturation by introducing a heterocyclic ring in place of the benzene ring.

The reactions of diene-conjugated nitrile ylides where either the α,β or γ,δ unsaturations were part of heterocyclic rings have been studied extensively by Sharp and co-workers[130]. The results of this work have been summarised in section **5.4** of the introduction to this thesis. The reactions which are to be examined in the current investigation are extensions of the examples where the α,β unsaturation of the dienyl system was part of a heterocyclic ring. The diene-conjugated nitrile ylides of this type (**381**) underwent 1.7-electrocyclisations to give fused azepines **382** (scheme **144**), in the same way that the analogue where the α,β unsaturation was part of a benzene ring did.



Scheme 144

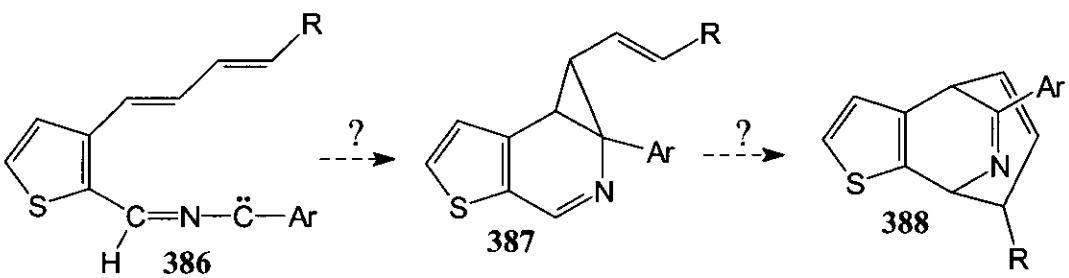
Examples where the γ,δ unsaturation was olefinic and the α,β unsaturation was part of a thiophene ring have also been studied[99]. The expected initial product, the cyclopropathienopyridine **384**, analogous with the cyclopropa[*c*]isoquinolines, was not isolable and the observed product of reaction of nitrile ylide **383** was the thienoazepine **385**.



1) 1,1-Cycloaddition 2) Ring expansion 3) Ring closure
4) [1,5] H shift 5) 1.7-Electrocyclisation

Scheme 145

It was therefore thought instructive to discover whether using a heterocycle to provide the α,β unsaturation in triene-conjugated nitrile ylides of the type **386** would cause any interesting reaction pathways to open. Specifically, it was hoped that the 1,1-cycloaddition to give analogues of the cyclopropa[*c*]isoquinolines (*e.g.* **387**) and subsequent rearrangements to yield novel fused heterocycles would occur (scheme **146**).

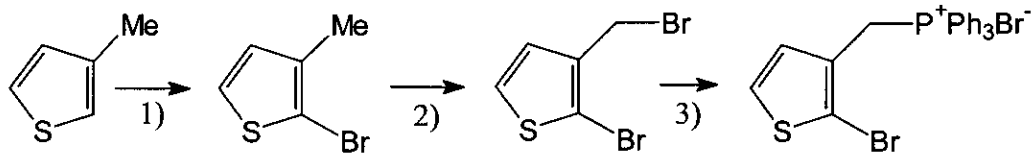


Scheme 146

To this end, the relatively stable thiophene ring was identified as a desirable candidate since, of the heterocycles, its chemistry is most similar to that of benzene. Thus it was expected that the established protocol for olefinations in this work would be viable in the thiophene system.

1.4.2 (*E*,*E*)-*N*-Benzoyl-2-aminomethyl-3-(4-phenylbuta-1,3-dienyl)thiophene (395)

Successive brominations of 3-methylthiophene (**389**), firstly at the 2-position on the ring to give **390**, then onto the methyl group (with promotion by peroxide radical), followed by reaction of the unstable, lachrymatory dibromo compound **391** with triphenylphosphine allowed access to the required phosphonium salt **392**.

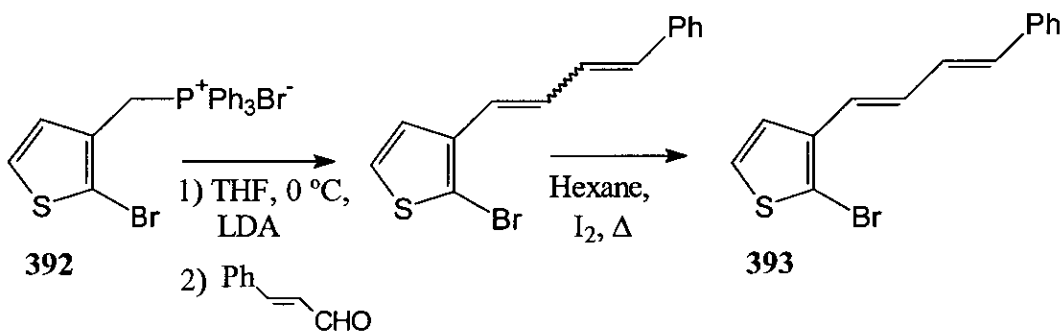


389 **390** **391** **392**

1) NBS, AcOH 2) NBS, CCl_4, Bz_2O_2, Δ 3) THF, PPh_3

Scheme 147

Generation of the ylid of **392** using LDA followed by reaction with cinnamaldehyde yielded the (*Z*,*E*) and (*E*,*E*) diene-conjugated bromothiophenes which were isomerised to the (*E*,*E*) isomer **393** in the usual manner.



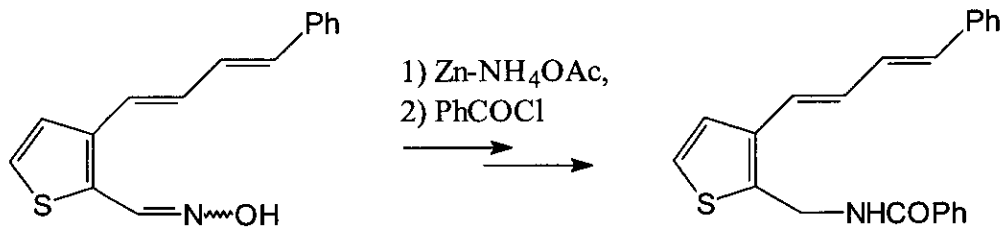
392 **393**

Scheme 148

The formylation reaction was performed taking care not to use a large excess of butyllithium, as the 5-position of the thiophene ring is also susceptible to

deprotonation[131], which could lead to unwanted side reactions. This complication did not arise in this experiment, with only the 2-formyl product being obtained.

The rest of the reaction series proceeded as expected, although interestingly the ^{1}H NMR spectrum of the oxime **394** showed both *syn* and *anti* isomers distinctly. This had not been observed in the spectra of any of the benzo analogues of the oxime, but it had no obvious bearing on the result of the zinc reduction.



394 **395**

Scheme 149

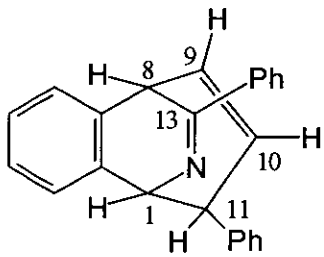
Once the amide **395** had been obtained it was chlorinated and cyclised in the usual manner, resulting in neither products nor starting material being recovered. The product mixture did not show any non-baseline spots upon TLC analysis, while the ^{1}H NMR spectrum and mass spectrum of the crude extract did not exhibit any of the expected features of any anticipated cyclisation products. This disappointing result is thought to reflect the higher lability of the thiophene analogues.

Another reaction was carried out, but in this case the reaction mixture was cooled in a cardice-acetone bath prior to addition of the base. Analysis of the product mixture by TLC suggested the presence of two new compounds. Quenching of the reaction mixture and purification and separation of the fractions by chromatography revealed that there were indeed two products.

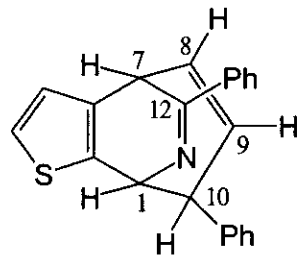
The first of these products to elute from the column was the bridged thienopyridine **396,** an analogue of the bridged isoquinoline **268** and a new heterocyclic system. The assumed intermediate cyclopropa[*c*]thienopyridine **397** was not observed at any point, even as a residue in the ^{1}H NMR spectrum of the crude extract. This was also reported to be the case when the analogous thiophene-containing diene-conjugated nitrile ylides were generated and reacted by Motion[99]. Nevertheless, the only

plausible mechanism for formation of this product is *via* an initial 1,1-cycloaddition followed by an aza-Cope rearrangement, as shown in scheme **150** and as observed for the benzo-fused analogues which yielded this type of product on thermolysis.

The compound **396** was identified by comparison of its NMR characteristics with those of the benzene analogue **268** (table **2**), and from the mass spectrum obtained.



268

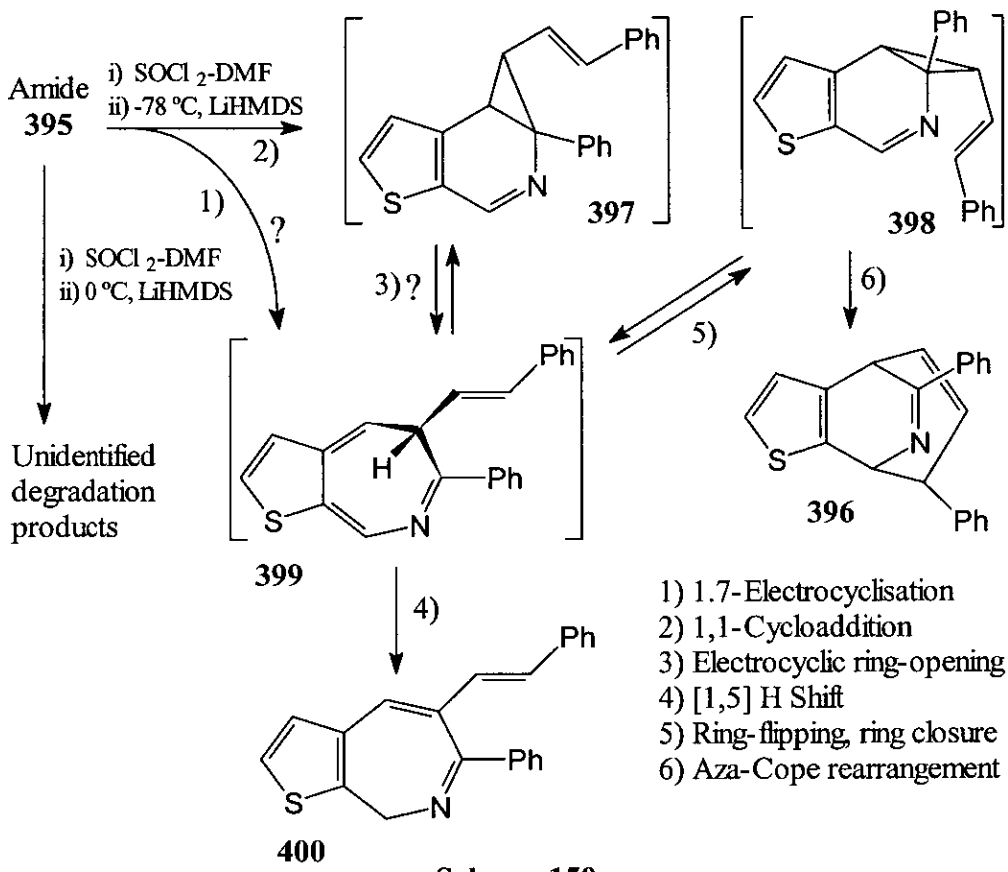


396

Table 2

Benzene analogue **268**			Thiophene analogue **396**		
δ_H (ppm)	Multi-plicity	*J* (Hz)	δ_H (ppm)	Multi-plicity	*J* (Hz)
3.76, H-11	ddd	3.5, 2.6, 2.6	3.79, H-10	m	-
4.67, H-8	d	8.3	4.88, H-7	d	8.1
5.27, H-10	dddd	10.5, 3.5, 1.7, 0.9	5.34, H-9	dm	10.6, -
5.45, H-1	dd	2.6, 1.7	5.65, H-1	dd	2.0, 2.0
6.32, H-9	ddd	10.5, 8.3, 2.6	6.36, H-8	ddd	10.6, 8.1, 2.5
δ_C (ppm)			δ_C (ppm)		
42.7, C-11			40.0, C-10		
47.0, C-8			46.8, C-7		
67.9, C-1			63.1, C-1		
123.8, C-10			123.4, C-9		
125.1, C-9			123.5, C-8		
175.9, C-13			174.0, C-12		

The second product eluted was the 5-alkenyl thieno-1*H*-2-azepine **400**, the minor (28 %) component of the product mixture. This was easily identified by its ^{13}C NMR spectrum, which showed a new CH_2 signal in the 3π/4 DEPT experiment.



Scheme 150

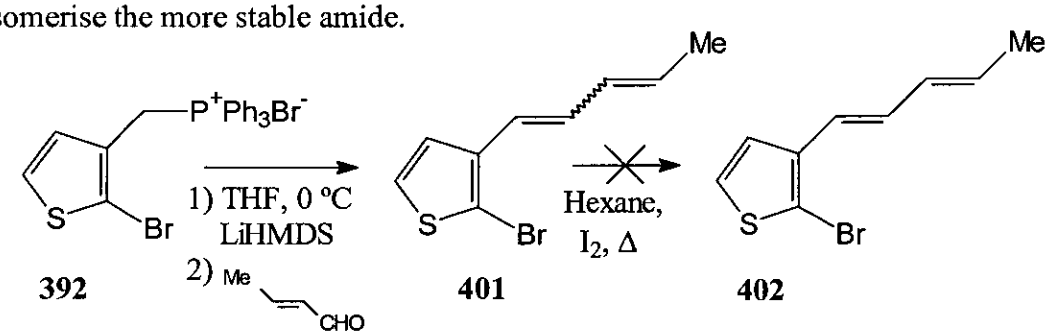
In contrast to the first product obtained (**396**) there are a number of possible ways in which the azepine **400** could be formed from the nitrile ylide. The most appealing theory is that both products arose from the inferred, but unisolated, intermediates (**397** and **399**) which could undergo a facile [1,5] H shift to yield the observed azepine (scheme **150**).

The thienoazepine is obviously formed *via* a [1,5] H shift in the intermediate **399**, but whether that species is formed directly from the nitrile ylide by 1.7-electrocyclisation or *via* the ring opening of **397** (which is definitely formed) is unclear, as it is for the benzo-fused analogues.

1.4.3 (*E,E*)-*N*-Benzoyl-2-aminomethyl-3-(penta-1,3-dienyl)thiophene (404)

It was decided to find out whether substituent effects in the thiophene analogues parallel those of the benzo-fused analogues.

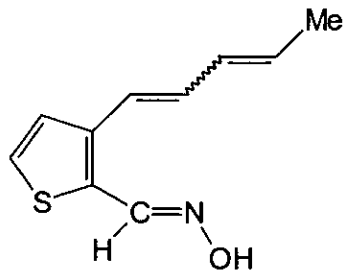
The initial target was the diene-conjugated bromothiophene **401**, which was successfully synthesised in the usual manner from reaction of the ylid of 2-bromo-3-thienylmethyltriphenylphosphonium bromide with crotonaldehyde which gave a 1:1 mixture of (*Z,E*) and (*E,E*) isomers of **401** in good yield. An attempt was made to isomerise the mixture to give only the (*E,E*) isomer by heating in the presence of iodine. This, however, caused extensive decomposition of the compound with little beneficial isomerisation having occurred and much black tar having formed after 1 hour. It was necessary, therefore, to carry the mixture through and hopefully isomerise the more stable amide.



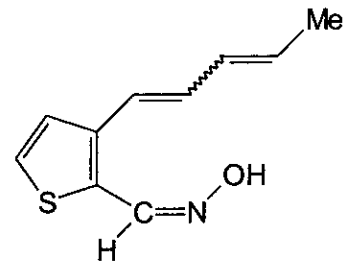
392 **401** **402**

Scheme 151

The reaction sequence as far as the amine proceeded in consistently good yields with no obvious problems caused by the reactive thiophene ring or the mixture of isomers. Two spots were observed upon TLC analysis of the hydroxylamine condensation reaction and it was hoped that chromatography would allow isolation of the desired (*E,E*) isomer. The ^{1}H NMR spectra revealed, however, that the spots corresponded to the *syn* and *anti* geometrical isomers of the (*E,E*) and (*Z,E*) mixture rather than the (*E,E*) and (*Z,E*) isomers of the oxime **403**, and the fractions were recombined and reduced as one batch.

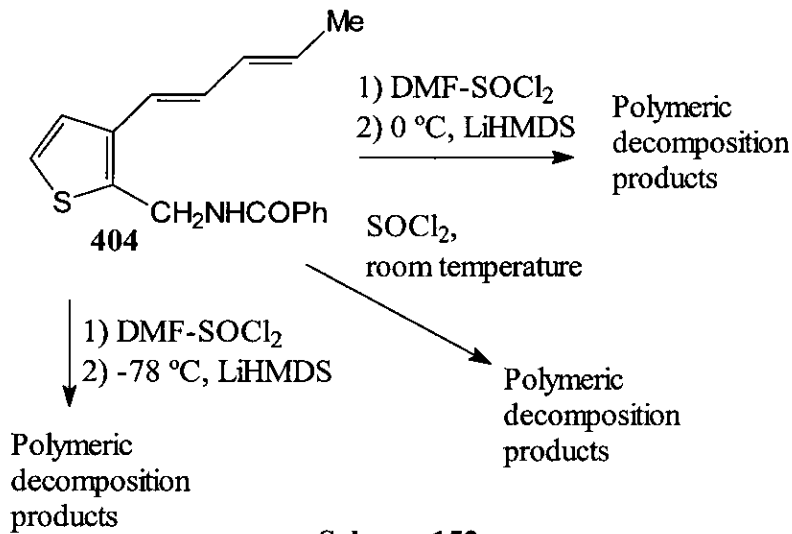


403, *anti*



403, *syn*

An attempt to isomerise the amide with iodine in refluxing chloroform resulted in partial polymerisation of the sample and a disappointing (22 %) yield of the entirely (*E*,*E*) amide **404** was recovered. Chlorination of this amide by the DMF/$SOCl_2$ method followed by addition of LiHMDS at 0 °C to effect the dehydrochlorination resulted in consumption of the starting material, but no new spots which could correspond to product were observed by TLC. The ^1H NMR spectrum of the crude extract after quenching of the reaction did not show any signals which could be interpreted. Much of the dark-coloured residue was practically insoluble in either organic solvents or water, suggesting that it was of a polymeric nature.



Scheme 152

A second attempt was carried out, with the reaction mixture being cooled to –78 °C before treatment with the base, but this gave a similar result. It is suspected that the complications arose in the reaction of the imidoyl chloride with LiHMDS, as TLC analysis of a residual sample of the imidoyl chloride solution prior to attempted

dehydrohalogenation indicated the presence of amide, which was not observed after addition of the base.

Harsher conditions at the chlorination stage, such as stirring the amide in neat thionyl chloride at room temperature or heating the amide with excess thionyl chloride at reflux in ether were found to cause rapid decomposition of the starting material. This was apparent by TLC analysis of the mixtures and the unpromising darkening of the solutions.

1.5 Summary and Conclusions

Table 3

R^1	R^2	R^4	Amide Ar	α,β	Amide No.	Cyclisation Products	Thermal Products
H	H	Ph	Ph	Benz.	**262**	**405** (74 %) [A]	**407** Quant.
H	H	Me	Ph	Benz.	**289**	**405** (64 %) [B]	Quant. 3:1 **407**:**406**
H	H	Me	*o*-Tol	Benz.	**299**	**405** (56 %) [B]	Quant. 3:1 **407**:**406**
H	H	H	Ph	Benz.	**274**	**405** (47 %) [B]	**406** (40 %), **407** (60 %)
Me	H	Ph	Ph	Benz.	**326**	**405** (79 %) [C]	**406** Quant.
Me	H	Me	Ph	Benz.	**338**	**405** (67 %) [B]	**406** Quant.
Me	H	H	Ph	Benz.	**343**	**405** (82 %) [B]	**406** Quant.
H	Me	Ph	Ph	Benz.	**372**	N/I [B]	**408** (63 %)
H	H	Ph	Ph	Thio.	**395**	- [B]	-
H	H	Ph	Ph	Thio.	**395**	N/I [D]	**406** (59 %), **407** (28 %)
H	H	Me	Ph	Thio.	**404**	- [B]	-
H	H	Me	Ph	Thio.	**404**	- [D]	-

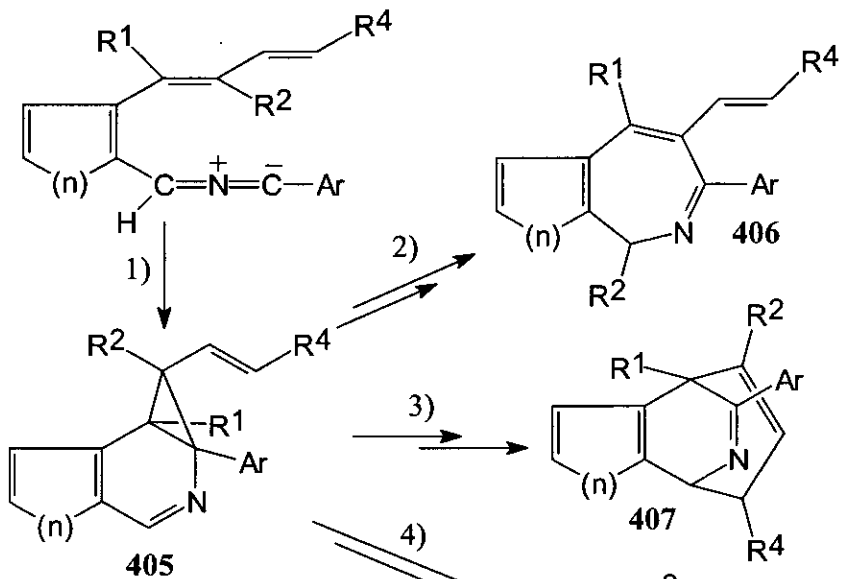
Superscripts in table 3 refer to cyclisation conditions;

A. $SOCl_2$, ether, reflux; 0 °C, LiHMDS **B.** THF, DMF-$SOCl_2$; 0 °C, LiHMDS

C. $SOCl_2$ (neat), room temp.; 0 °C, LiHMDS **D.** THF, DMF-$SOCl_2$; -78 °C, LiHMDS

N/I; Not isolated.

- ; No identifiable new product.



(n) = (CH=CH); benzene
(n) = S; thiophene
1) 1,1-Cycloaddition.
2) Electrocyclic ring-opening, [1,5] H shift.
3) Ring-flipping, aza-Cope.
4) [1,5] Cyclopropyl walk, Diels-Alder.

Scheme 153

In all but two cases the triene-conjugated nitrile ylides where the γ,δ unsaturation is in the (*E*,*E*) configuration have been shown to undergo intramolecular 1,1-cycloaddition as the primary step in their reaction, apparently to the exclusion of all other feasible inter- or intramolecular processes. The initial product in all cases was the 1-alkenyl-*exo*-cyclopropa[*c*]isoquinoline **405**, which was isolable in all but two cases. In the two cases where such compounds were not isolated as primary products

the subsequent chemistry indicated that they had been present as transient species in the main reaction paths.

Thermolysis of the cyclopropa[*c*]isoquinolines resulted in one or two of three observed rearrangement process occurring, causing formation of either one or two new heterocyclic products in each case. These rearrangement pathway(s) were found to be highly influenced by the substitution pattern about the triene system (table **2**). The benzazepine system can only be formed in the cases where R^2 = H, *i.e.* a group easily migratable in sigmatropic shift reactions. However, this process was **not** always dominant in the cases where it was possible, *e.g.* reaction of cyclopropa[*c*]isoquinoline **265**. Where only the ζ-position bore a substituent (R^1 and R^2 = H) then the favoured processes were the aza-Cope rearrangement and the [1,5] H shift, yielding the bridged isoquinolines and the 1*H*-2-benzazepines respectively.

The nature of the ζ-substituent was found to have an effect on the favoured product, with an aromatic substituent leading exclusively to the bridged isoquinoline, and an alkyl substituent favouring the 1*H*-2-benzazepine. Where there were no substituents (*i.e.* $R^1 = R^2 = R^4$ = H) then the two products were formed in almost equal amounts.

When a methyl group was situated at the γ-position (R^1 = Me) then the only products obtained from thermolysis of the cyclopropa[*c*]isoquinolines were the 1*H*-2-benzazepines, regardless of the identity of R^4 (Ph, Me or H). This was ascribed to acceleration of the hydrogen shift due to the steric bulk of the vicinal methyl group in the non-aromatic ring-opened intermediates.

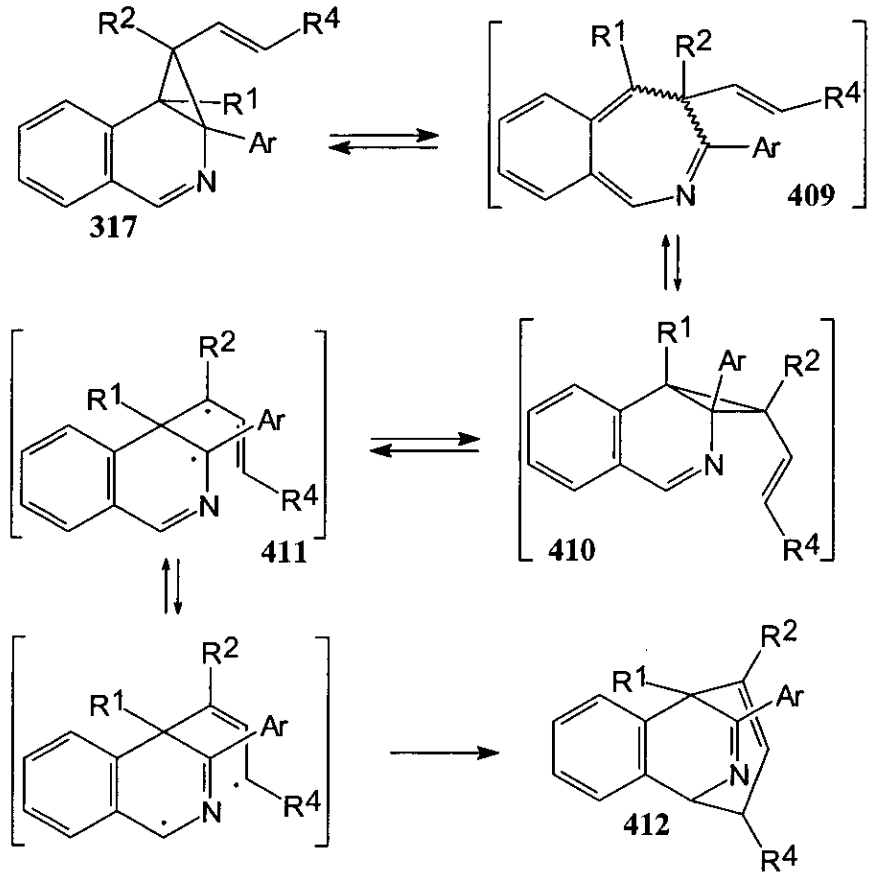
Where the δ-position bore a methyl group and the ζ-position held a phenyl group then the cyclopropa[*c*]isoquinoline was not isolable and the only product obtained was derived from a [1.5] cyclopropyl walk rearrangement followed by an intramolecular Diels-Alder reaction to give product type **408** (n = HC=CH, R^1 = H, R^2 = Me, R^4 = Ph, Ar = Ph). No entirely satisfactory explanation for these observations can be deduced based on the current ideas about the mechanisms of these reactions.

In cases where R^1 or R^2 = Me the aza-Cope rearrangement of the 1-alkenyl cyclopropa[*c*]isoquinolines was clearly disfavoured. An argument centring on the relative orientation of the substituents on the cyclopropyl ring appears consistent with these observations.

If R^2 = Me the *endo*-cyclopropa[*c*]isoquinoline **374** has the Ar and Me groups *cis*-related across the cyclopropyl ring and the *exo*-isomer **373**, in which these groups are *trans* to each other, is more stable. The *exo*-isomer cannot react *via* the aza-Cope rearrangement and the observed product (**378**) is formed from this by an alternative mechanism.

Where R^1 = Me both the *exo* **and** the *endo*-isomers of the cyclopropa[*c*]isoquinolines have Ar and R^1 *cis*-related across the cyclopropyl ring. This is proposed to promote ring opening of **317** to the non-aromatic intermediate **409** and also to disfavour ring closure of **409** to either the *exo* or *endo* isomers of the starting material (**317** or **410**). Accordingly, the only product obtained from thermolysis of compounds of the type **317**, where R^1 = Me and R^2 = H derived from a [1,5] H shift in the non-aromatic intermediates of the ring-flipping process.

The observations are also consistent with the intermediacy of a diradical transition state (**411**) for the aza-Cope reaction (scheme **154**). Non-aromatic substituents at the olefinic system appear to destabilise this putative species, leading to decreased favourability of the aza-Cope rearrangement relative to the other possible mechanisms where R^4 is not aromatic.



Scheme 154

Increasing the steric bulk of the aryl group Ar on the C-3 terminal of the nitrile ylide was found not to affect the product distribution compared to the phenyl analogue, but the rate of the rearrangement was found to be significantly slower.

Using a thiophene group to provide the α,β unsaturation and including a phenyl ring at the ζ-position of the triene again appeared to make the thermolytic processes more facile. The products isolated from the cycloaddition reaction of the nitrile ylide derived from the amide **395** were the bridged thienopyridine **396** and the 1*H*-2-thienoazepine **400**, with the former predominating.

The fact that the bridged thienopyridine **396** was recovered implicates the alkenyl cyclopropathienopyridine **397** as an intermediate, which must have rapidly undergone an aza-Cope rearrangement to give **396**. A proportion of the inferred intermediate **399** could also have undergone a sigmatropic [1,5] H shift to yield the

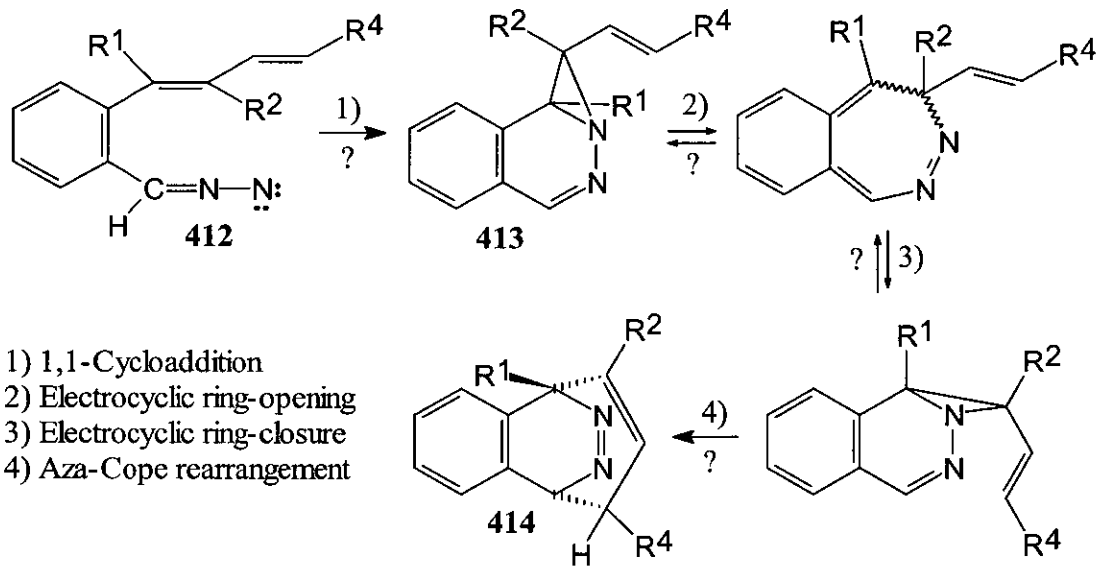
observed azepine **400**, although this could feasibly have formed directly by a [1.7] electrocyclisation of the nitrile ylide. The fact that the initial cycloaddition product could not be isolated leaves the mechanism of formation of this azepine open to speculation, although all other azepines of this type obtained in this work have been derived from the 1,1-cycloaddition products.

The thiophene-containing nitrile ylide **404** where the ζ-substituent was a methyl group proved to be too unstable under the conditions used for generation and reaction of the imidoyl chloride and no products or starting material could be isolated from any reaction.

2 Generation and Reactions of Triene-Conjugated Diazoalkanes

Programme of Research

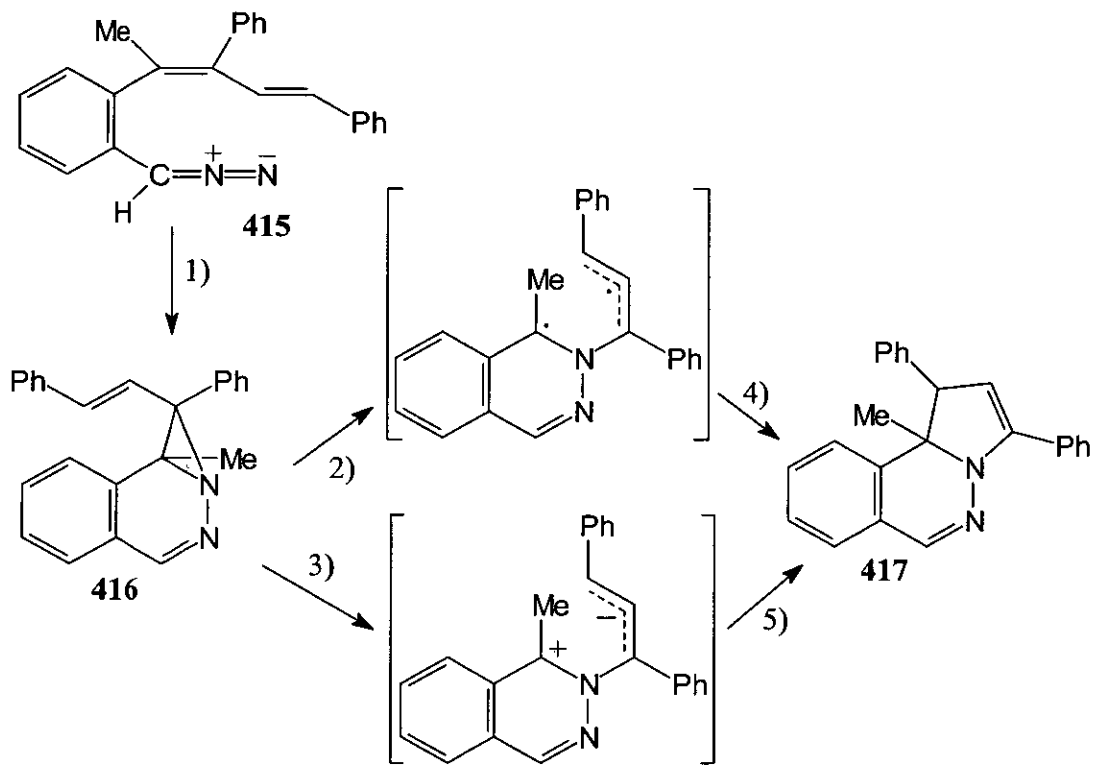
The observed universality of the 1,1-cycloaddition of triene-conjugated nitrile ylides of the type **247** led directly to the next part of this investigation, on the cycloadditions of the analogous triene-conjugated diazoalkanes **412**. Work of this kind was initially undertaken by Wilson[132], in the hope of generating analogues (**414**) of the bridged isoquinolines as illustrated in scheme **155**. The key step in this process would be generation and rearrangement of the intermediate vinylaziridine analogue **413**. It was hoped that these intermediates would behave in a manner directly parallel to the 1-alkenylcyclopropa[*c*]isoquinolines **317**, familiar from the previous section.



Scheme 155

The formation of intermediates of the type **413** was thought to be a viable objective as diazoalkanes are known to undergo 1,1-cycloadditions[81,83] , as discussed below. This is best envisaged by consideration of their nitrenoid resonance representation **412**, analogous to the carbenoid representation of nitrile ylides (**247**) which is crucial to that dipole's proven propensity to undergo intramolecular 1,1-cycloadditions with conjugated trienes.

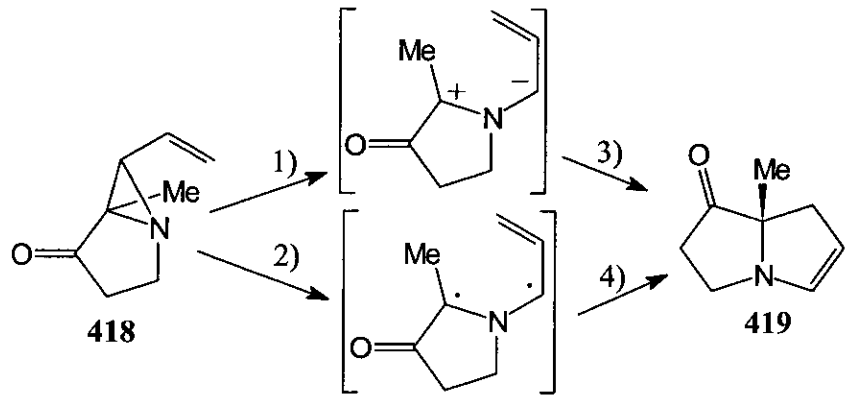
However, in the event it was found by Wilson[133] that the *cis* triene-conjugated diazoalkane **415** underwent intramolecular reactions to yield the phthalazine **417**, most likely *via* the processes shown in scheme **156**, implicating a 1,1-cycloaddition as the initial step.



1) 1,1-Cycloaddition 2) Homolytic bond cleavage 3) Heterolytic bond cleavage
4) Diradical ring closure 5) Ionic ring closure

Scheme 156

Literature precedent for the type of intramolecular rearrangements proposed to explain the formation of compounds of the type **417** exists in the form of a report by Hudlicky and co-workers[134]. Reaction of the vinylaziridine **418** was observed to yield product **419**, probably *via* one of the possible mechanisms illustrated in scheme **157**.



1) FVP or LiI and Δ; Heterolytic fission
2) FVP or LiI and Δ; Homolytic fission
3) Ionic ring closure
4) Diradical ring closure

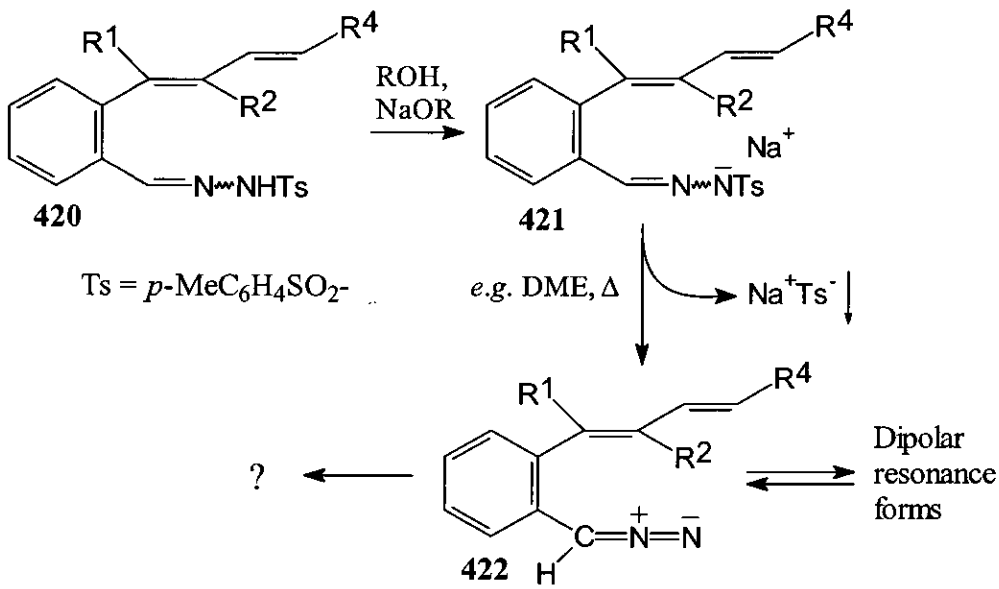
Scheme 157

Wilson's observation provided the first evidence for intramolecular 1,1-cycloadditions of diazoalkanes and it was felt that much further investigation was required to rationalise this process and determine if the process was common to all diazoalkanes of the type **415**.

The intention was to conduct further research into the reaction yielding the phthalazines, varying the substituents about the olefinic system and, in particular, the stereochemistry of the triene. The research into the nitrile ylide analogues reported here previously has shown the rearrangements of the intermediate 1-alkenylcyclopropa[*c*]isoquinolines to be strongly influenced by the substitution pattern about the conjugated triene system. It was hoped that the analogous rearrangements of the diazoalkanes could be similarly influenced to persuade them to yield compounds of the type **414** as well as, or instead of, the phthalazines **417**.

The fact that earlier work in this investigation showed that the initial 1,1-cycloaddition reactions of triene-conjugated nitrile ylides appears to be largely independent of the nature of substituents about the triene system gave added impetus to this part of the investigation.

Generation of the diazo-compounds was to be achieved by the method of Bamford and Stevens[65]. This involves treatment of the tosylhydrazones **420** with a sodium alkoxide to give the salts **421** which, when dried and heated in dry aprotic solvents, extrude sodium *p*-toluenesulfinate to give the diazoalkanes **422**. These can then undergo the chemistry dictated by their structure.



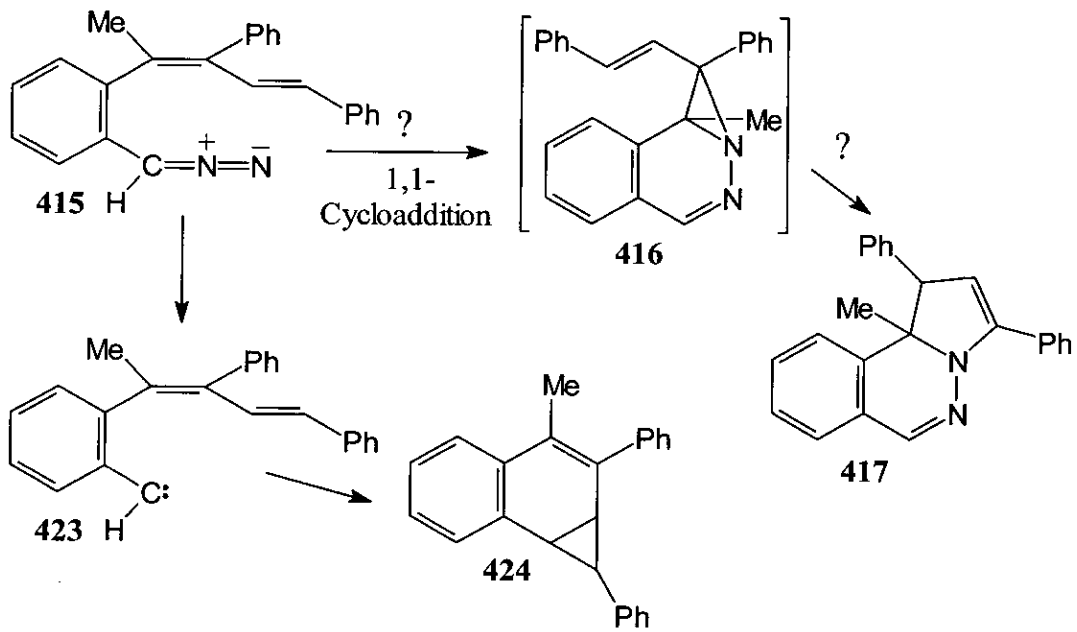
Scheme 158

Recent work within the group of Sharp[133] has shown that, in cases similar to those which will be investigated here, heating is not always required to liberate the diazoalkanes (**422**) from the salts (**421**). This observation was contrary to previous findings and was ascribed to steric acceleration of the loss of the *p*-tosyl group caused by the bulky substituted olefins at the *ortho* position on the ring. This phenomenon could be advantageous in the ensuing investigation if thermolabile intermediates or products such as alkenyl aziridines **416** are formed from cycloadditions of the dipoles.

2.1 Generation and Reactions of the Diazoalkanes Derived from 1',2',4'-Trisubstituted 2-(Buta-1',3'-dienyl)benzaldehyde Tosylhydrazones

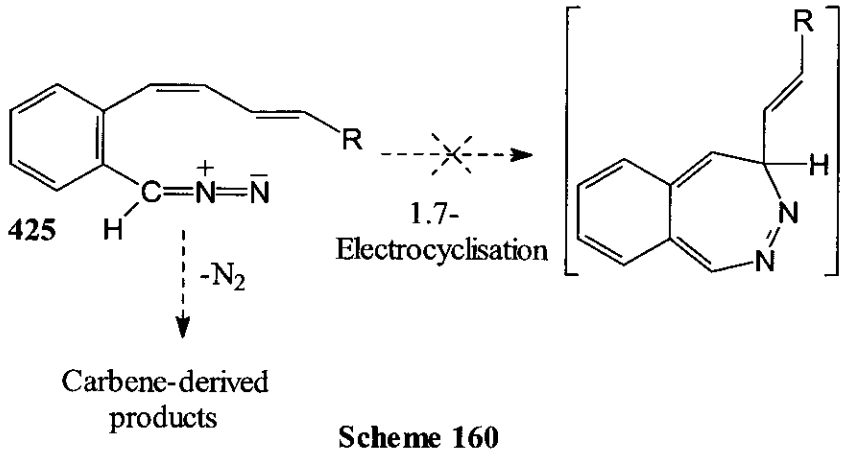
2.1.1 Preamble

The observation which initiated this part of the investigation involved cycloaddition of the diazoalkane **415** to give the phthalazine **417**. This was found to be the minor (26 %) product of reaction of the (*E*,*E*) isomer **415**, where the ε,ζ olefin is closer to the dipole, *cis* across the γ,δ olefin with respect to the benzene ring. The major (70 %) product was the cyclopropa[*a*]naphthalene **424**, formed by intramolecular reaction of the carbene **423** following loss of nitrogen from the diazoalkane **415**.



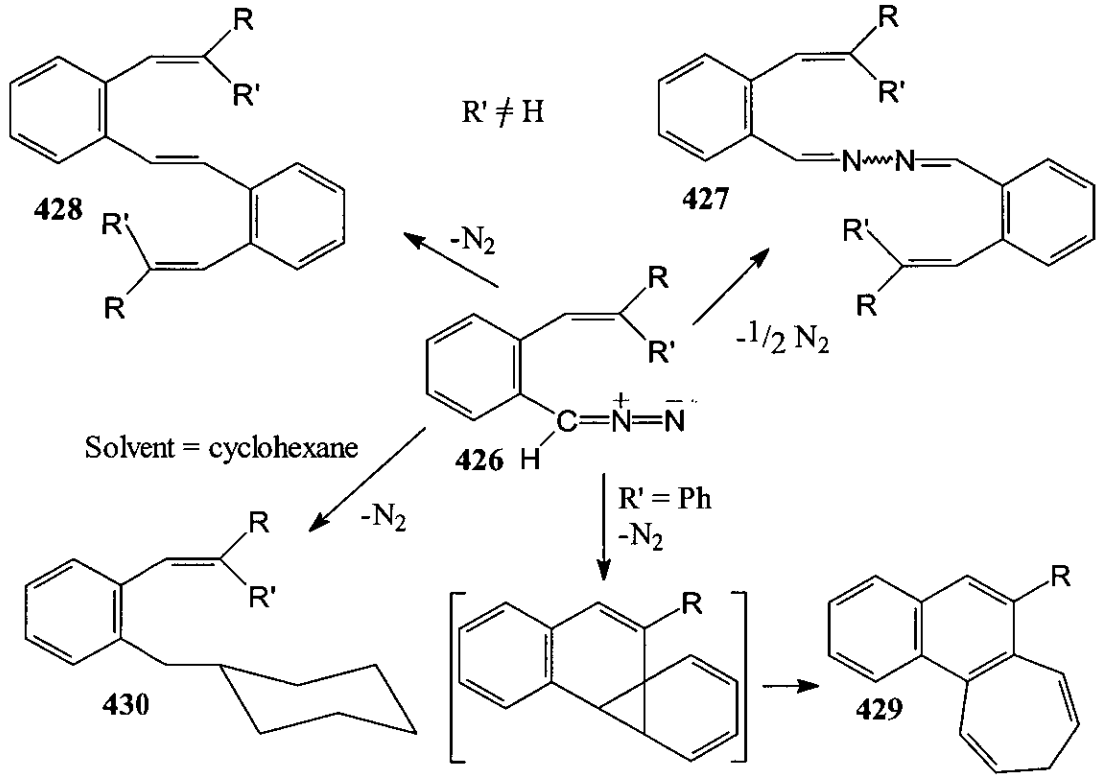
Scheme 159

It is worthy of note at this point that the (*Z*,*E*) isomer of the triene-conjugated diazoalkane **425** would **not** be expected to undergo [1.7]-electrocyclisation as the reaction site at the olefinic δ carbon would be blocked (*i.e. cis* δ-substituent ≠ H) (scheme **160**). In all cases studied previously, [1.7]-electrocyclisation only occurred where the *cis* substituent at the δ-position was H.



Scheme 160

The failure of the [1.7]-electrocyclisation has previously been observed[88] with the diene-conjugated diazoalkanes **426**. A non-H *cis*-substituent at the terminal δ position of the diene (R') causes the products isolated from the reactions to derive only from *inter*molecular reactions, as azines (**427**) and olefins (**428**), or intramolecular reactions of the carbenes (from loss of N_2 from the diazoalkane) to give indenes or cyclohepta[*a*]naphthalenes (**429**, scheme **161**). It is also possible to obtain products of insertion of the carbenes into solvent molecules (*e.g.* **430**), depending on the identity of the solvent. As will be discussed later, however, the 1,1-cycloaddition is not precluded by such a substitution pattern.



Scheme 161

It is thought that the [1.7]-electrocyclisation mechanism of the reactions of diazocompounds (*e.g.* **426**) is precluded in the cases where the *cis* δ substituent is larger than H because of interference by the large substituent (R') with the diazo group in the helical transition state. The attainment of this arrangement is thought to be vital[89] for the 1.7-electrocyclisation to proceed (figure **12**).

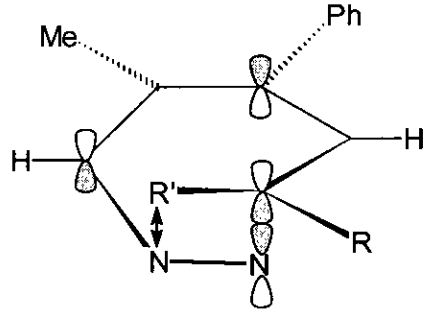
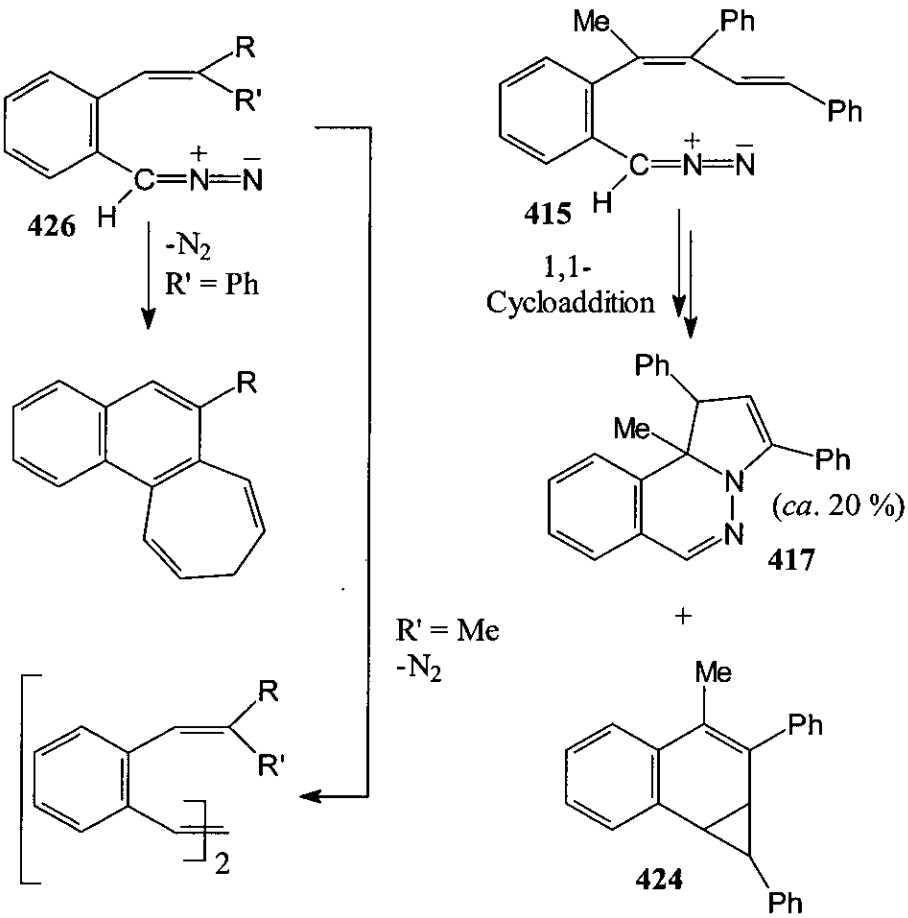


Figure 12

However, it appears that the 1,1-cycloaddition process is not subject to the same constraint, since the diazo-compound **415** apparently reacts *via* this route to give **417**. Such reactions are presumably reversible and do not lead to isolable nitrogen-

containing products in the reaction of compounds[135] of the type **426** but, in the case of **415**, the presence of the terminal double bond appears to provide a viable forward route to the phthalazine **417**.

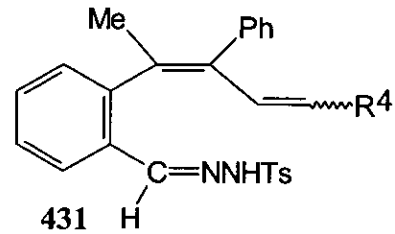


Scheme 162

The aim of this area of investigation was to identify the factors affecting the favourability of the 1,1-cycloadditions and subsequent rearrangements of 1,2,4- or γ,δ,ζ-trisubstituted triene conjugated diazoalkanes similar to **415**. In this section the triene has *cis* [formally (*E*,*E*)] geometry at the γ,δ bond, with the ε,ζ double bond being *cis* to the α,β unsaturation, and thus closer to the dipole.

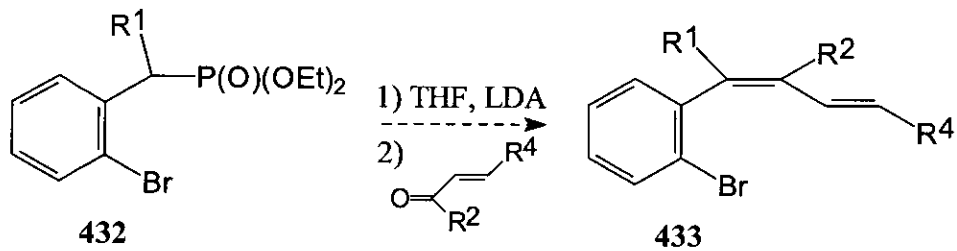
2.1.2 General Synthetic Strategy

The synthetic route to the γ,δ,ζ-trisubstituted triene-conjugated tosylhydrazones **431** was different to that utilised to obtain the nitrile ylide precursors generated previously in this work.



431

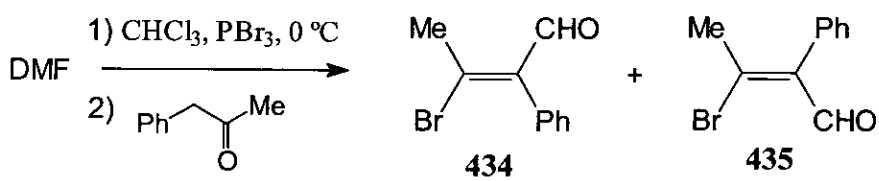
The established olefination protocol used up to this point would be unlikely to be applicable to generation of a disubstituted γ,δ olefin (*e.g.* in **433**) as this would entail the use of both a ketone and the substituted phosphonate **432**. Diaryl or dialkyl ketones are inherently less reactive than aldehydes in Wittig or Wadsworth-Emmons olefinations (reflected in the poor yield of bromocompound **371**). It was thought likely that the extra steric hindrance provided by the substituent R^1 at the reaction site of the phosphonate would make the reaction outlined in scheme **163** unfeasible.



432 **433**

Scheme 163

The route employed[136, 137] (scheme **165**) began with an Arnold bromoformylation reaction with phenylacetone (scheme **164**). This allowed access to both the (*E*) and (*Z*) isomers of the bromoacrylaldehyde (**434** and **435** respectively), which are separable by MPLC. These compounds could then be utilised in Wittig or Wadsworth-Emmons olefination reactions with a variety of reagents to yield the required 2-bromopenta-2,4-dienes *e.g.* **436**.

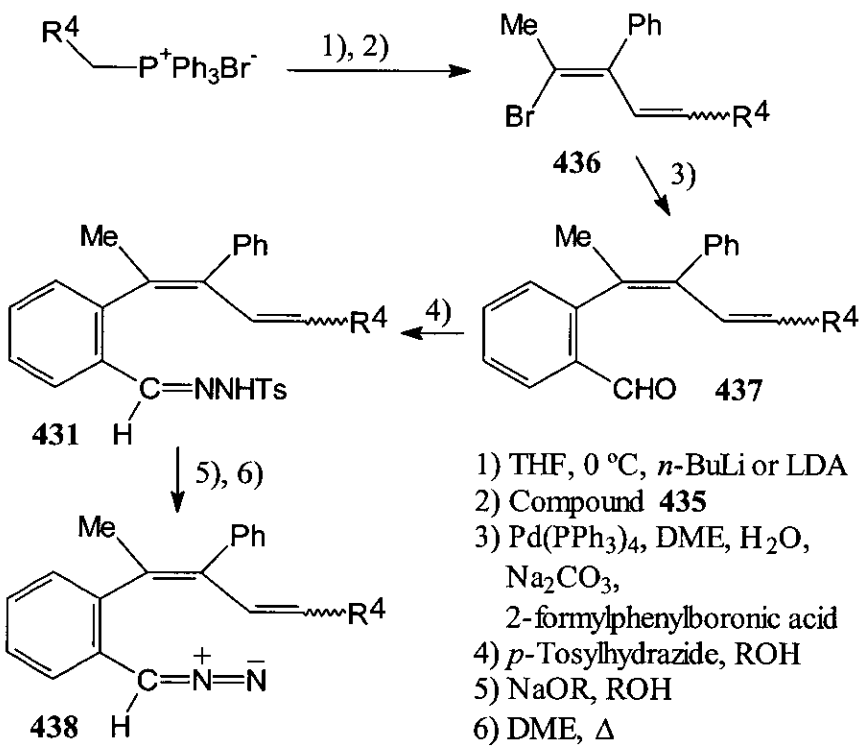


434 **435**

Scheme 164

As the *E*- and *Z*-bromoacrylaldehydes **434** and **435** were generated as a mixture and separated by chromatography the work of this investigation was carried out in parallel with that on the (*Z*,*E*) isomers, which will be discussed later in this thesis. Tosylhydrazones of the type **431** were the required dipole precursors in this work, with the required geometry about the γ,δ olefin achieved simply by using the (*Z*) isomer of the bromoacrylaldehyde (**435**) in the initial olefination reactions to yield the required 2-bromopenta-2,4-dienes **436**.

These compounds were then used in Suzuki reactions with the readily available 2-formylphenylboronic acid to obtain the substituted *ortho*-dienyl benzaldehydes **437**. These reactions used Gronowitz's modified conditions[138] (DME solvent, $Pd^{(0)}(PPh_3)_4$ catalyst) and generally proceeded quickly and in good yields to give the desired products. Minimal heating was required for these reactions to proceed, which is fortunate as the bromodienes were often found to be highly thermolabile, some examples decomposing overnight at sub-zero temperatures. Surprisingly, the bromodienes were less stable than the bromoacrylaldehydes, which could be stored effectively in a deep freeze for a number of months without decomposing.

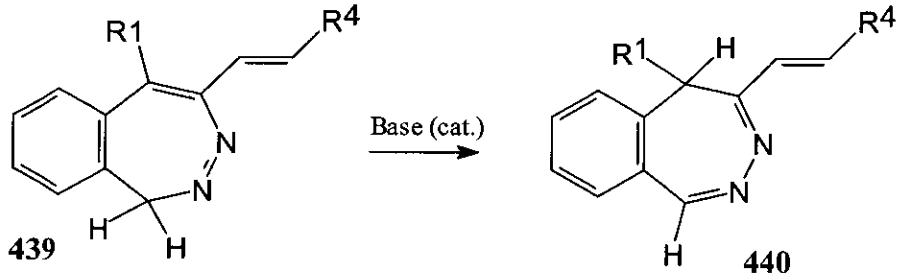


Scheme 165

Condensation of the obtained aldehydes (**437**) with *p*-tosylhydrazide gave the tosylhydrazones **431**. The sodium salts of these compounds were then used to generate the diazoalkanes **438**.

Some care was required in the handling of the tosylhydrazones as, in addition to the propensity of the olefins to polymerise, the tosylhydrazone functionality is known to be photosensitive. The synthesis, storage and generation and decompositions of the salts of these compounds were all carried out in vessels wrapped in aluminium foil to exclude as much light as possible. The tosylhydrazones were also found to degrade readily in chlorinated solvents such as chloroform and DCM and the use of these solvents was avoided.

In all of the ensuing reactions between tosylhydrazones and sodium alkoxides a deficiency of the alkoxide (approximately 0.95 equivalents) was used. This is because a possible initial product-type, the 1*H*-2,3-benzodiazepines **439**, can easily undergo a subsequent base-catalysed isomerisation to the more thermodynamically stable 5*H*-2,3-benzodiazepines[109] **440** (scheme **166**).

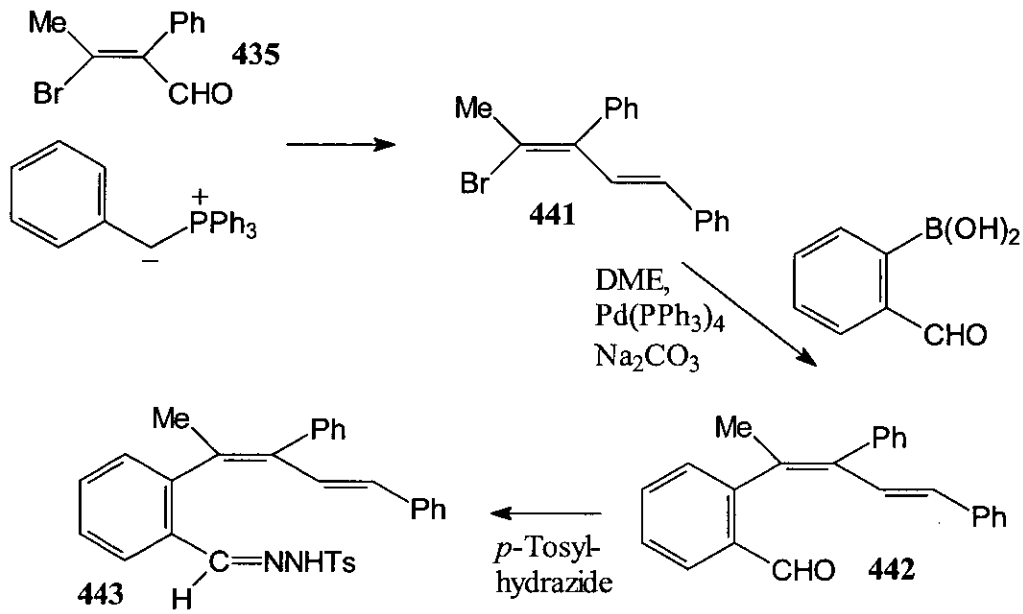


439 **440**

Scheme 166

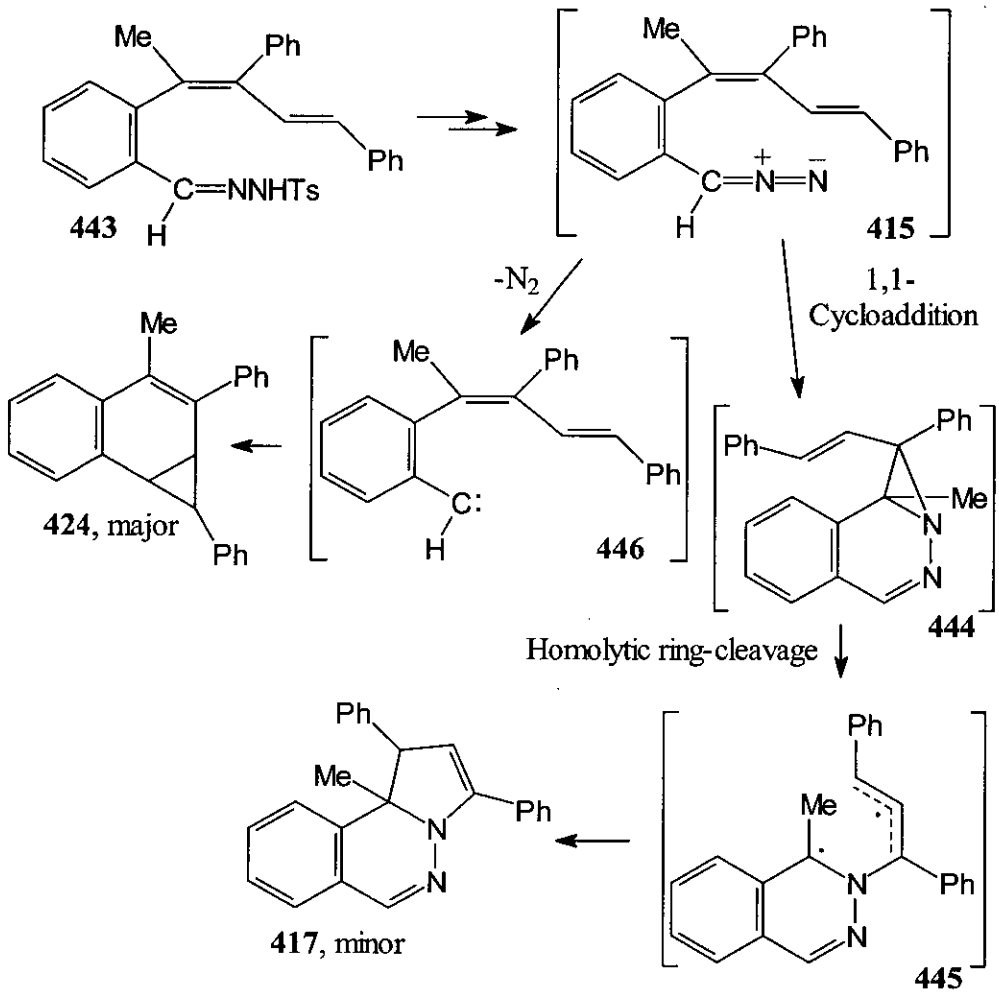
2.1.3 (*E*,*E*)-2-(1-Methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone 443

The first objective in the section was to repeat the Wilson experiment (generation and reaction of the diazoalkane **415**) and verify the observation independently. The first target in this section was therefore the *cis* triene-conjugated tosylhydrazone **443**.



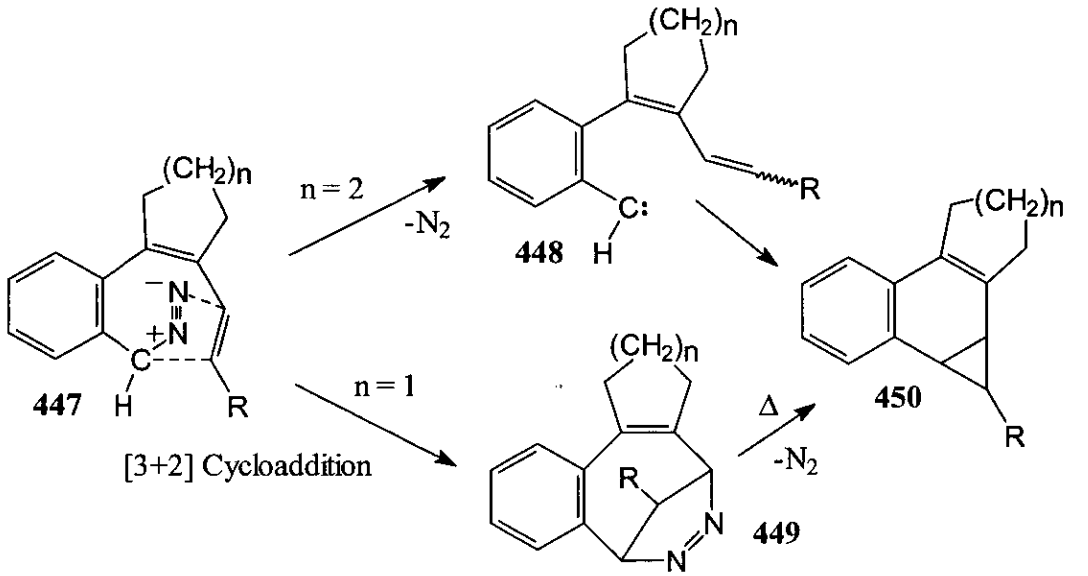
Scheme 167

The tosylhydrazone **443** was obtained in good overall yield and the sodium salt was generated and thermally decomposed in the usual manner to generate the diazoalkane **415**. The reaction gave two products which were separated by chromatography. The major product was the carbene-derived cyclopropa[*a*]naphthalene **424** (53 %). The second product to be eluted from the column was the pyrrolophthalazine **417** (25 %). This result was almost identical with that obtained by Wilson.



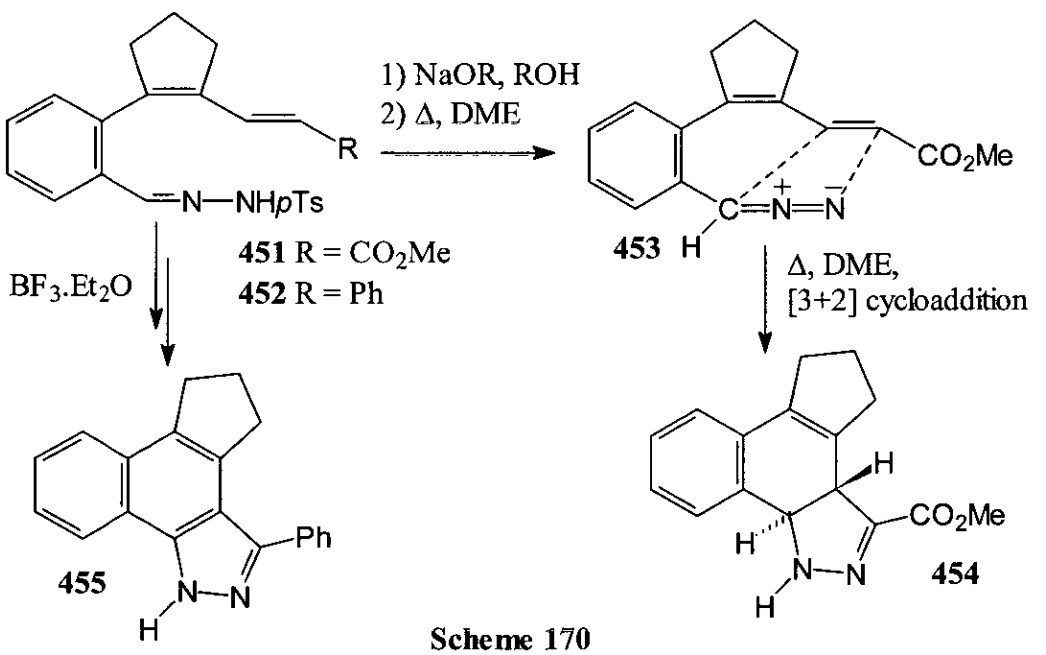
Scheme 168

This result is quite different from other reactions between the ε,ζ olefin and the diazo group which have been observed previously in similar systems to those under investigation[133]. In cases where the γ,δ olefin formed part of a cyclopentenyl ring (**447**, n = 1, scheme **169**) the molecules reacted *via* [3+2] cycloadditions, resulting in the formation of diazocines **449**.



Scheme 169

Effects of substituents at the ζ-position on the triene appeared to have little influence on the outcome of the cycloadditions in these cases, except where an activating (electron-withdrawing) methyl ester was incorporated at this position (**451**, scheme **170**). In this case the cycloaddition proceeded with the opposite regioselectivity, yielding the dihydrobenzo[*g*]indazole **454**. This reaction showed the regioselectivity expected for an intermolecular cycloaddition with an alkene substituted with a strong electron-withdrawing group.

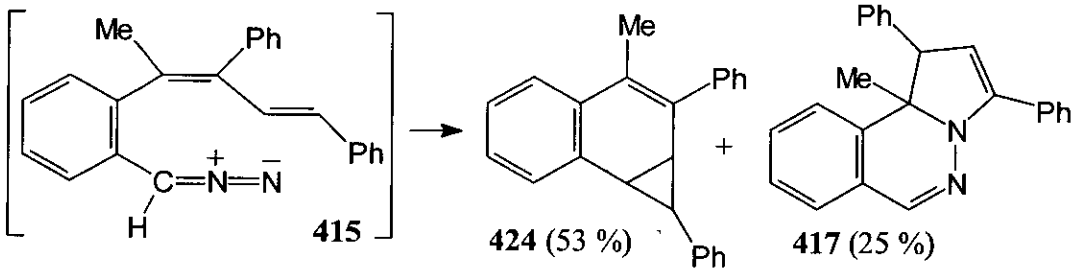


Scheme 170

This regioselectivity was also observed upon reaction of the tosylhydrazone **452** in the presence of the Lewis acid boron trifluoride diethyletherate. This reaction, however, proceeds by a stepwise ionic mechanism to give the benzo[*g*]indazole **455**, rather than *via* a cycloaddition reaction.

Interestingly [3+2] cycloaddition reactions were not observed at all when the γ,δ double bond was part of a cyclohexenyl ring (scheme **169**, n = 2). The only product was the hexahydrocyclopropa[*l*]phenanthrene **450** (n = 2, R = Ph). This change in the observed reaction path was attributed to the differences in molecular geometry between the analogues with the 5- and 6-membered rings which disfavoured the helical transition state (figure **12**) required for the [3+2] cycloaddition when n = 2 (*i.e.* when a 6-membered ring was incorporated).

The result of this experiment therefore confirmed the unique result reported by Wilson and the inference that these systems can react *via* a 1,1-cycloaddition reaction with the γ,δ double bond. However, it is clear that this is a minor reaction path in this case which is only just competitive with the loss of N_2 to give carbene-derived products.

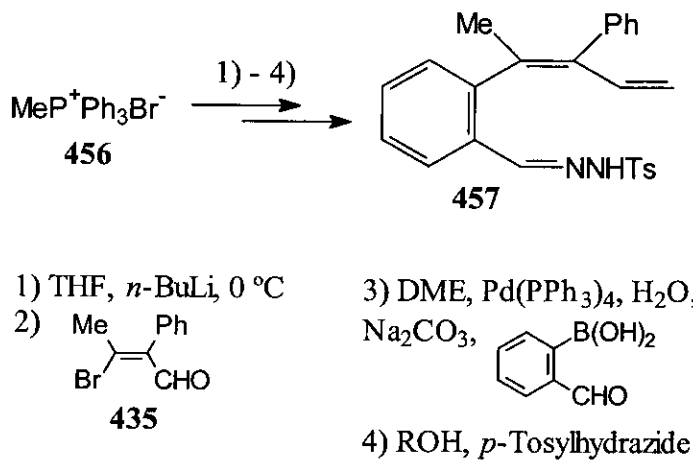


Scheme 171

2.1.4 (*E*,*E*)-2-(1-Methyl-2-phenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (457)

In order to further probe the reactivity pattern of the *cis* triene-conjugated diazoalkanes a similar strategy to that followed in the previous section was adopted,

i.e. systematic alteration of the substitution pattern about terminal diene system. The first example studied was the decomposition of the diazo-compound **458,** with H at the ζ-position. The Wittig reaction between methyltriphenylphosphonium bromide **456** and the (*Z*)-isomer of the bromoacrylaldehyde (**435**) proceeded as expected, as did the subsequent reactions to obtain the tosylhydrazone **457**.



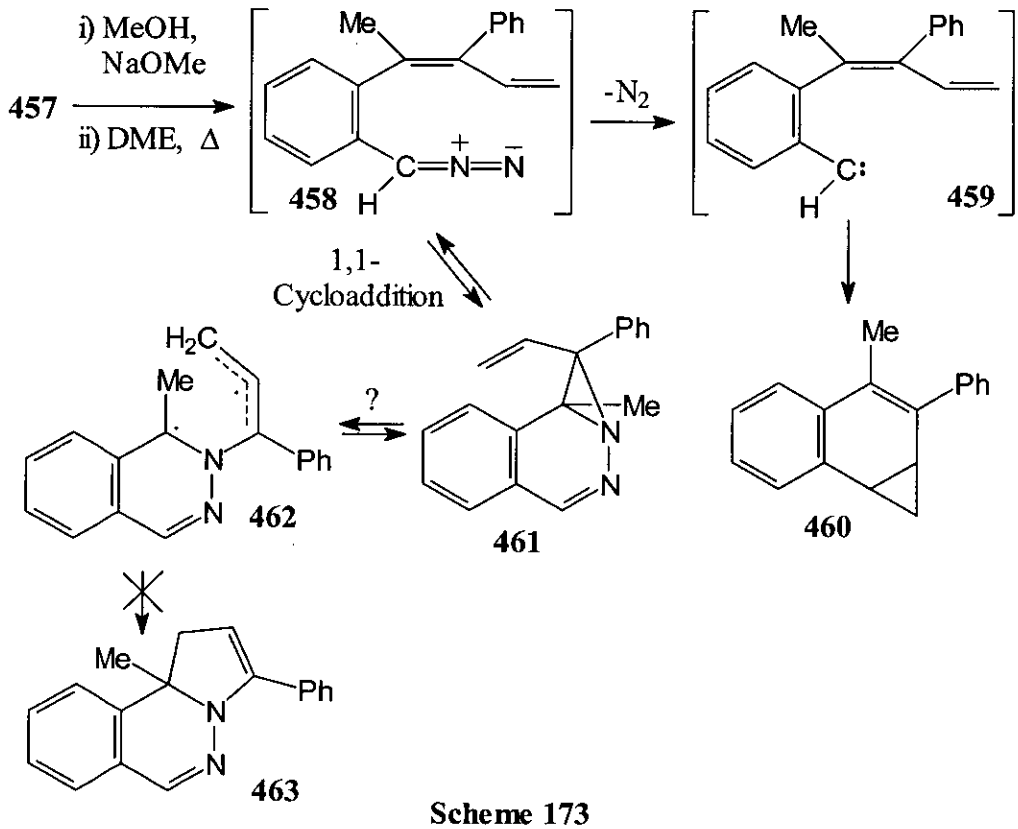
Scheme 172

Decomposition of the sodium salt of **457** in the usual manner yielded only the cyclopropa[*a*]naphthalene **460**, presumably *via* the mechanism described previously (scheme **173**). Apparently, removing the phenyl substituent at the ζ-position of the triene has disfavoured phthalazine formation in favour of the competing carbene process. In principle, this effect could be due either to an effect on the initial 1,1-cycloaddition **or** on the subsequent rearrangement processes.

The most likely explanation is that the 1,1-cycloaddition is unaffected but that the resulting adduct **461** fails to undergo rearrangement to the phthalazine **463** at a rate which is competitive with the reverse 1,1-cycloaddition back to **458**. The diazoalkane will then decompose via loss of nitrogen to give the carbene **461** and ultimately product **460**.

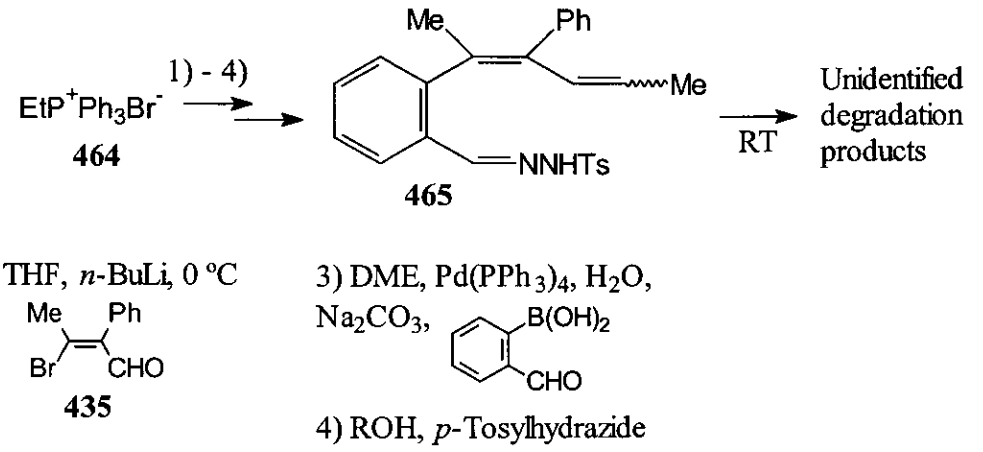
The failure of **461** to rearrange is possibly due to a more difficult cleavage of the aziridine ring in **461** to give the diradical intermediate **462**. The latter, with only one conjugating Ph group, would be less stabilised by radical delocalisation than the

analogue **446** which has two conjugating phenyl rings. Thus, if the transition state for the cleavage process is product-like, the activation energy would be higher and the reaction less competitive.



Scheme 173

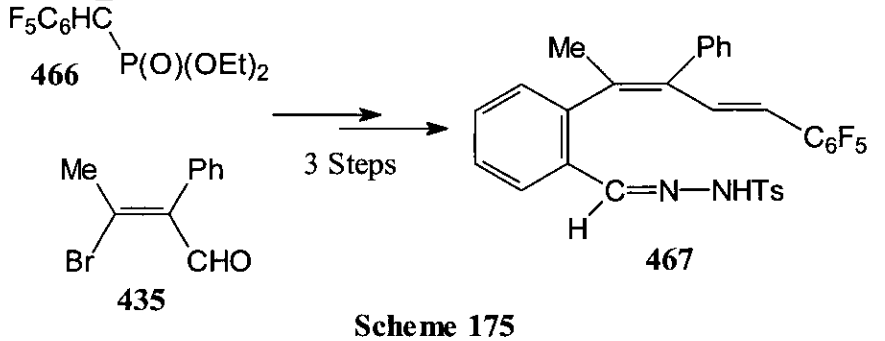
Synthesis of the example where the triene ζ-substituent was a methyl group was attempted using phosphonium halide **464**, but the tosylhydrazone **465** proved unstable and decomposed to give a complex mixture of degradation products before it could be sufficiently purified to be used to generate the diazoalkane.



Scheme 174

2.1.5 (*E*,*E*)-2-(1-Methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl)benzaldehyde Tosylhydrazone (467)

In view of the disappointing results from the ζ-alkyl analogues of the *cis* triene-conjugated diazoalkanes it was decided to use various aromatic groups at this position instead. This, it was hoped, would bring about changes in product composition which could be related to the electronic and steric properties of the aromatic substituent. The first analogue to be synthesised was the tosylhydrazone **467**, where $R^4 = C_6F_5$, the perfluorophenyl group.



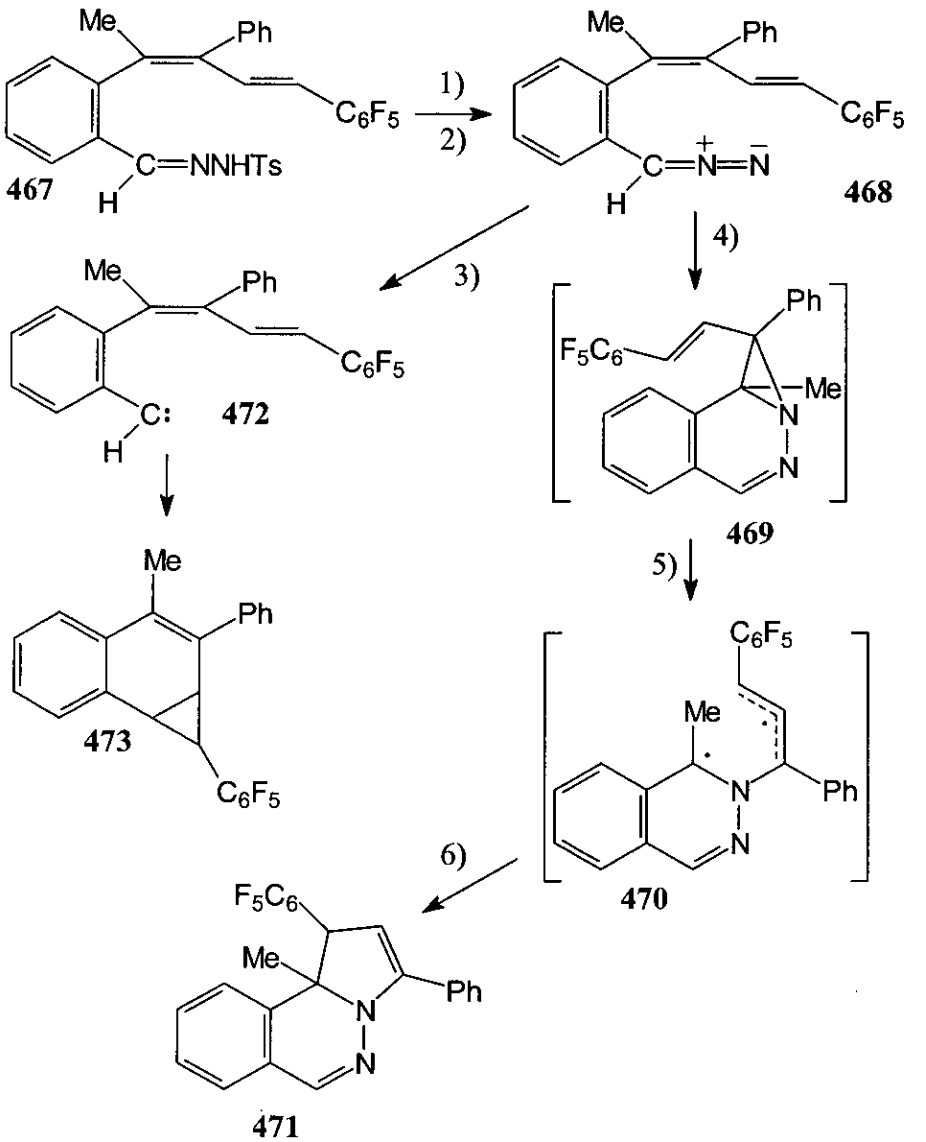
Scheme 175

It was thought that the electron-withdrawing character of the perfluorophenyl group could stabilise the diazoalkane **468** with respect to N_2 loss relative to the phenyl analogue **444**. This effect would hopefully further promote 1,1-cycloaddition and ultimately increase the yield of the phthalazine **471**. It was also believed that the

increase in steric bulk caused by including fluoro substituents in place of hydrogen atoms would be minimal, hopefully circumventing further complications which could be caused by increasing substituent bulk.

The tosylhydrazone **467** was produced in good yield by the established procedure outlined previously in this section, starting with phosphonate ylide **466**. A complication in the spectral analysis of the perfluorophenyl compounds was that fluorine-19 causes splitting of signals from both ^{1}H and ^{13}C nuclei in their NMR spectra. This was especially evident in the signals of the quaternary carbon atoms bonded directly to fluorine, the signals from which were so complicated and heavily split in the ^{13}C NMR spectrum as to be unobserved. The aromatic quaternary carbon of the pentafluorophenyl ring appeared as a triplet ($^{3}J_{CCF}$ 10.8 Hz) in the ^{13}C NMR spectrum. An advantage of incorporating the ^{19}F nuclei was that spectra could also be obtained from this nucleus.

Generation and reaction of the diazoalkane **468** in the usual manner gave rise to a mixture of products.



1) MeOH, NaOMe 2) DME, Δ 3) $-N_2$ 4) 1,1-Cycloaddition
5) Homolytic ring opening 6) Diradical ring closure.

Scheme 176

Analysis of the product mixture by ^{1}H NMR spectroscopy prior to chromatography showed it to consist of a 2:1 mixture of the cyclopropa[*a*]naphthalene **473** and the phthalazine **471**. Chromatography gave the products in yields of 46 % and 23 % respectively. It appeared that the perfluorophenyl substituent at the ζ-position had exerted an influence in the expected direction, making the 1,1-cycloaddition more favourable and so promoting the formation of the phthalazine **471**.

This observation is consistent with the rationalisation given for the previous example concerning the reaction of the diazoalkane **457** (R^4 = H). In this case the increased scope for delocalisation of the radical in the intermediate **470** when R^4 is aromatic serves to stabilise the diradical species and allow further rearrangement to yield the phthalazine.

Decomposition of another sample of the sodium salt of the tosylhydrazone **467**, this time at room temperature over a five-day period was found to provide a similar mixture of the two products **471** and **473** as was obtained by heating a sample of the salt of **467** at 80 °C for 4 hours. This suggests that the cyclopropa[*a*]napthalenes recovered from this series of reactions do not derive from initially-formed nitrogen-containing products.

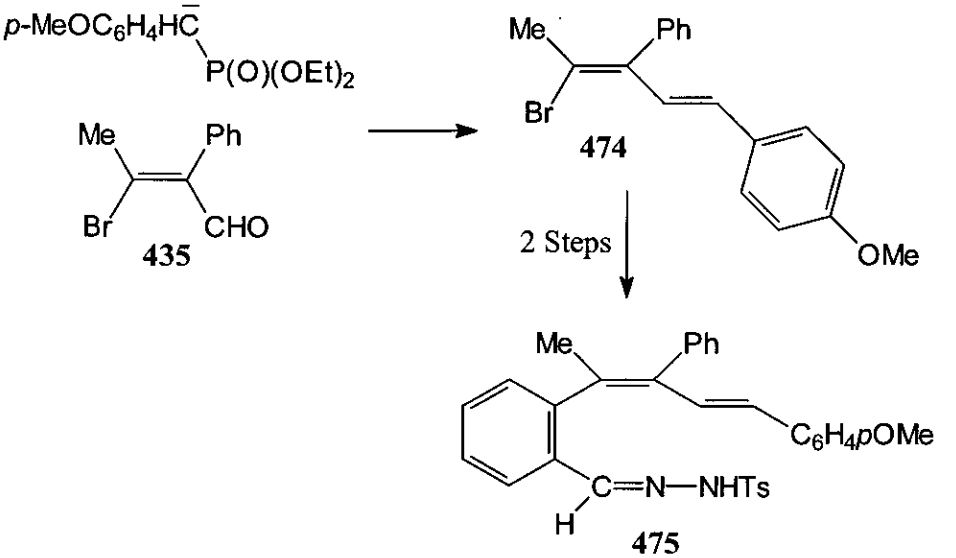
The phthalazines generated would appear to be stable under conditions used to form them, at least for the limited periods they are exposed to the elevated temperatures. It therefore does not appear that the cyclopropa[*a*]napthalenes are products of degradation of the phthalazines. It is more likely that the diazoalkane reacts so slowly at room temperature that decomposition to the carbene becomes competitive, while at higher temperatures both processes (1,1-cycloaddition and nitrogen extrusion) are accelerated. Further experimentation with reacting the diazoalkane at a variety of temperatures and observing the product distribution would have proven interesting.

2.1.6 (*E*,*E*)-2-(1-Methyl-2-phenyl-4-(*p*-methoxyphenyl)buta-1,3-dienyl)benzaldehyde Tosylhydrazone (475)

The study was next extended to an analogue **475** with an electron-rich aryl group at the ζ-position.

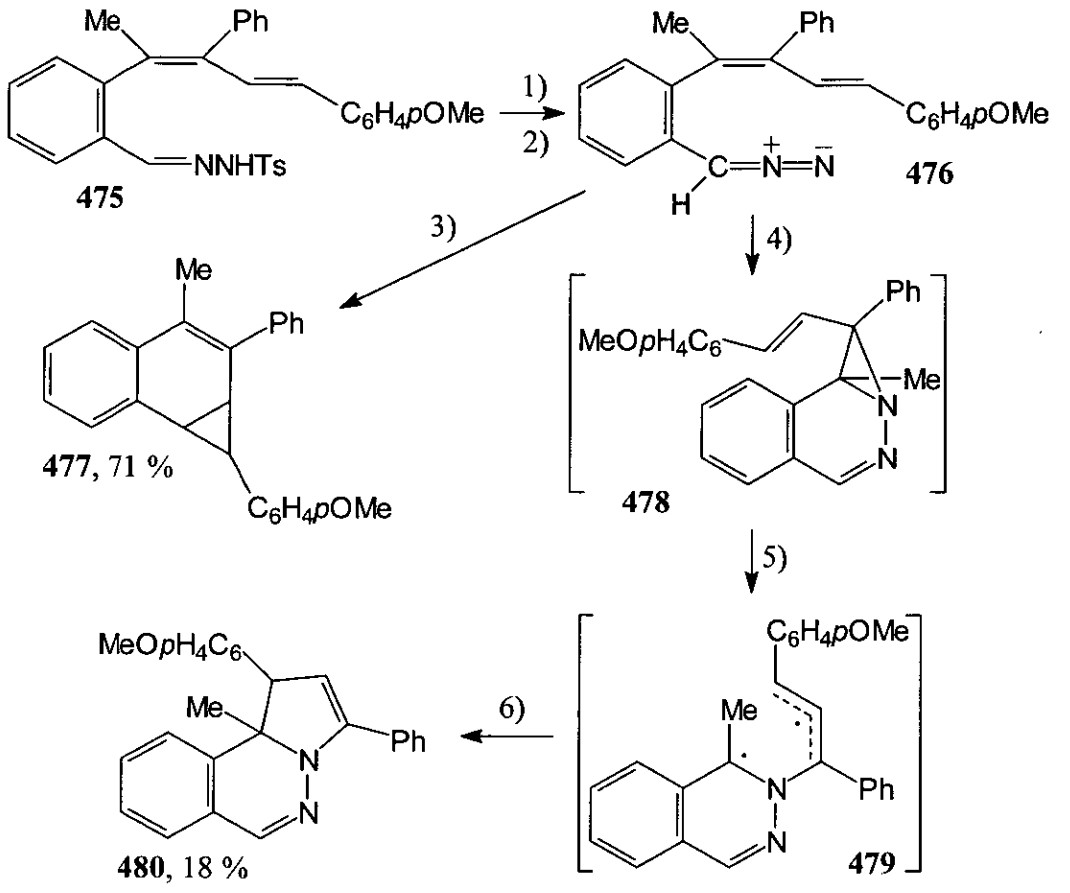
The initial Wadsworth-Emmons olefination reaction (scheme **169**) furnished the required bromodiene **474**, albeit in poor yield (16 %). Nevertheless, a sufficient

amount of this bromodiene was isolated to allow synthesis of the tosylhydrazone **475**, *via* the established Suzuki coupling / *p*-tosylhydrazide condensation route.



Scheme 177

Generation and reaction of the diazoalkane **476** from the precursor **475** in the usual manner again gave a mixture of products, which was revealed by ^{1}H NMR spectroscopy to consist of the cyclopropa[*a*]naphthalene **477** and the phthalazine **480**, in a 4:1 ratio. Separation by chromatography gave these products in yields of 71 % and 18 % respectively. Thus, the proportion of phthalazine in the product mixture is only *ca.* half that obtained from reaction of diazo-compound **468** (where $R^4 = C_6F_5$, electron-poor aryl ring).



1) MeOH, NaOMe 2) DME, Δ 3) $-N_2$ 4) 1,1-Cycloaddition
5) Homolytic bond cleavage 6) Diradical ring closure

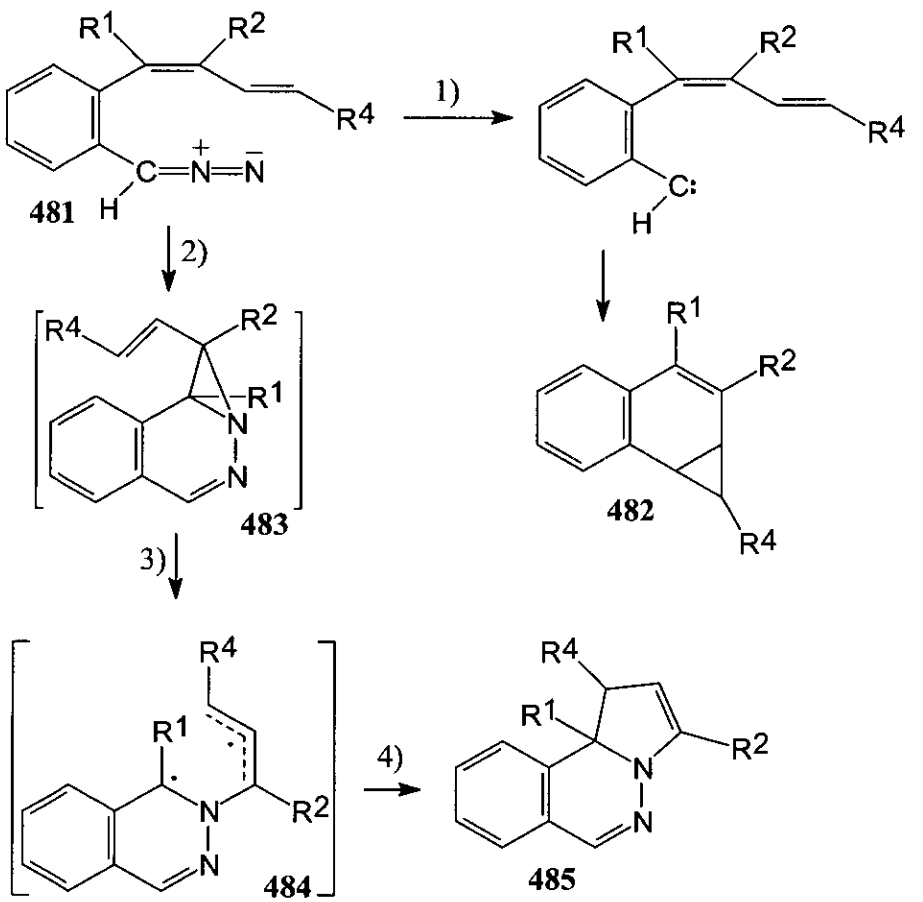
Scheme 178

This observation provides further evidence for the rationalisation put forward for the three previous examples. Again, an aromatic substituent at the ζ-position of the triene has caused formation of the heterocyclic phthalazine in significant, but still minor, amount. This provides further support for the view that phthalazine formation is promoted by the terminal aryl group which stabilises the diradical species **479**.

2.1.7 Conclusions

Table 4

R^1	R^2	R^4	Diazoalkane No.	Temp. (°C)	Products
Me	Ph	Ph	**415**	80	**482** (53 %) + **485** (25 %)
Me	Ph	C_6F_5	**468**	80	**482** (46 %) + **485** (23 %)
Me	Ph	C_6F_5	**468**	*ca.* 20	**482** (46 %) + **485** (23 %)
Me	Ph	*p*-C_6H_4OMe	**476**	80	**482** (71 %) + **485** (18 %)
Me	Ph	H	**458**	80	**482** (63 %)



1) -N_2 2) 1,1-Cycloaddition 3) Homolytic bond-cleavage
4) Diradical ring-closure

Scheme 179

The work detailed here on cycloaddition reactions of 1,2,4-trisubstituted (*E,E*) triene-conjugated diazoalkanes where the geometry of the γ,δ olefin holds the ε,ζ olefin in close proximity to the dipole is summarised in table **4**. These results indicate the fundamental importance of the identity of the ζ-substituent in determining the favoured reaction pathways.

The initial example, where the ζ-substituent was a phenyl ring (diazoalkane **415**), gave predominantly the carbene-derived cyclopropa[*a*]naphthalene **424** with a small but significant amount of phthalazine **417** also being formed. The former was the sole product-type where R^4 = H. Interestingly, including the perfluorophenyl group (which is more electron-deficient than a phenyl ring) at the ζ-position was found to increase the proportion of phthalazine formed. The opposite effect was observed where the ζ-position bore a *p*-methoxyphenyl ring, which conversely is more electron-**rich** than the phenyl ring.

Two reaction paths have been observed to be open to the diazoalkanes generated in this section. The balance between them is proposed to be dependent upon the stabilisation of the putative diradical intermediate (**484**) by the substituents R^2 and R^4. Where R^2 and R^4 are aromatic this stabilisation is thought to be sufficient to allow the intermediates **483** to rearrange to yield phthalazines. Where R^4 is non-aromatic this stabilisation is lessened, with the result that only carbene-derived products are isolated from reactions of those dipoles.

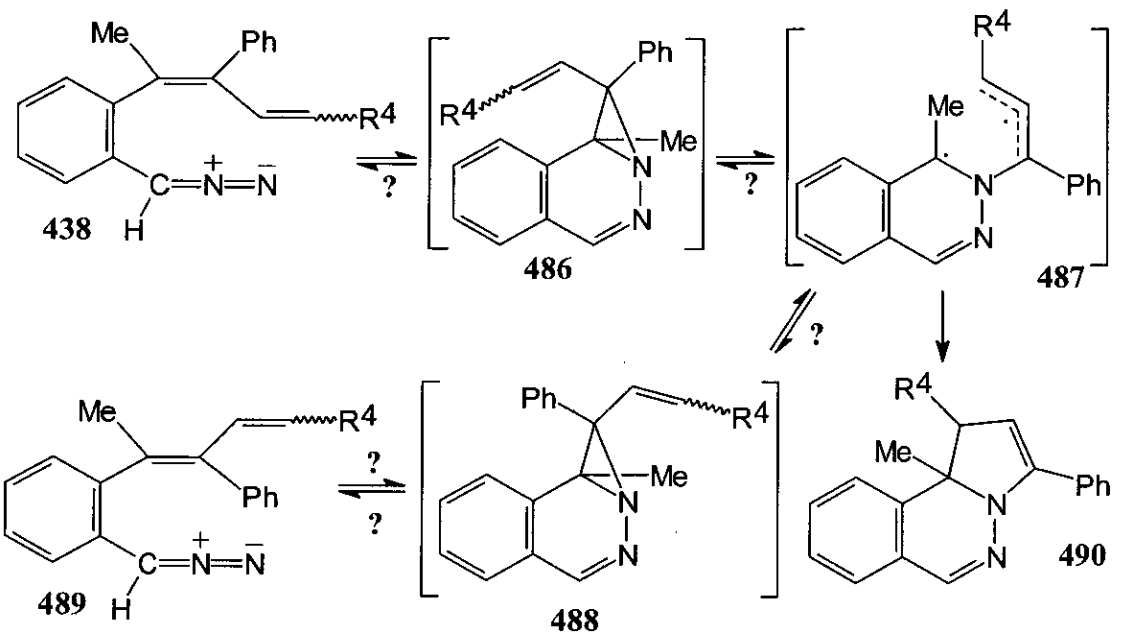
In all cases, however, the cyclopropa[*a*]naphthalenes **482** predominated as the major products.

2.2 Generation and Reactions of Diazoalkanes Derived from 1',2',4'-Substituted (*E,E*)-2-(Buta-1',3'-dienyl)benzaldehyde Tosylhydrazones

2.2.1 Preamble

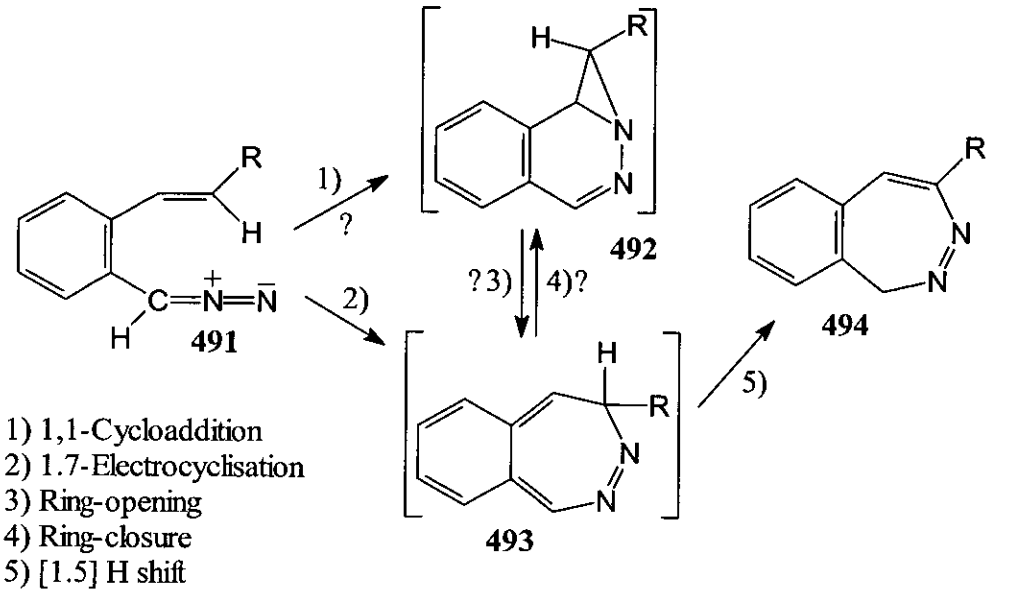
In this section the objective was to discover the effects of (i) inverting the stereochemistry at the γ,δ double bond, and (ii) reducing the number of substituents on the pendant diene system.

The mechanism of the 1,1-cycloaddition and subsequent rearrangement of the intermediate is feasibly the same for both the *cis* (**438**) and *trans* (**489**) isomers of these diazoalkanes (scheme **180**).



Scheme 180

Much work has been carried out in the past with *trans* diene-conjugated diazoalkanes of the type **491**.



1) 1,1-Cycloaddition
2) 1.7-Electrocyclisation
3) Ring-opening
4) Ring-closure
5) [1.5] H shift

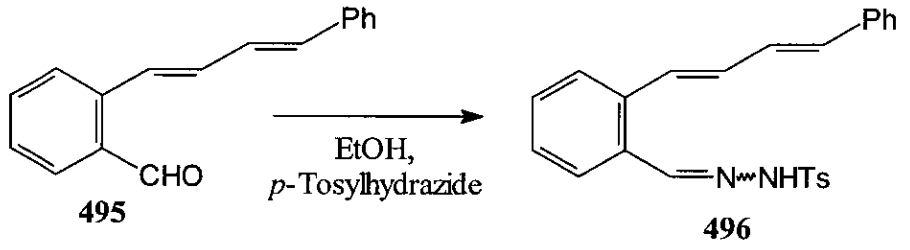
Scheme 181

Those which, like the example shown (**491**), have a *cis* H atom at the terminus of the diene system cyclise readily give 1*H*-2,3-benzodiazepines **494**. This reaction is thought to proceed *via* a 1.7-electrocyclisation, giving **493** as the primary product, which undergoes a facile [1,5] H shift to give the isolated product.

It is possible[133] that the diazepine **494** does not form *via* a [1.7] electrocyclisation but by an initial 1,1-cycloaddition of the diazoalkane **491** to give the aziridine **492**. This intermediate could then undergo an electrocyclic ring opening to **493** and a subsequent re-aromatising [1,5] H shift to give the diazepine **494** (scheme **181**). No direct evidence has been obtained in these systems for the formation of **492**, either by 1,1-cycloaddition or *via* ring contraction of **493**. The only evidence for such intermediates comes from the formation of the phthalazines **490** (scheme **180**) from the triene-conjugated diazoalkanes **438**, as discussed in the previous section. In those cases the absence of a *cis* H atom at the δ-position of the triene precludes [1,5] H shift and thus diazepine formation.

2.2.2 (*E*,*E*)-2-(4-Phenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (496)

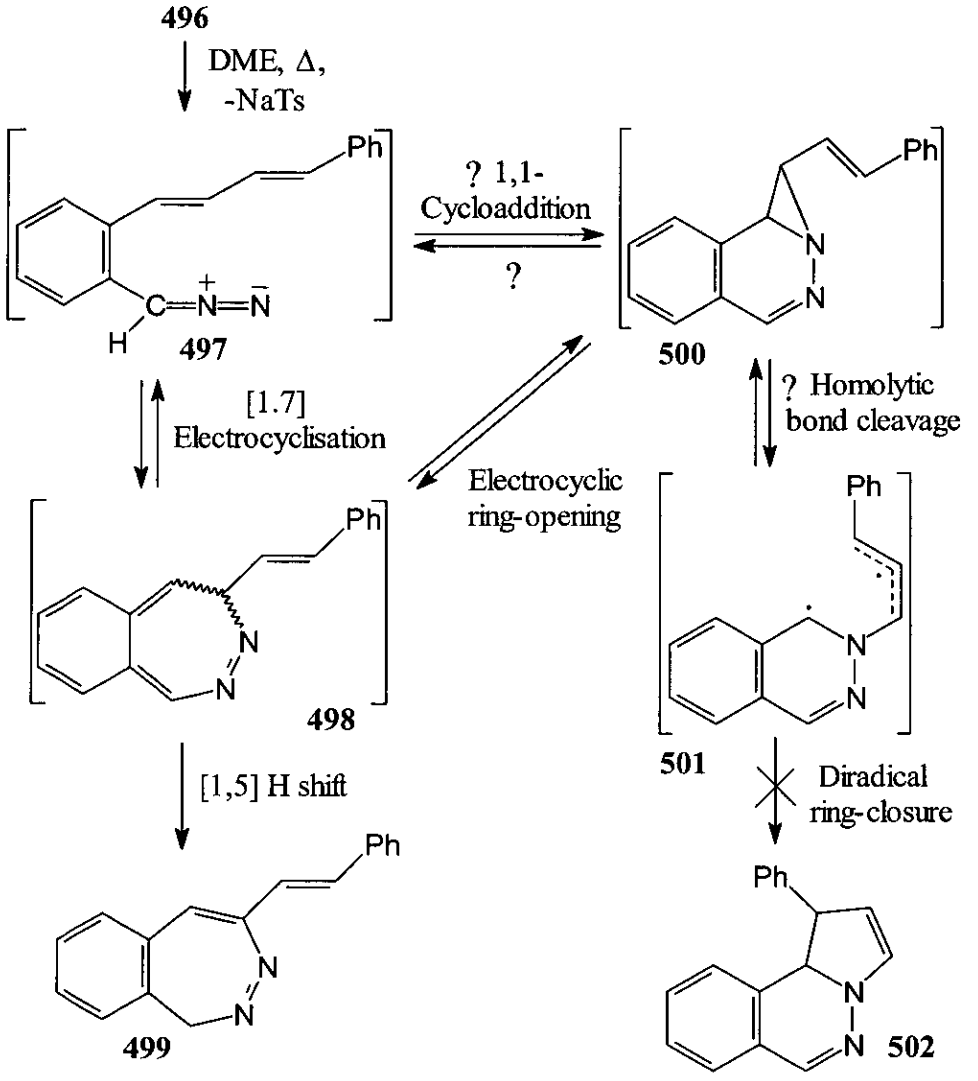
The first target was the tosylhydrazone **496**. The synthesis of the aldehyde **495** was identical to that detailed in the nitrile ylide work. It was then condensed with *p*-tosylhydrazide in alcohol to give the tosylhydrazone **496**. The condensation reaction (scheme **182**) proceeded smoothly, going to completion in *ca.* 3 hours. The tosylhydrazone product **496** was identified readily by TLC and by the peak arising from the methyl group in the ^{1}H NMR spectrum. All other spectroscopic analyses were consistent with this structure.



495 **496**

Scheme 182

The sodium salt of the tosylhydrazone **496** was prepared under anhydrous conditions and heated in dry DME at 80 °C. TLC showed the formation of one new product. This product was isolated by dry-flash column chromatography and identified by ^{1}H NMR spectroscopy as the 4-alkenyl-1*H*-2,3-benzodiazepine **499**. The most indicative features of the ^{1}H NMR spectrum were two broad doublets at δ 3.09 and δ 6.38, which are caused by the two methylene protons at the 1-position of the diazepine ring. The ^{13}C NMR spectrum showed a single methylene peak at δ 69.2 in the 3π/4 DEPT experiment, arising from C-1.

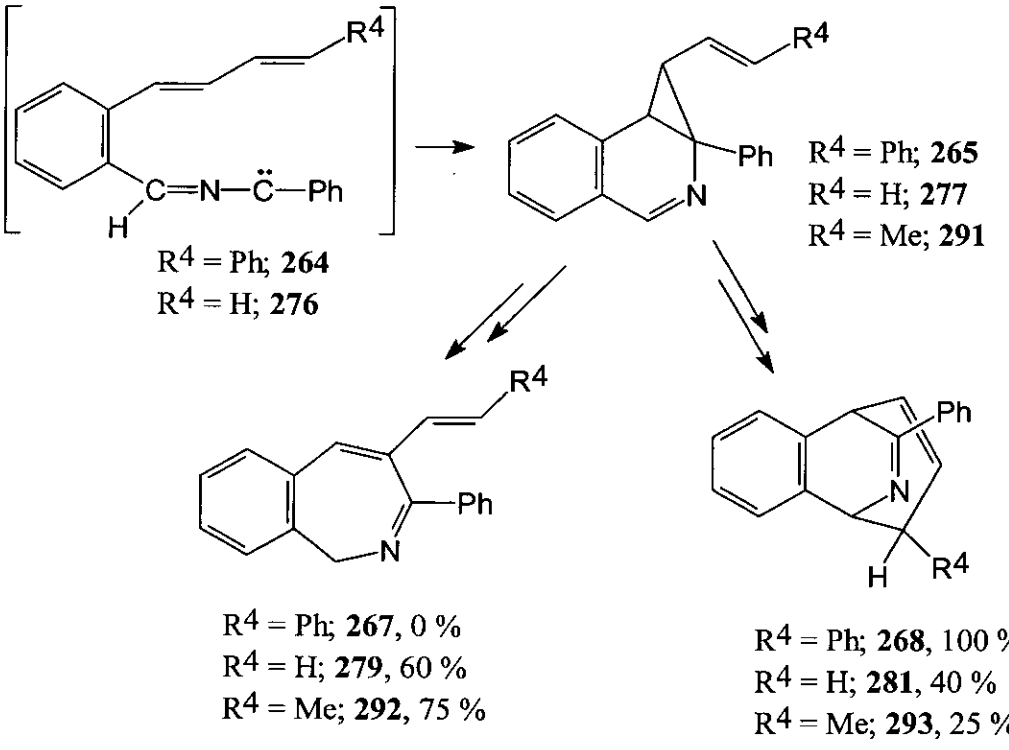


Scheme 183

The observed reaction of diazoalkane **497** is analogous with that expected of (*E*) diene-conjugated diazoalkanes[88], *e.g.* **491**, where the *cis* δ-substituent on the olefinic unsaturation is H (scheme **181**). It appears, therefore, that the presence of the terminal alkene group (the ε,ζ bond) in diazoalkane **497** has not opened up the reaction path leading to the phthalazine **502**, and thus has provided no evidence for the existence of the intermediate **500**.

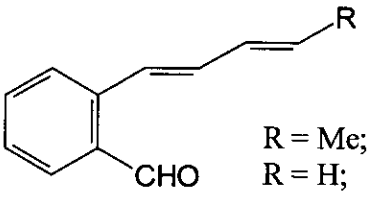
2.2.3 (*E*,*E*)-2-(Penta-1,3-dienyl)benzaldehyde Tosylhydrazone (505) and (*E*)-2-(Buta-1,3-dienyl)benzaldehyde Tosylhydrazone (506)

It was decided that the strong influence that the ζ substituent (R^4) on the trienyl system held over the direction of post-cycloaddition rearrangements in the nitrile ylide work (scheme **184**) made further investigations in this area worthwhile. In the nitrile ylide work, aromatic substituents at the ζ-position of the triene favoured aza-Cope rearrangement of the cycloaddition products, while non-aromatic substituents favoured formation of the 1*H*-2-azepines *via* [1,5] H shifts, where possible.



Scheme 184

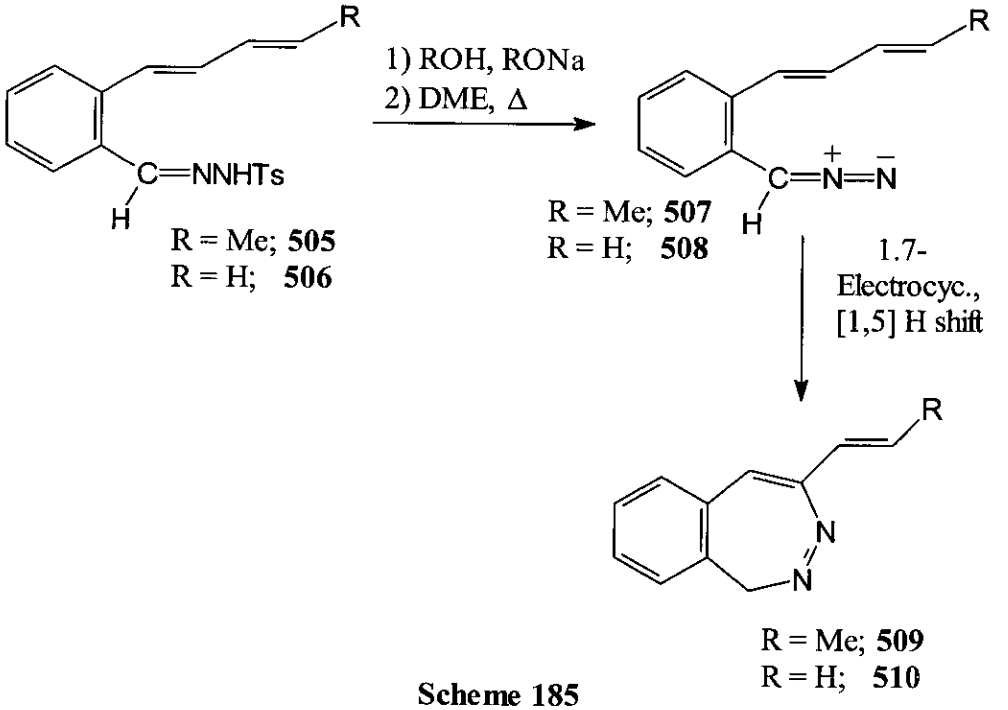
Again, the syntheses of the aldehydes **503** and **504** had already been achieved, so obtaining the required dipole precursors was simply a case of condensing the aldehydes with *p*-tosylhydrazide to obtain the tosylhydrazones **505** and **506**. The dipole with a methyl group at the ζ position of the triene (compound **507**) was generated first, in the usual manner.



R = Me; **503**
R = H; **504**

Periodic analysis of the reaction mixture by TLC showed a single high-running product to form rapidly on heating the mixture. The ^{1}H NMR spectrum of the crude product showed the presence of only the 4-alkenyl-1*H*-2,3-benzodiazepine **509**, which was isolated by dry-flash chromatography in 91 % yield.

Again, a pair of broad doublets (at δ 2.99 and δ 6.30, ^2J 9.2 Hz) due to the protons at C-1 were the most characteristic feature of the ^{1}H NMR spectrum. The methyl group gave rise to a doublet at δ 1.93 (^3J 5.1 Hz) and the two olefinic propenyl protons appeared superimposed upon each other. This showed that the ε,ζ double bond of the triene-conjugated diazoalkane **507** was intact and had been unchanged by any reactions with the dipole or subsequent rearrangements. The proton at the 5-position of the diazepine ring was observed as a singlet at δ 6.51. The ^{13}C spectrum exhibited the C-1 methylene atom at δ_C 68.9 and mass spectrometry confirmed that nitrogen had been retained in the product



R = Me; **505**
R = H; **506**

R = Me; **507**
R = H; **508**

R = Me; **509**
R = H; **510**

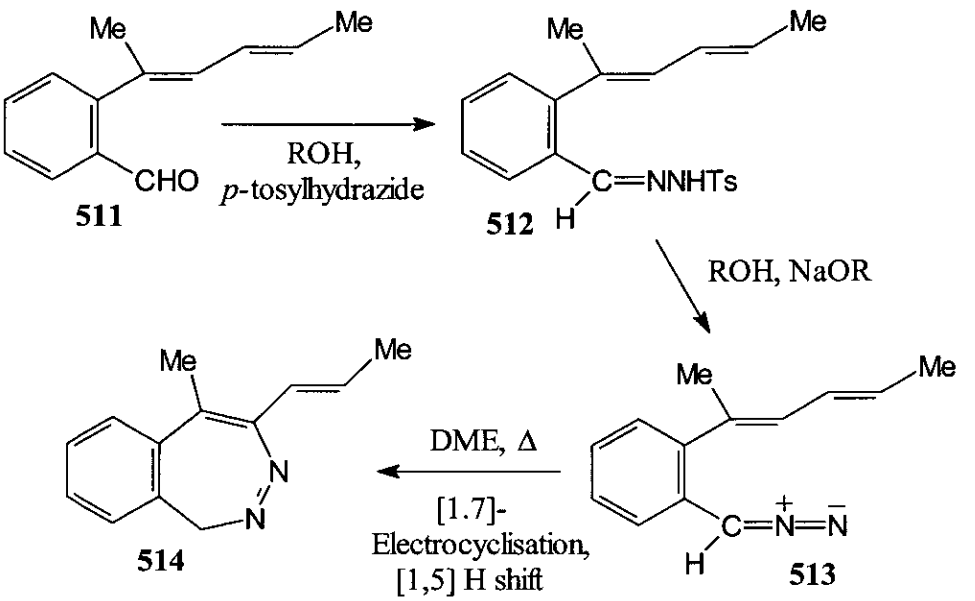
Scheme 185

An identical experiment was performed using the tosylhydrazone **506**, where the ζ-substituent = H. Analysis of the product mixture from the decomposition of the salt by ^{1}H NMR spectroscopy again showed the presence of only one product; the 4-alkenyl-1*H*-2,3-benzodiazepine **510**, which was isolated by dry-flash chromatography in 79 % yield. The ^{1}H NMR spectrum again showed the C-1 methylene protons as two broad doublets (δ 3.00 and δ 6.36, ^2J 9.3 Hz), the protons of the intact ε,ζ olefin and a singlet due to H-5 of the diazepine ring. The ^{13}C spectrum exhibited the methylene signal from C-1 at δ_c 69.1 along with the expected signals from the remainder of the structure.

In view of the previous two results, the formation of the 4-alkenyl-1*H*-2,3-benzodiazepine **510** was expected, and it was interesting to observe that the identity of the ζ-substituent had no influence over the favoured pathway of intramolecular reaction in diazoalkanes of this type.

2.2.4 (*E*,*E*)-(1-Methylpenta-1,3-dienyl)benzaldehyde Tosylhydrazone (512)

The work with triene-conjugated nitrile ylides had indicated that substitution at the γ-position on the olefin had a profound effect on the thermal rearrangements of cycloaddition products. It was thought it would be useful to discover whether this also applied in the case of triene-conjugated diazoalkanes.



Scheme 186

The tosylhydrazone **512** was synthesised by the usual method from the aldehyde **511**, previously prepared for the nitrile ylide work. Generation of the sodium salt and decomposition in the usual conditions gave only one product, which was readily identified as the *E*-5-methyl-4-(prop-2-enyl)-1*H*-2,3-benzodiazepine **514**. Dry-flash chromatography of the crude product allowed isolation of this diazepine in 76 % yield.

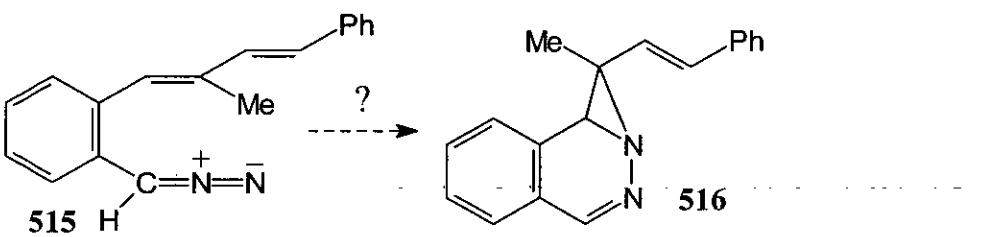
The ^{1}H NMR spectrum of the product showed the characteristic pair of broad doublets (at δ 3.16 and δ 6.09, ^{2}J 9.9 Hz), signals consistent with the intact propenyl system in the *trans* configuration (^{3}J 15.4 Hz) and a singlet due to the methyl group at the 5-position of the diazepine ring.

The isolation of the 1*H*-2,3-benzodiazepine **514** was consistent with previous results and showed that the methyl group at the γ-position of the triene had no discernible effect on the course of the reaction.

2.2.5 (*E,E*)-(2-Methyl-4-phenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (518)

The previous results have shown that diazepine formation *via* 1.7-electrocyclisation and [1,5] H shift is the dominant pathway when the triene-conjugated diazoalkane has a *cis* H at the δ-position. In order to block this path it was decided to impose a substituent at this position, as in **515**.

As previously stated, non-H *cis* substituents at the δ-position in *diene*-conjugated diazoalkanes prohibit intramolecular reactions of the dipole and lead to carbene formation (schemes **161** and **162**). While the *cis* triene-conjugated diazoalkanes from the previous section, which reacted intramolecularly *via* the diazoalkane, had non-H *cis* substituents (*i.e.* arylethenyl) at the δ-position, no work had been performed on analogous cases where the triene was also in the *trans* configuration.

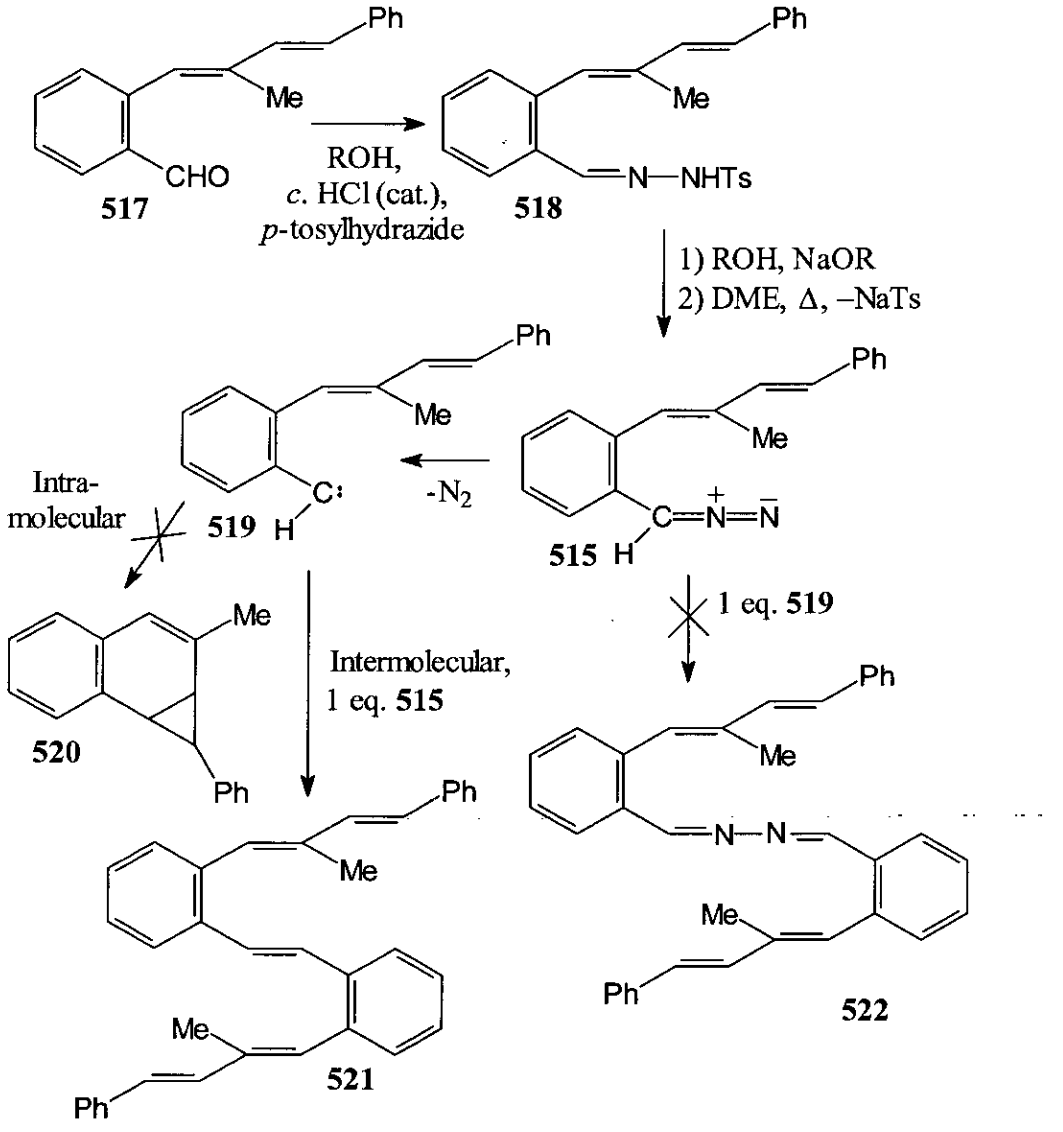


Scheme 187

Again, the aldehyde **517** had previously been synthesised in the course of this work and the tosylhydrazone **518** was easily obtained in the usual manner. Generation and thermal decomposition of the sodium salt proceeded to give a reaction mixture which showed a single product as a high-running spot by TLC. Isolation of this fraction by chromatography gave a product which was found by ^{1}H NMR spectroscopy to consist of the carbene-derived alkene **522**, in 78 % yield.

The mass spectrum of the product showed it to be of greater molecular weight than the parent diazoalkane and that nitrogen had not been retained (*m/z* 464.2493). The ^{1}H NMR spectrum showed the olefinic and methyl protons to be arranged in a

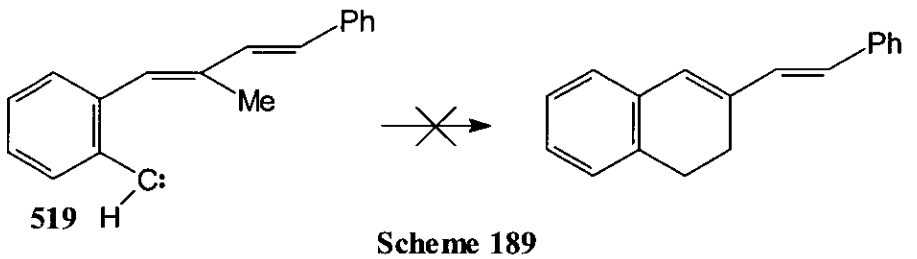
similar manner to those in the precursors (*i.e.* the bromocompound **371**, the aldehyde **517** and the tosylhydrazone **518**), suggesting that the γ,δ and ε,ζ double bonds had not been involved in any reaction. The signals observed in the ^{13}C spectrum were consistent with this identification.



Scheme 188

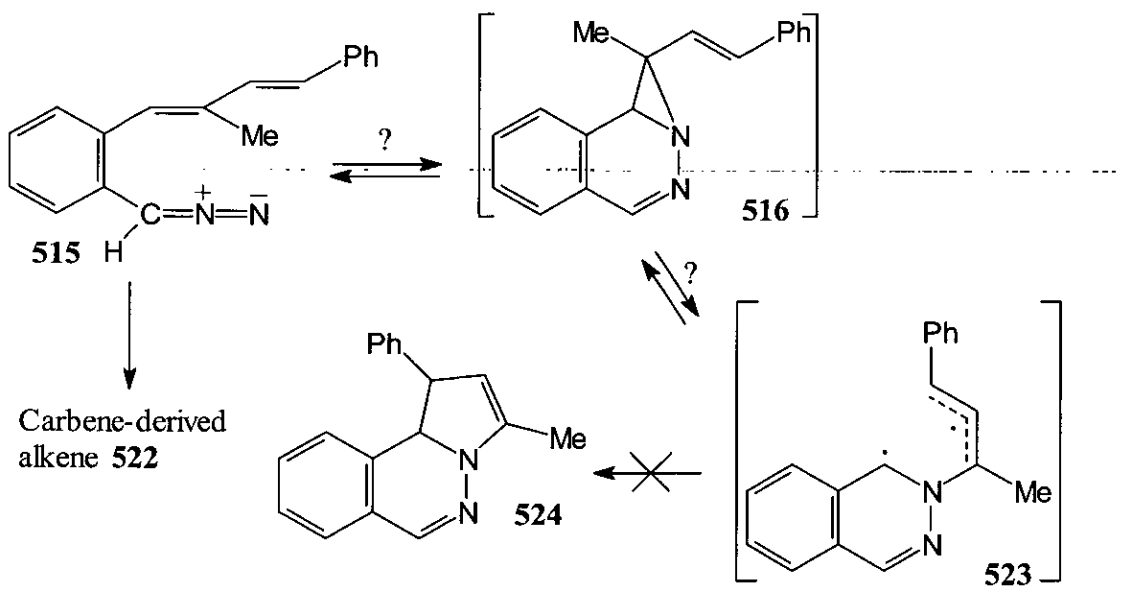
This result clearly shows that intramolecular reactions *via* the diazoalkane have been precluded by the presence of the methyl group at the olefinic δ position. In view of the product obtained it is most likely that the only reactions which did take place did so *after* extrusion of nitrogen from the diazoalkane to give the carbene **519**.

It is remarkable, however, that the carbene did not react *via* intramolecular electrocyclisation or insertion into the *cis* Me group (scheme **189**).



Scheme 189

This result (formation of alkene **521**) is in accordance with previous findings from diene-conjugated diazoalkanes where a non-H *cis* δ substituent was found to disfavour strongly the [1.7]-electrocyclic reaction. As in the preceding examples the presence of the terminal (ε,ζ) alkene moiety did not open up the route to the phthalazine **524**. This may, again, be due to the lack of stabilisation in the diradical **523**, however, in this case the methyl group might have been expected to provide some extra stabilisation compared with the cases where R^2 = H. If this was the case it was clearly not enough to promote that reaction path.

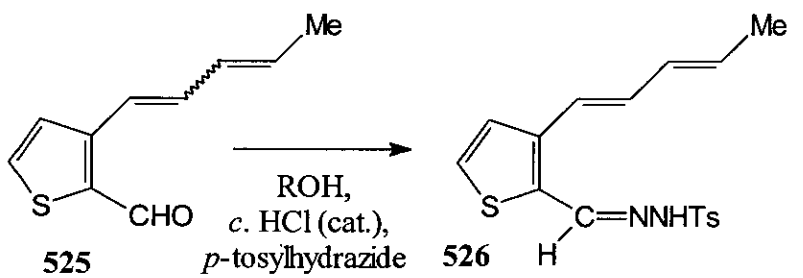


Scheme 190

This theory concerning the stability of intermediates of the type **523** is consistent with the observed reactivity of **515** and also that of the *cis* diazoalkanes from the previous section.

2.2.6 (*E*,*E*)-2-Formyl-3-(Penta-1,3-dienyl)thiophene Tosylhydrazone (526)

In view of the interesting result of the cyclisation reaction of the nitrile ylide derived from amide **395**, where the α,β unsaturation was part of a thiophene ring, it was decided to synthesise an analogous diazoalkane (**529**). This was achieved straightforwardly, with the previously synthesised aldehyde **525** simply being condensed with *p*-tosylhydrazide in the presence of mineral acid to give the (*E*,*E*) triene-conjugated tosylhydrazone **526**, and the diazoalkane being generated from this in the usual manner.

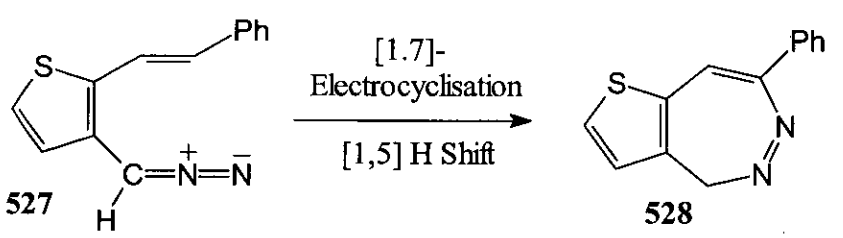


525 526

Scheme 191

Heating of the sodium salt of the tosylhydrazone **526** at reflux in dry DME gave one high-running product observed by TLC. This product was identified as the sulfur-containing cyclopropa[*a*]naphthalene analogue **531** from its ^{1}H and ^{13}C NMR characteristics, with signals from the cyclopropyl CH's appearing at low-shift in both spectra. A chromatographically inseparable, unidentified impurity appeared also to be present, even after distillation.

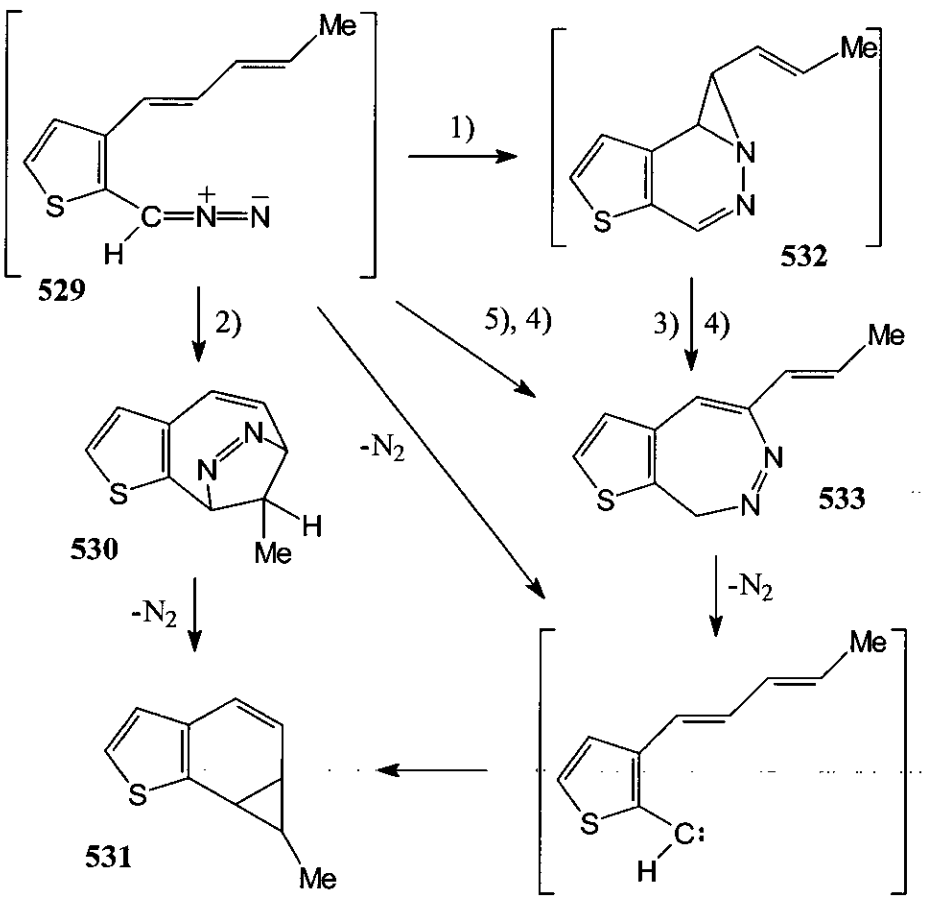
This result was inconsistent with previous work on diene-conjugated diazoalkanes where the α,β unsaturation was part of a thiophene ring[109] (**527**). In that case, nitrogen was conserved and the thienodiazepine (**528**) was obtained in high yield (scheme **192**).



527 528

Scheme 192

It is therefore possible that the 6-thia-cyclopropa[*e*]indene **531** obtained as the main product of this reaction is in fact a secondary product, formed by extrusion of nitrogen from a primary cycloaddition or cyclisation product (**530** or **533** respectively, scheme **193**).



1) 1,1-Cycloaddition 2) [3+2] Cycloaddition 3) Electrocyclic ring-opening 4) [1,5] H Shift 5) 1.7-Electrocyclisation

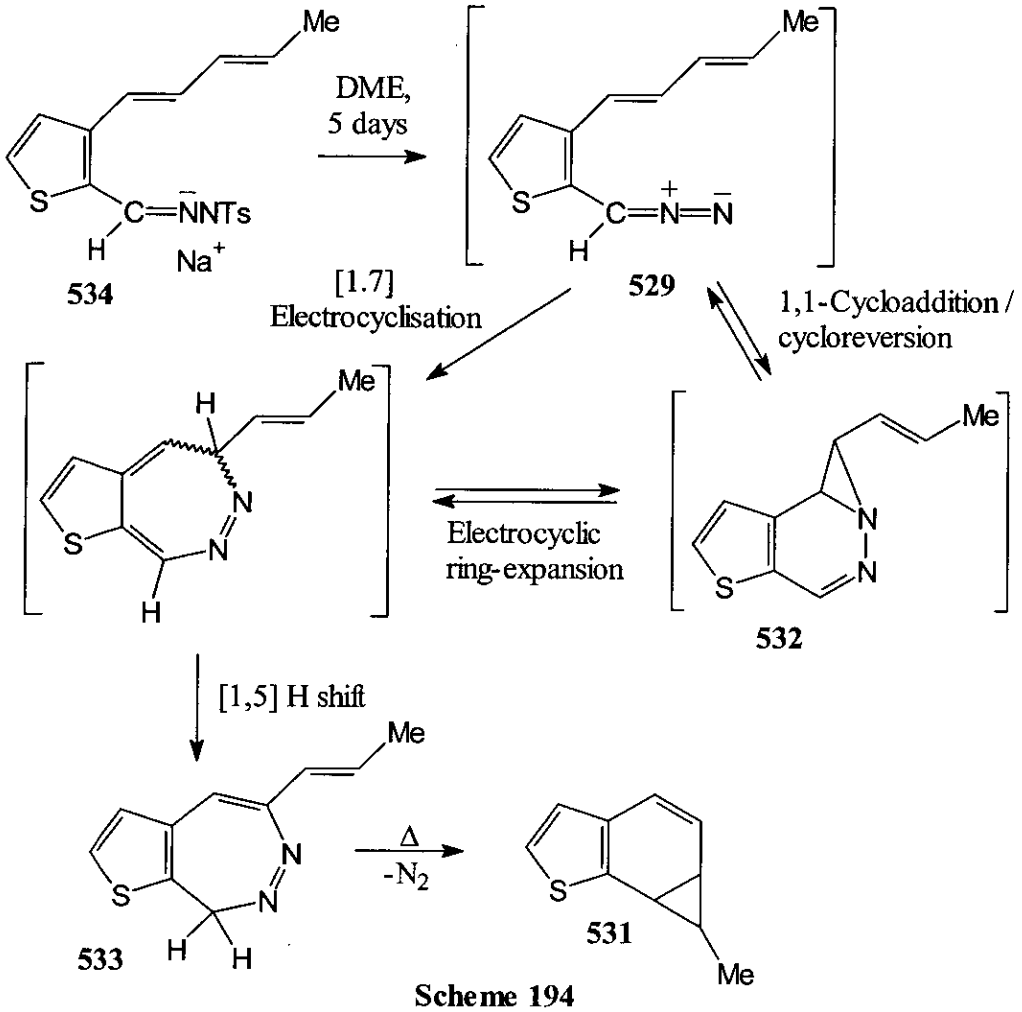
Scheme 193

It was therefore decided to repeat the reaction at a lower temperature. A sample of the tosylhydrazone salt **534** was generated and dried as usual, but in this case the solution in DME was not heated, but stirred in the dark, under nitrogen and at room temperature, for 5 days. Slow deposition of the usual white precipitate of sodium *p*-toluenesulfinate was observed over this period, and TLC analysis showed the gradual

appearance of a new spot, with a slightly lower R_f value than that of the 6-thia-cyclopropa[*e*]indene **531**. Once it became apparent that the reaction had finished it was worked up in the usual manner.

Analysis of the ^1H NMR spectrum of the crude product showed it to consist mainly of the 4-alkenyl thieno-1*H*-[3,2-d]diazepine **533**, which was isolated in good (74 %) yield after chromatography. Mass spectrometry indicated retention of nitrogen and ^{13}C NMR showed a CH_2 peak in the 3π/4 DEPT experiment, at the chemical shift expected for the methylene moiety of a 1*H*-2,3-diazepine ring.

This result suggests either that the product **531** obtained at 80 °C had in fact formed from loss of nitrogen from the primary [1.7]-electrocyclisation product **533**, or that carbenic reaction predominates at higher temperatures and the electrocyclisation of the diazoalkane **529** is uncompetitive.



Scheme 194

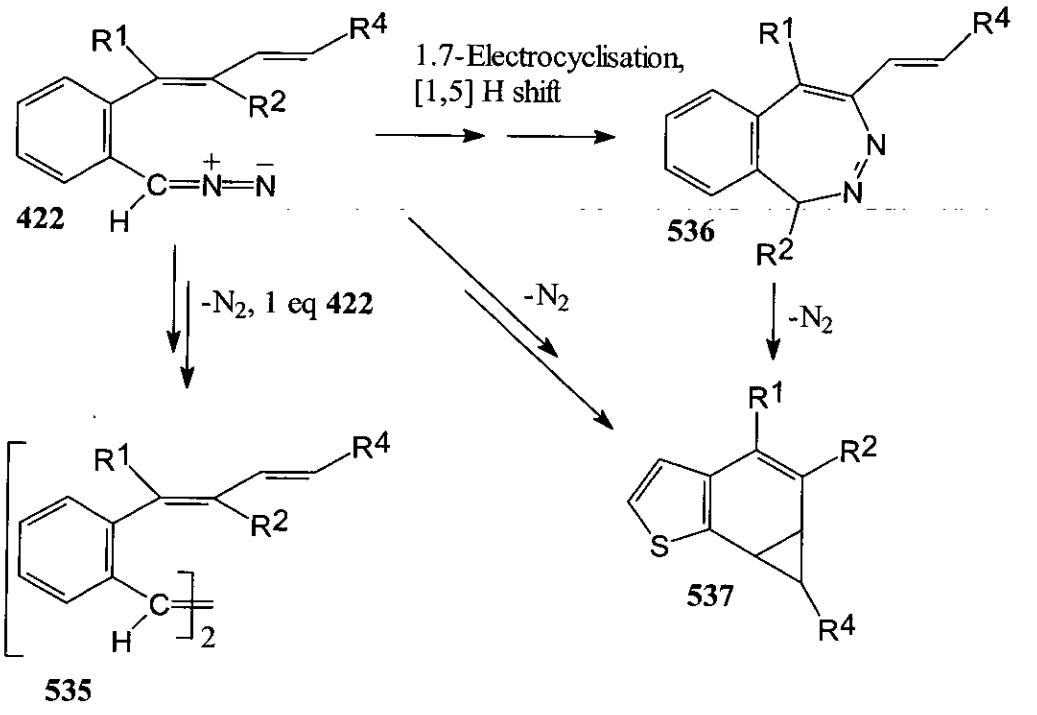
The thermal instability of the diazepine **533** was confirmed while attempting to determine the coalescence temperature of the methylene protons in the ^{1}H NMR spectrum. It decomposed rapidly on warming the sample to 90 °C, by which point the doublets from the methylene C-1 atom had broadened into the baseline, but not coalesced to a singlet at the mid-point of the doublets as would be expected.

The expected methylene doublet signal at higher shift (which appeared at *ca.* 6.0 ppm in previous analogues) was obscured in the ^{1}H NMR spectrum of **533**. A COSY experiment, however, revealed that the broad methylene doublet at lower chemical shift (2.83 ppm, ^2J 10.1 Hz) was coupling with a proton which gave a signal at ~ δ 6.0, but which was obscured by the signals from H-5 and an olefinic proton in that region.

2.2.7 Conclusion

Table 5

R^1	R^2	R^4	α,β bond	Diazoalkane No.	Temp (°C)	Product type
H	H	Ph	Benzene	**497**	80	Diazepine **536** (80 %)
H	H	Me	Benzene	**507**	80	Diazepine **536** (91 %)
H	H	H	Benzene	**508**	80	Diazepine **536** (79 %)
Me	H	Me	Benzene	**513**	80	Diazepine **536** (76 %)
H	Me	Ph	Benzene	**515**	80	Alkene **535** (78 %)
H	H	Me	Thiophene	**529**	80	6-Thia-cyclopropa-[*e*]indene **537** (56 %)
H	H	Me	Thiophene	**529**	*ca.* 25	Diazepine **536** (74 %)



Scheme 195

The experiments carried out in this part of the investigation demonstrate strong consistency in the reactions of *trans* (*E*,*E*) triene-conjugated diazoalkanes **422**. Providing that the δ position of the triene bears a hydrogen atom (*i.e.* R^2 = H) then the product will be the corresponding 4-alkenyl-1*H*-2,3-diazepine **536**. This appears to be independent of the nature of substituents R^1 and R^4 at the γ and ζ positions of the triene. These factors had been found to be highly influential in the rearrangements of products derived from triene-conjugated nitrile ylides, as observed in the first part of this investigation.

It appears that the [1.7]-electrocyclisation and subsequent [1,5] H shift are so facile when the δ-position of the triene is unsubstituted (*i.e.* where R^2 = H) that they will occur to the exclusion of all other processes. Where this position was blocked by a methyl group then the system reacted only *via* loss of nitrogen to give carbene-derived product **521** and no evidence was obtained for the occurrence of 1,1-cycloaddition. Such a process may be possible, as in the case of the analogous nitrile ylides, but if so it did not lead to any nitrogen-containing products.

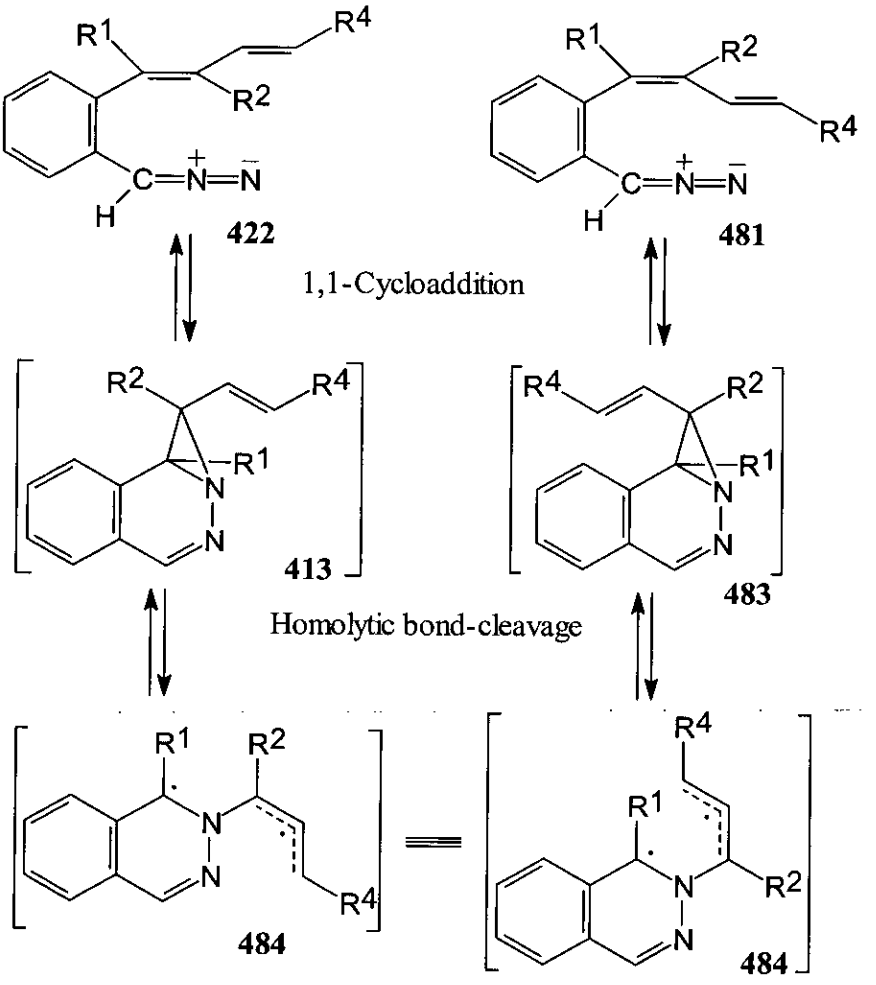
In the case where the α,β double bond was between the 2- and 3-positions of a thiophene ring the reactivity was basically the same as the benzene analogues, although the product **533** and/or the diazoalkane **529** was less thermally stable with respect to loss of nitrogen.

2.3 Generation and Reactions of 1',2',4'-Trisubstituted (*Z*,*E*)-2-(Buta-1',3'-dienyl)benzaldehyde Tosylhydrazones

2.3.1 Preamble

Up to this point in this investigation the reactions of the *trans* isomers (**422**) of the *cis* triene-conjugated diazoalkanes (**481**) which were generated in the first part of this section had not been studied.

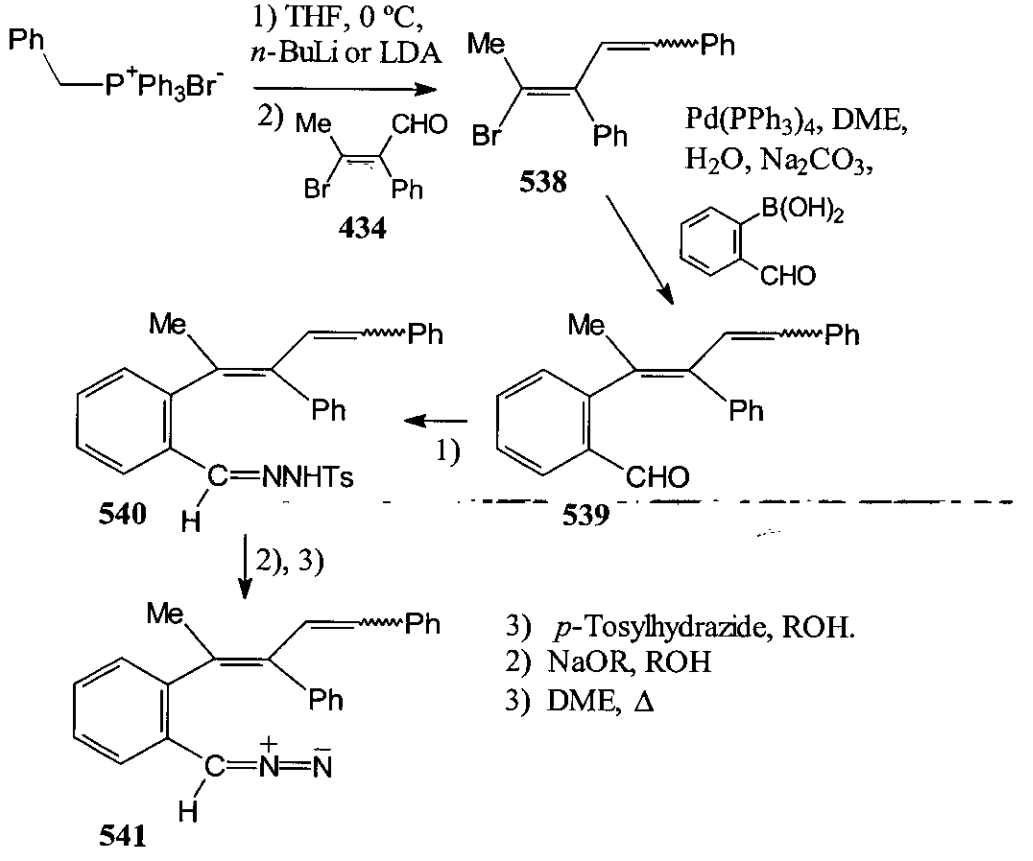
If the mechanism proposed here for phthalazine formation is correct then the fact that the γ,δ olefin is in the *Z* configuration (*i.e.* the ε,ζ double bond is remote from the dipole) should not preclude formation of the phthalazines. The diradical intermediate **484** could feasibly form from both the *exo*- and *endo*-vinylaziridines (**413** and **483** respectively, scheme **196**) leading to the same product regardless of the stereochemistry about the γ,δ bond in the triene-conjugated diazoalkane.



Scheme 196

2.3.2 (*Z*,*E*)-2-(1-Methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (540)

The (*E*)-isomer of the bromoacrylaldehyde **434** was used in a Wittig reaction with benzylphosphononium bromide to give the 2-bromopenta-2,4-diene **538** with the desired (*Z*) geometry about the bromine-bearing olefin. This was used in the Suzuki reaction to obtain the *ortho*-dienyl benzaldehyde **539,** which in turn gave the tosylhydrazone **540** upon treatment with tosylhydrazide.

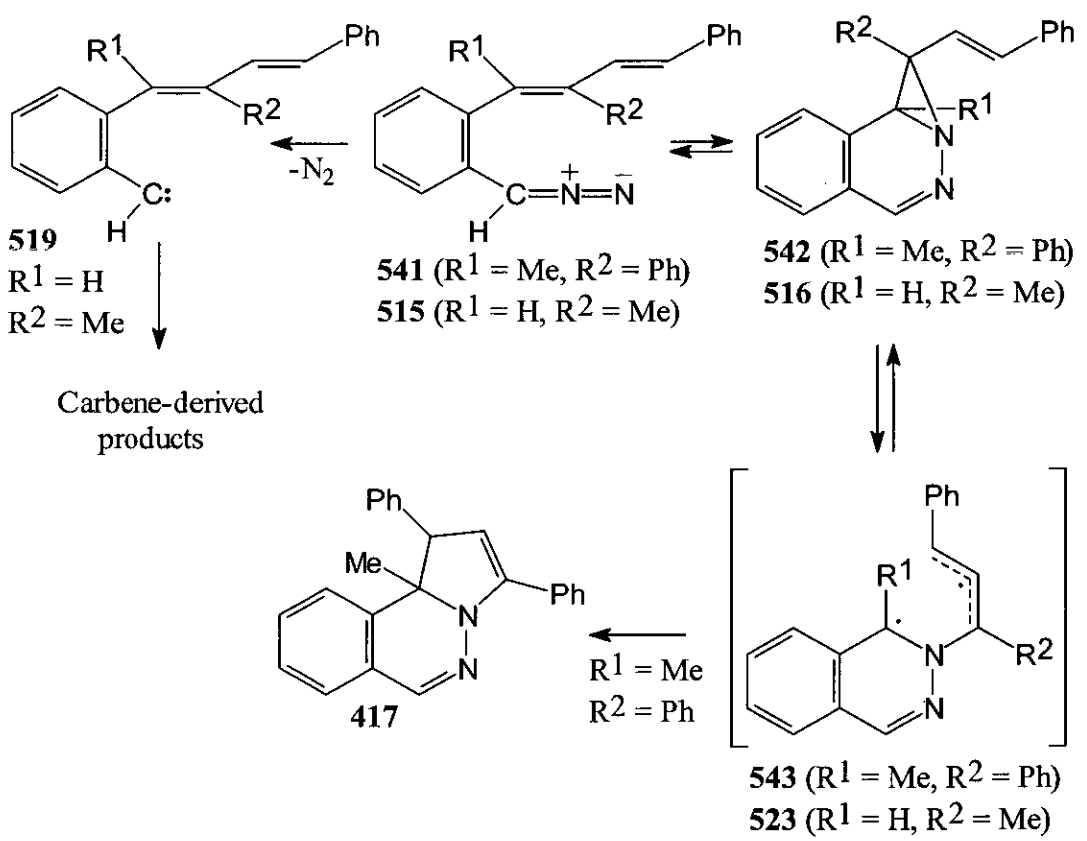


Scheme 197

Generation of the diazoalkane **541** in the usual manner was found to give a single product, which was isolated in 75 % yield. This product was identified by ^{1}H NMR spectroscopy as the phthalazine **417**, identical with that obtained by Wilson. This result showed that in the competition between phthalazine formation and the carbenic

reaction, the former is much more strongly favoured for the *trans* reactant **541** than for its *cis* analogue **415** which gave the phthalazine **415** in only 25 % yield. This could be due either to a difference in the activation energy for the 1,1-cycloaddition process, or to a difference in the ease with which the aziridine ring is opened in the formation of the diradical **543**.

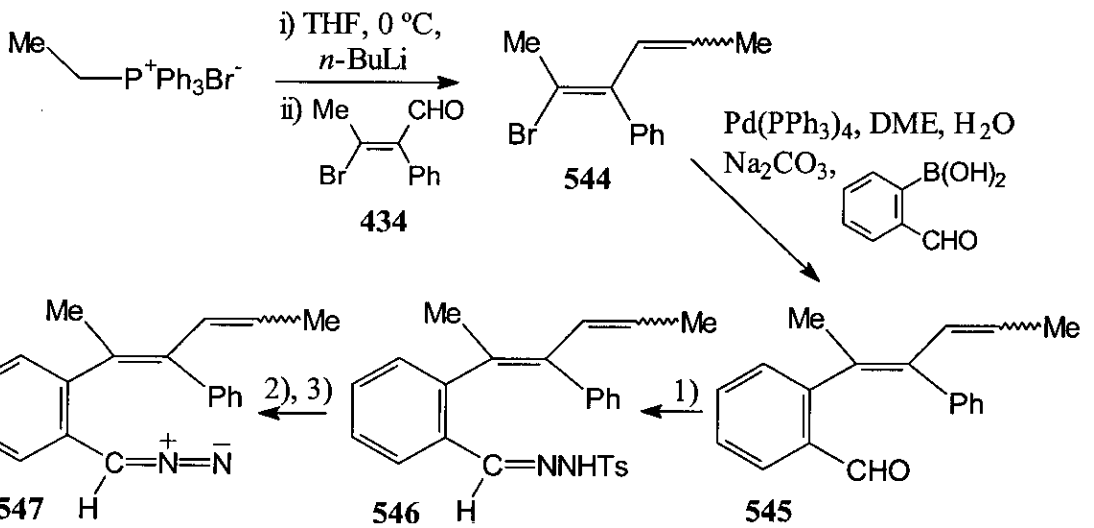
The most likely reason for the observed result is that the diradical intermediate **543** is more stable (as R^2 is aromatic) and is thus capable of further reaction. Where R^2 = Me (*i.e. trans* diazoalkane **515**) the analogous intermediate (**523**) would be less stabilised than **543**, with the result that the product from reaction of diazoalkane **515** is derived from the carbene. The carbene **519** could be formed either directly, by decomposition of the diazoalkane **515**, or by competitive reversion of the vinylaziridine analogue **516** to regenerate the diazoalkane, which would then decompose *via* extrusion of nitrogen.



Scheme 198

2.3.3 (*Z*,*E*)-2-(1-Methyl-2-phenylpenta-1,3-dienyl)benzaldehyde Tosylhydrazone (546)

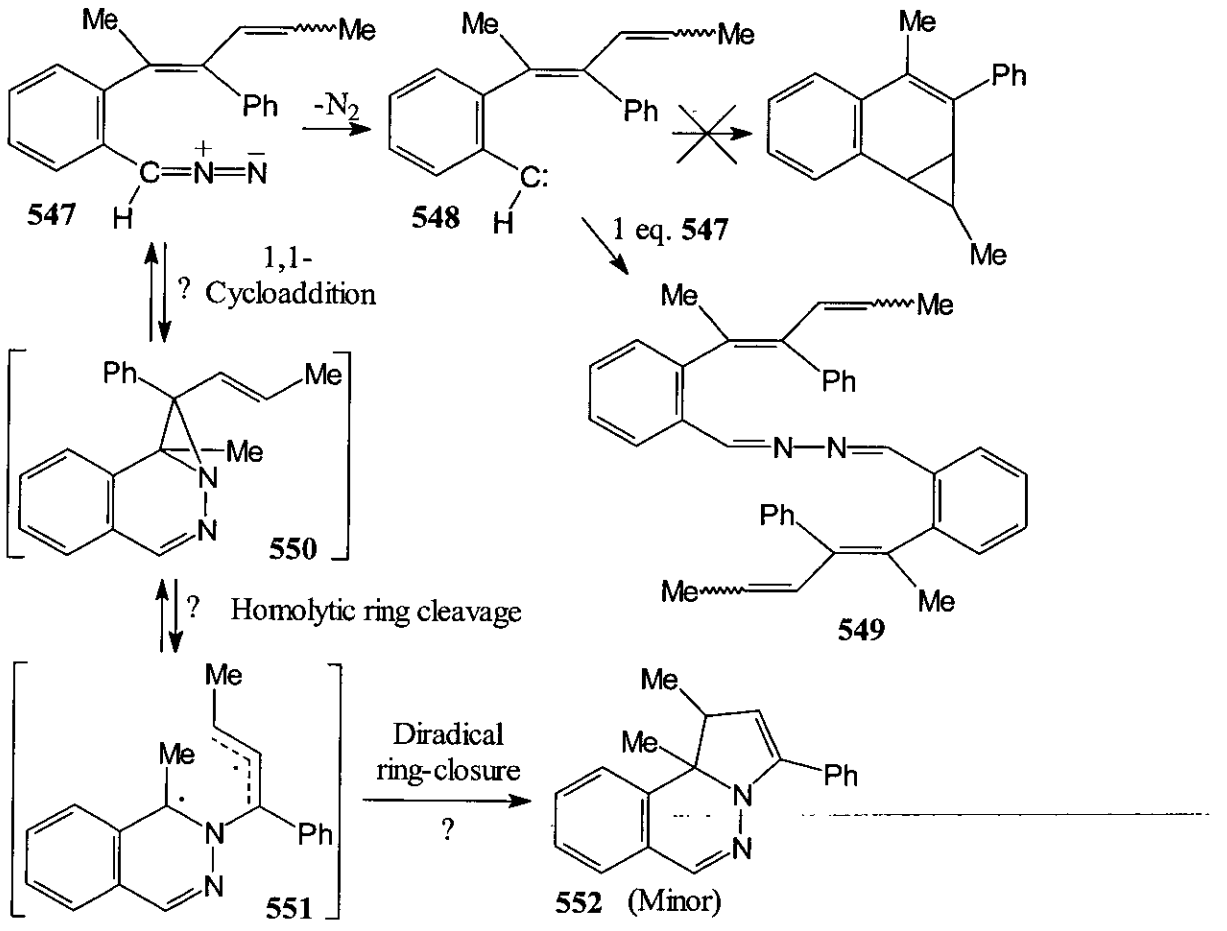
The next step in elucidating the influences at play in the cyclisation of dipoles such as **541** was to vary the ζ substituent on the conjugated triene. This variation was achieved simply by using ethyltriphenylphosphonium bromide in the Wittig reaction with the (*E*)-bromoacrylaldehyde **434** to yield the required (*Z*)-bromodiene **544**. This compound was found to be highly unstable, but the corresponding aldehyde **545** was obtainable nonetheless and the tosylhydrazone **546** was obtained from this.



1) *p*-Tosylhydrazide, ROH
2) NaOR, ROH
3) DME, Δ

Scheme 199

Thermal decomposition of the sodium salt of **546** in the usual manner was found to yield one major product with a high TLC R_f value, even when eluting with hexane. On isolation, this product was found to be the carbene-derived azine **549**. This compound exhibited the same signal patterns in the ^1H NMR spectrum from the olefinic hydrogen atoms as the precursor tosylhydrazone. This gave a strong indication that the γ,δ and ε,ζ unsaturations had not been involved in reaction with the dipole. The mass spectrum of the product strongly suggested that it was "dimeric" and that nitrogen was present (*m/z* 521.2957 $(M+H)^+$. $C_{38}H_{37}N_2$ requires $(M+H)^+$ 521.2957).



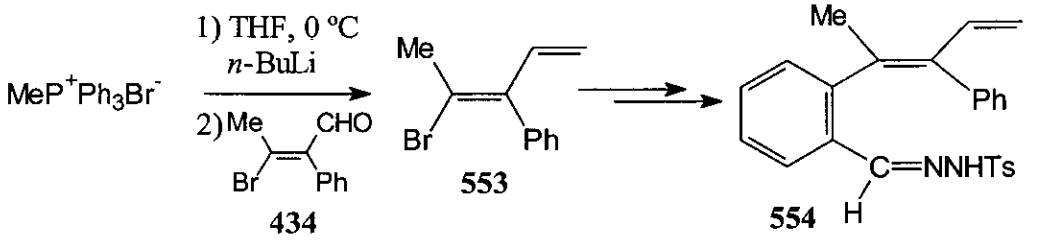
Scheme 200

A small amount of a lower-running fraction was also recovered by chromatography. This was tentatively identified as the phthalazine **552** on inspection of its ^{1}H NMR spectrum, with characteristic doublets with small *J* value couplings. This compound unfortunately decomposed before it could be properly identified.

The isolation of predominantly carbene-derived product can be rationalised by consideration of the intermediates implicated in the proposed mechanism of the formation of the phthalazines (scheme **200**). The only triene-conjugated diazoalkanes which have been found to give phthalazines possess phenyl groups at both the δ- and ζ-positions of the triene. It appears that in this case, as in that of diazoalkane **515** (R^1 = H, R^2 = Me) the diradical intermediate is insufficiently stabilised to make phthalazine formation a competitive process.

The substituent at the ζ position of the triene has, again, been shown to have a fundamental influence on the reaction path taken by triene-conjugated 1,3-dipoles.

The tosylhydrazone **554** (R^4 = H) was synthesised in the same way as the previous example, except for the use of methyltriphenylphosphonium bromide in the Wittig reaction to obtain the bromodiene **553**. This tosylhydrazone, however, was found to degrade very readily, giving a complex mixture of several degradation products prior to the salt-generation stage. This part of the investigation was abandoned.



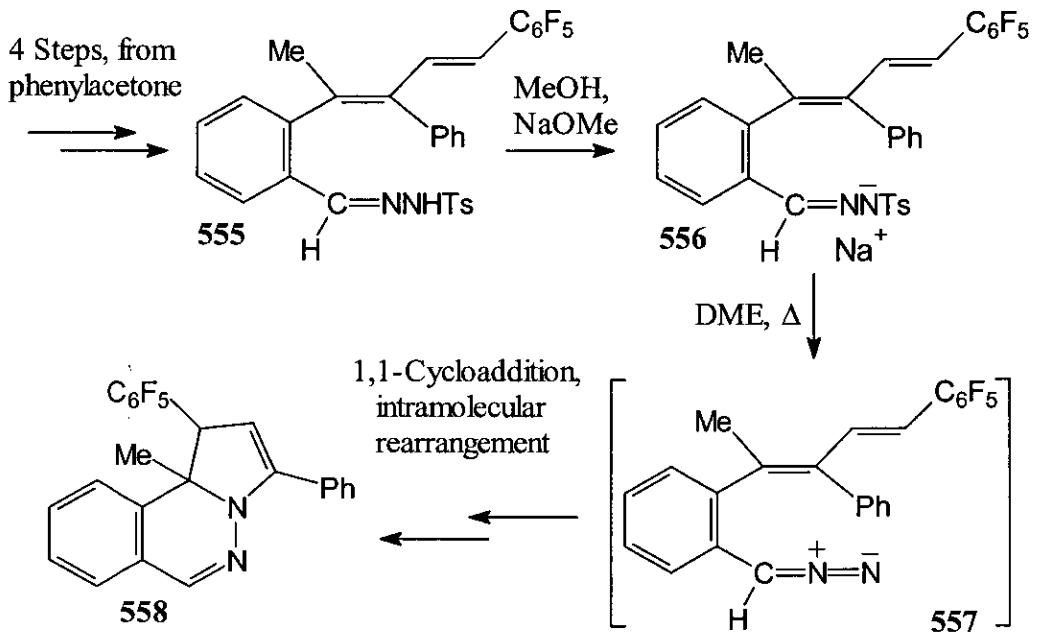
Scheme 201

2.3.4 (*Z*,*E*)-2-[1-Methyl-2-phenyl-4-(pentafluorophenyl)]benzaldehyde Tosylhydrazone (555)

It was decided to investigate the effect of using substituted benzene rings at the ζ position instead of alkyl groups. To this end the tosylhydrazone **555** was synthesised, again by the route previously outlined in this work, using diethyl perfluorobenzylphosphonate in a Wadsworth-Emmons reaction with the *E*-bromoacraldehyde **434**. It was hoped that the electron-withdrawing effect of the fluoro substituents would perturb the product distribution obtained from the reaction of the diazo-compound and allow elucidation of some of the governing factors.

The tosylhydrazone salt **556** was generated and reacted in the usual manner, with the progress of the reaction being tracked by TLC. This showed the appearance of a new, high-running spot and disappearance of the starting material. Once the reaction was judged to have gone to completion it was worked up in the usual manner.

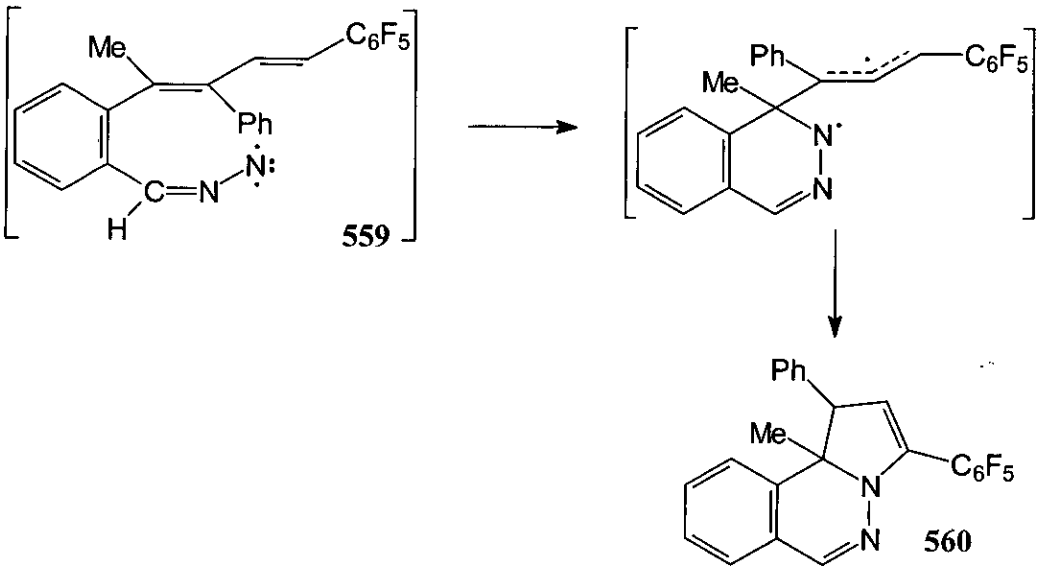
Chromatographic isolation of the product allowed its identification as the phthalazine **558**, the sole product of the reaction, in 73 % yield.



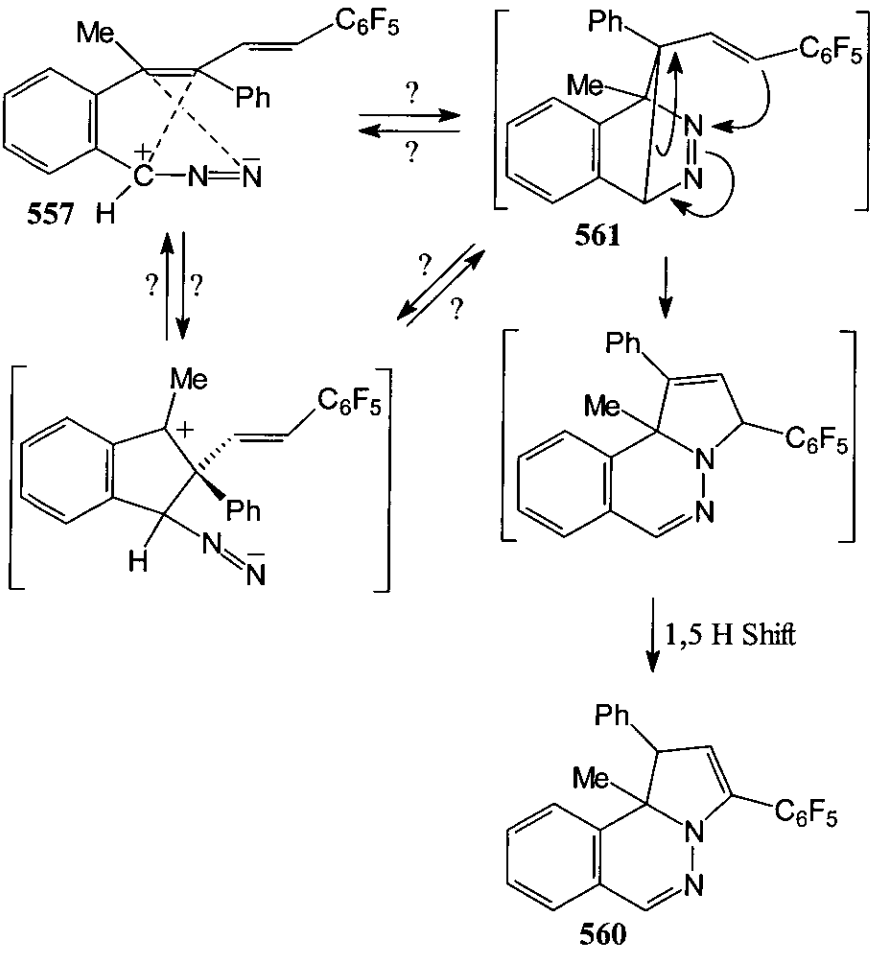
Scheme 202

This result showed that the electron-withdrawing nature of the aryl substituent in **557** does not perturb the cycloaddition process and again shows that *trans* stereochemistry at the γ,δ bond strongly favours phthalazine formation.

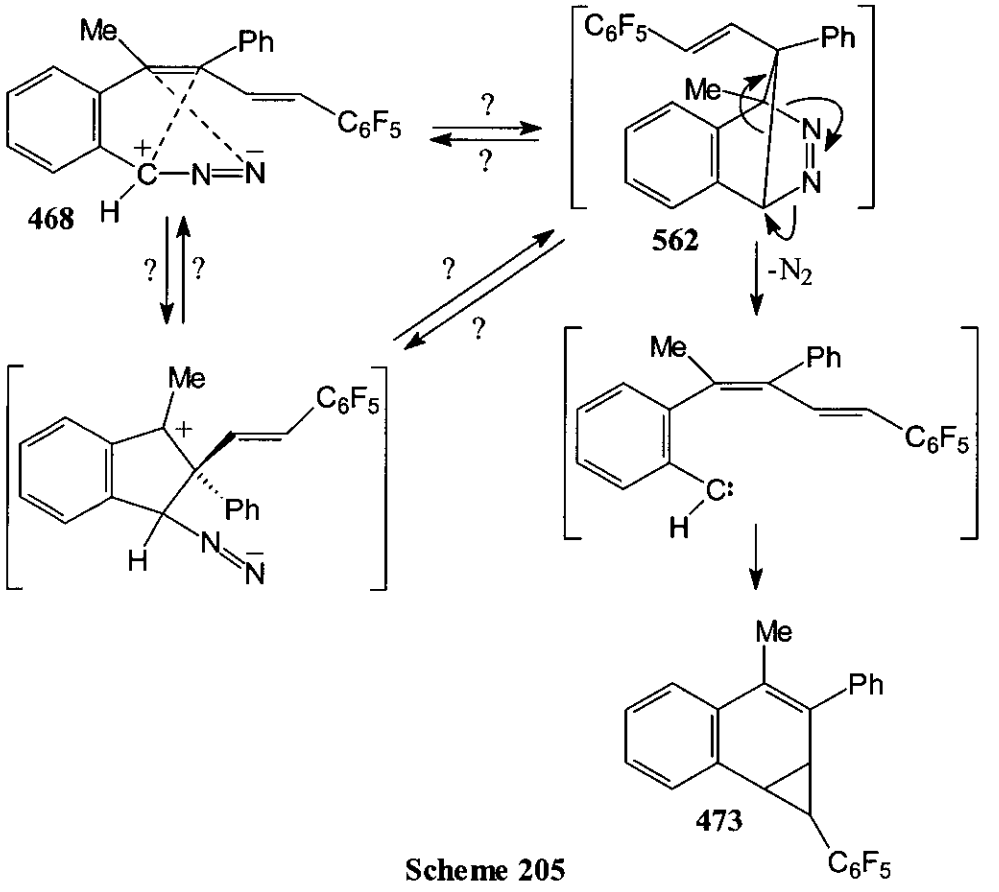
Different aryl substituents at the δ (Ph) and ζ (C_6F_5) positions of the reactant **557** were used to test the proposed mechanism of the phthalazine formation (scheme **198**). Alternative mechanisms considered included the stepwise addition of a triplet "nitrene" intermediate **559** (scheme **203**), and a [3+2] cycloaddition to the γ,δ bond followed by skeletal rearrangement (schemes **204** and **205**). Compounds of the type **561** and **562** have been prepared by Padwa[86, 139], *via* reactions of diene-conjugated diazoalkanes in the presence of Lewis acid catalysts.



Scheme 203



Scheme 204



Scheme 205

In the case of the *cis* reactants (scheme **205**) it is possible that *cis-trans* isomerism (**468** ? **557**) could occur during one of the reversible steps, explaining the formation of small amounts of phthalazine from these compounds.

Both of these processes, however, would lead to phthalazines (**560**) which have the Ph and C_6F_5 groups transposed *c.f.* **558**. In this context it was therefore important to be absolutely certain of the location of the two aryl substituents in the reaction product.

Various 2D NMR experiments were carried out to determine the connectivity of the carbon skeleton of phthalazine **558**. An NOE experiment was performed and analysis of the results showed the absence of interactions between the proton at the saturated carbon atom C-1 and any of the aromatic protons except for the proton on the fused benzene ring (see figure **13**). This suggests that H-1 is not close in space to

a phenyl ring, but is likely to be close to the perfluorophenyl ring, interaction with which would not cause a nuclear Overhauser effect. H-2, however, does show an interaction with two phenyl protons appearing at *ca.* δ 7.70 ppm. These observations suggest that the perfluorophenyl ring occupies the C-1 position and thus that the pyrrolophthalazine was formed *via* the 1,1-cycloaddition and subsequent rearrangement rather than the alternative mechanisms suggested. An interaction was also observed between the methyl protons and the H-1 proton, confirming that the methyl and perfluorophenyl groups are *trans*-related.

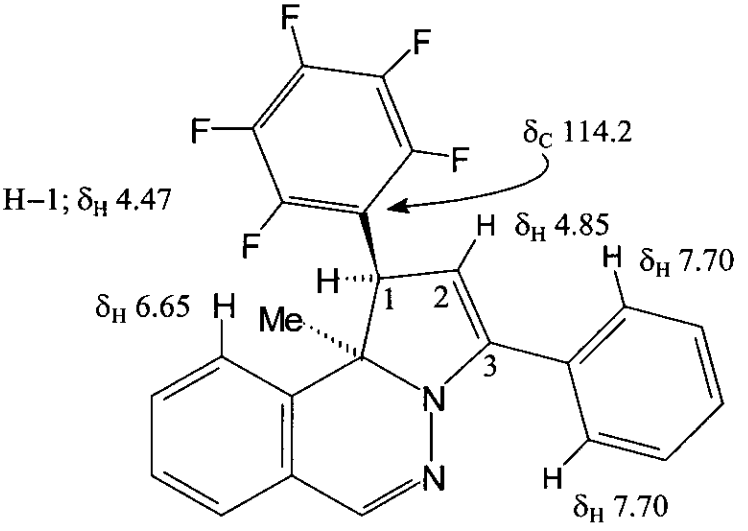


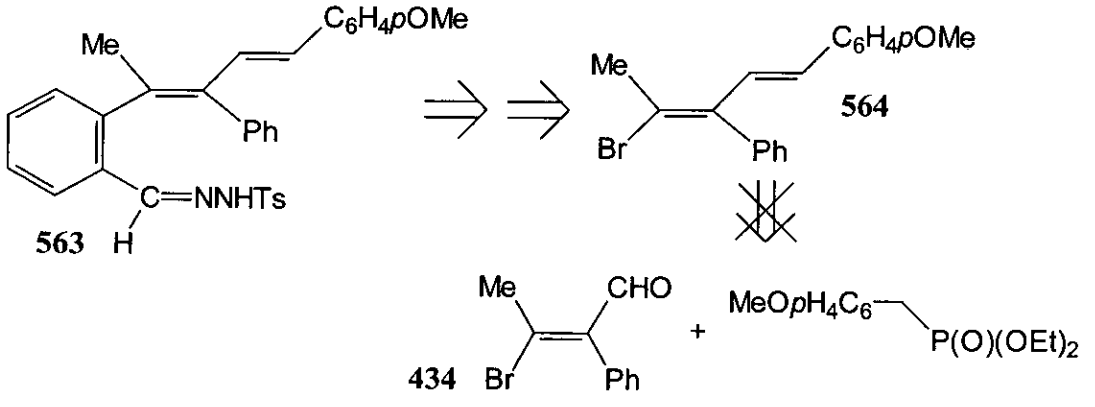
Figure 13

A second piece of evidence which bolstered this initial finding was provided by the results of an HMBC (^{13}C-^{1}H) experiment. This experiment showed that the proton at C-1 was coupling with the methyl group and with C-2, but not with any of the phenyl carbon atoms in the molecule. An interaction *was* observed, however, between this proton (H-1) and a carbon atom giving rise to a signal at higher δ_c value (145-150 ppm) than those assigned to the benzene ring CH's. This signal was not obvious in the 1D ^{13}C NMR spectrum and was assigned to the heavily split perfluorophenyl ring carbon atoms which merged into the baseline. These signals in the ^{13}C spectrum are most likely due to the *ortho* perfluoro ring carbons, which would be closest in the molecular framework to H-1.

The proton on C-1 was also observed to interact with a quaternary carbon atom at δ_C 114.2, which was assigned as the quaternary carbon of the perfluorophenyl ring which is not directly attached to a fluorine atom and so is only moderately split into a triplet. The hydrogen atom at C-2 was not observed to interact with this quaternary atom suggesting that the perfluorophenyl ring is closer to C-1 than to C-3. H-2 was observed to interact with a carbon atom at δ_C 148.9, assigned as the quaternary olefinic atom C-3. H-1 was observed to interact with C-3 less strongly than C-2 was, as expected from the 1-2-3 connectivity. The signal from C-3 in the 1 D ^{13}C NMR spectrum was a single peak suggesting that C-3 was not structurally close to the perfluorophenyl ring and that it was instead substituted with the phenyl ring.

These results confirm that the R^4 group of the triene-conjugated diazoalkanes adopts the C-1 position in the phthalazines, with R^2 attached to C-3 in that product. These findings eliminate the possibility that these products are formed by the other mechanisms suggested. Although this does not conclusively prove the occurrence of the 1,1-cycloaddition or the intermediacy of the vinylaziridines, it is consistent with this mechanism.

An attempt to synthesise the tosylhydrazone **563** (R^4 = *p*-C_6H_4OMe) repeatedly failed at the first stage, with the bromodiene **564** proving unobtainable *via* the Wadsworth-Emmons reaction illustrated in scheme **206**.



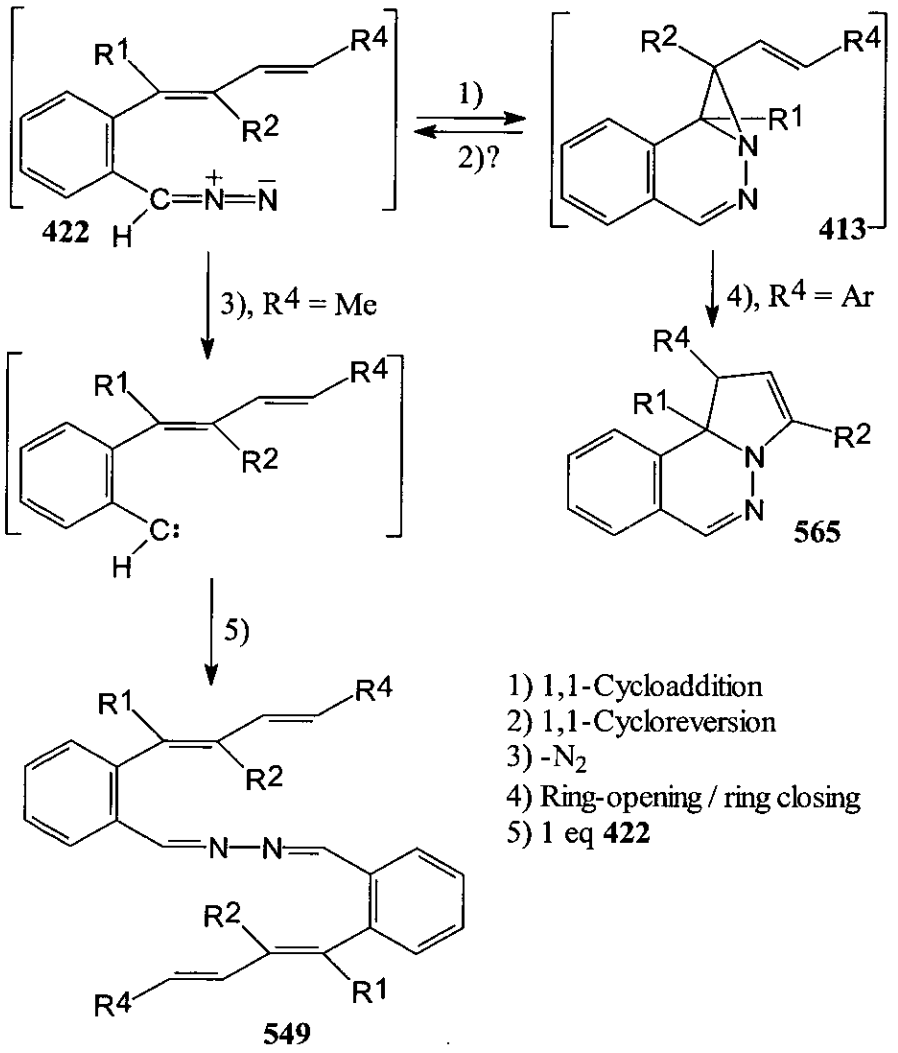
Scheme 206

Even when a large excess of base was employed no reaction was observed, with the high-R_f spot expected of the bromodiene **564** not being observed in any attempt at this reaction. Experiments carried out with varied deprotonation times and temperatures also failed. This approach was abandoned.

2.3.5 Conclusions

Table 6

R^1	R^2	R^4	Diazoalkane No.	Temp (°C)	Product(s)
Me	Ph	Ph	**541**	80	**565** (75 %)
Me	Ph	C_6F_5	**557**	80	**565** (73 %)
Me	Ph	Me	**547**	80	**549** (77 %)



Scheme 207

This set of results demonstrates the sensitivity of the intramolecular reactions of triene-conjugated diazoalkanes to influences exerted by seemingly remote substituents. This finding parallels those from the work on the analogous triene-conjugated nitrile ylides.

Again, aromatic substituents at the terminal ζ-position of the triene are demonstrated to furnish the most interesting heterocycles, in this case the phthalazines **417** (R^4 = Ph) and **558** (R^4 = C_6F_5) which were the exclusive products, even at the high temperatures used. This suggests that they are formed *via* a process which competes very effectively with nitrogen extrusion from their diazoalkane precursors. Taken

with the earlier results this shows that both substituent effects and the geometry about the triene system are highly influential.

Imposing a methyl substituent at the ζ-position of the triene-conjugated diazoalkane (**547**) had a dramatic effect on the outcome of the reaction, in that it inhibited phthalazine formation in favour of intermolecular dimerisation reactions of the carbene with its diazo precursor to yield azine **549**.

The result obtained by replacing the phenyl substituent at the olefinic ζ-position with a methyl group is slightly surprising in view of results obtained by Sharp's group. In that work[90], [1.7]-electrocyclisations of diene-conjugated diazoalkanes were found to be much more favourable when the terminal substituent on the alkene was a methyl group rather than a phenyl group. Obviously, however, the different processes involved (1.7-electrocyclisation *vs.* 1,1-cycloaddition) mean that substituent effects on rates of reaction between the dipole and the diene are altered.

The most appealing explanation for the different reactivity modes which were favoured as the substitution patterns were varied rests upon the nature of the intermediate implicated in the formation of the phthalazine. If this intermediate is, as has been postulated, diradical in nature (*e.g.* **484**) then it would be expected that aromatic substituents would provide greater resonance stabilisation. This is in accordance with the observation that significant amounts of the phthalazines **565** were only formed when this species was stabilised by two conjugating aryl substituents.

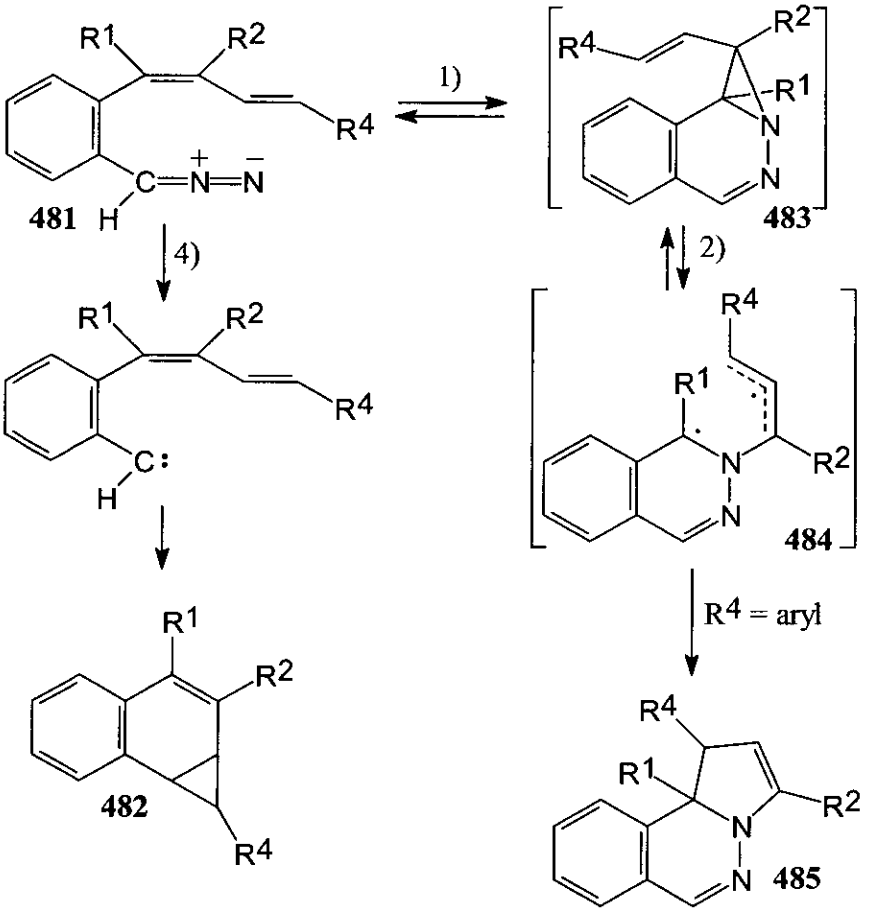
Where these aromatic rings were replaced by hydrogen or alkyl groups then greater proportions of carbene-derived products were obtained from reaction of the dipole, consistent with the proposed transition state being less stable and therefore less accessible. Imposition of electron-withdrawing groups on the benzene ring at the R^4 position appeared to cause no discernible increase or decrease in the yield of phthalazine.

3 Overall Summary and Conclusions

Table 7

γ,δ-*cis* Diazoalkanes

R^1	R^2	R^4	Diazoalkane No.	Product type(s)
Me	Ph	Ph	**415**	**482** (53 %), **485** (25 %)
Me	Ph	C_6F_5	**468**	**482** (46 %), **485** (23 %)
Me	Ph	*p*-C_6H_4OMe	**476**	**482** (71 %), **485** (18 %)
Me	Ph	H	**458**	**482** (63 %)



1) 1,1-Cycloaddition 2) Homolytic bond cleavage
3) Diradical ring-closure 4) $-N_2$

Scheme 208

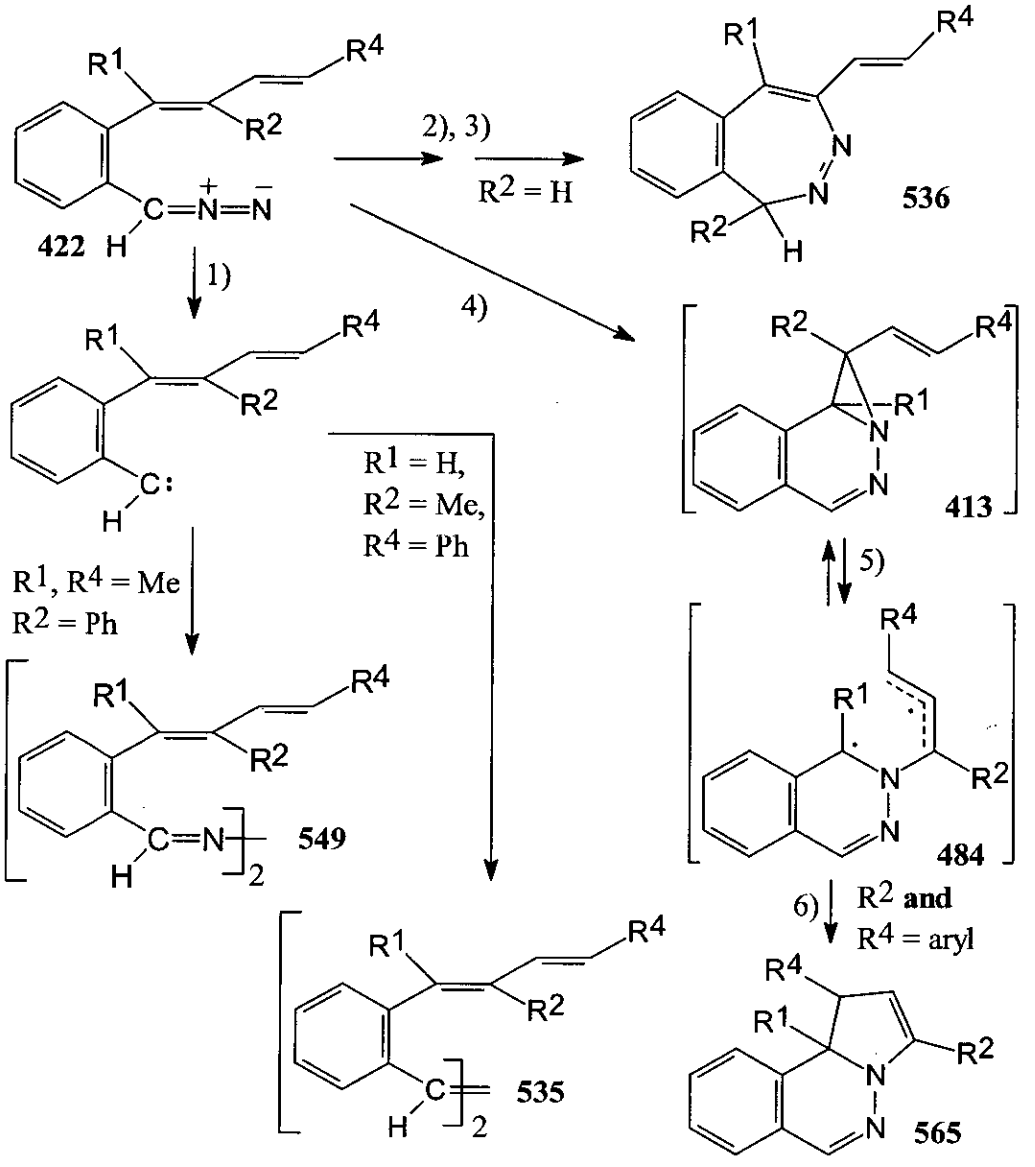
Systematic alteration of the substitution pattern about the γ,δ-*cis* triene-conjugated diazoalkanes has been shown to cause various reaction pathways to become favourable. In cases where the trienyl system was in the *cis* configuration with non-H substituents at R^1, R^2 and R^4 then two reaction pathways appeared to be open (scheme **208**). In all cases the most favourable of these involved decomposition of the diazoalkanes **481** to give the carbenes, which reacted intramolecularly with the ε,ζ double bond to yield the cyclopropa[*a*]naphthalenes **482**. In cases where R^4 was aromatic an alternative pathway was operative, which is thought to proceed *via* an initial 1,1-cycloaddition followed by intramolecular rearrangement of **483**, *via* a diradical species **484**, to yield the phthalazines **485**. Where R^4 was non-aromatic then only the carbene-mediated pathway was operative.

The rationalisation put forward for the influence which R^4 holds over the balance between the two modes of reactivity is centred upon the stability of the diradical intermediate **484**. Where both R^2 and R^4 are aromatic then there is much scope for delocalisation of the radical and thus stabilisation of the intermediate. Where R^4 is non-aromatic then the extent of delocalisation possible is lessened and the intermediate is accordingly less stable. This has the result that the ring-opening of the aziridine ring in **483** and the subsequent rearrangement to give the phthalazine only occurs to a significant extent when both R^2 and R^4 are aromatic.

Table 8

γ,δ-*trans* Diazoalkanes

R^1	R^2	R^4	α,β	Diazoalkane No.	Product type(s)
H	H	Ph	Benzene	**497**	**536** (80 %)
H	H	Me	Benzene	**507**	**536** (91 %)
H	H	H	Benzene	**508**	**536** (79 %)
Me	H	Me	Benzene	**513**	**536** (76 %)
H	Me	Ph	Benzene	**515**	**535** (78 %)
H	H	Me	Thiophene	**529**	**536** (74 %)
Me	Ph	Ph	Benzene	**541**	**565** (75 %)
Me	Ph	C_6F_5	Benzene	**557**	**565** (73 %)
Me	Ph	Me	Benzene	**547**	**549** (77 %)

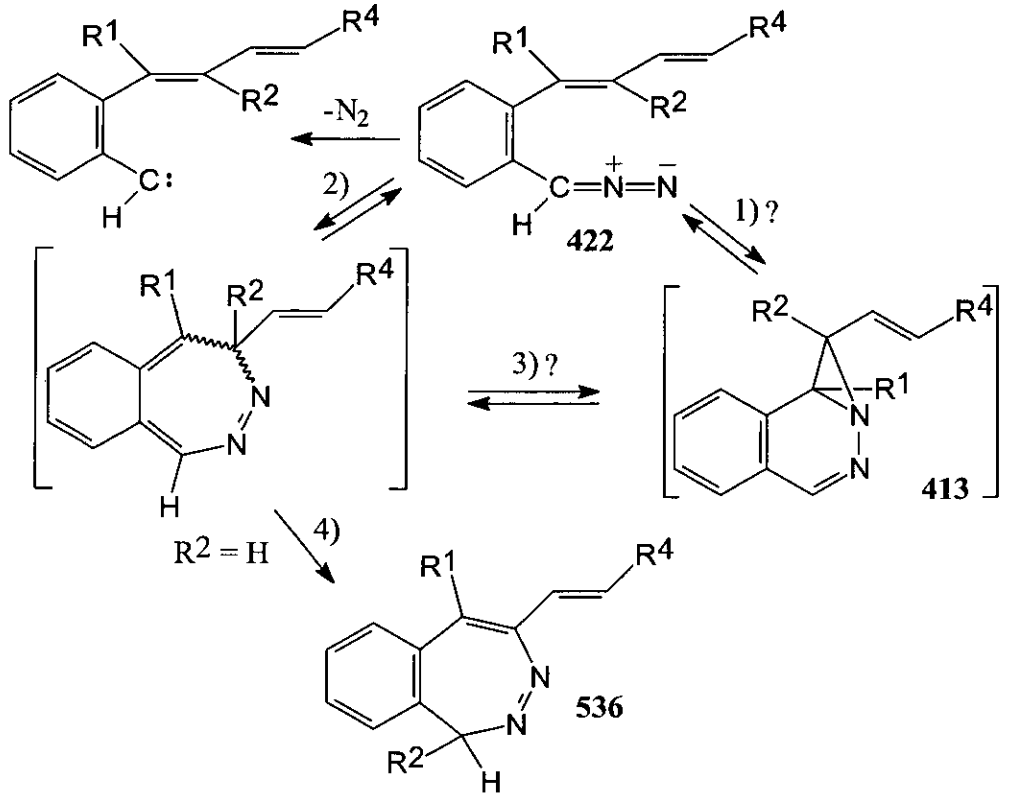


1) $-N_2$ 2) 1.7-Electrocyclisation 3) [1,5] H shift 4) 1,1-Cycloaddition
5) Homolytic bond cleavage 6) Diradical ring closure

Scheme 209

Triene-conjugated diazoalkanes where the olefinic system was in the (*E,E*) configuration and the δ-substituent was hydrogen (*i.e.* R^2 = H) were found to yield diazepines exclusively upon reaction, irrespective of the identity of R^1 and R^4. This type of product was also formed where the α,β unsaturation of the trienyl system was incorporated as the 2,3 bond of a thiophene ring.

The diazepines were most likely formed by 1.7-electrocyclisation of the diazoalkanes followed by an irreversible [1,5] H shift, in the same manner as the diene-conjugated diazoalkanes where the *cis* δ-substituent is H. No evidence for the initial step of this process being a 1,1-cycloaddition was found.



1) 1,1-Cycloaddition 2) 1.7-Electrocyclisation
3) Electrocyclic ring-opening 4) [1,5] H shift

Scheme 210

The incorporation of non-hydrogen substituents as R^2 completely inhibited the diazepine-forming reaction. This was expected, since it has previously been shown with *diene*-conjugated diazoalkanes that methyl and phenyl groups at this position interfere with the transition state for 1.7-electrocyclisation.

Where R^2 was a methyl group (diazoalkane **515**, R^1 = H, R^2 = Me, R^4 = Ph), all intramolecular reactions appeared to become unfavourable and the only product obtained was the carbene-derived olefin **535**. This, initially surprising, result is consistent with the theory that where R^2 or R^4 are non-aromatic the diradical

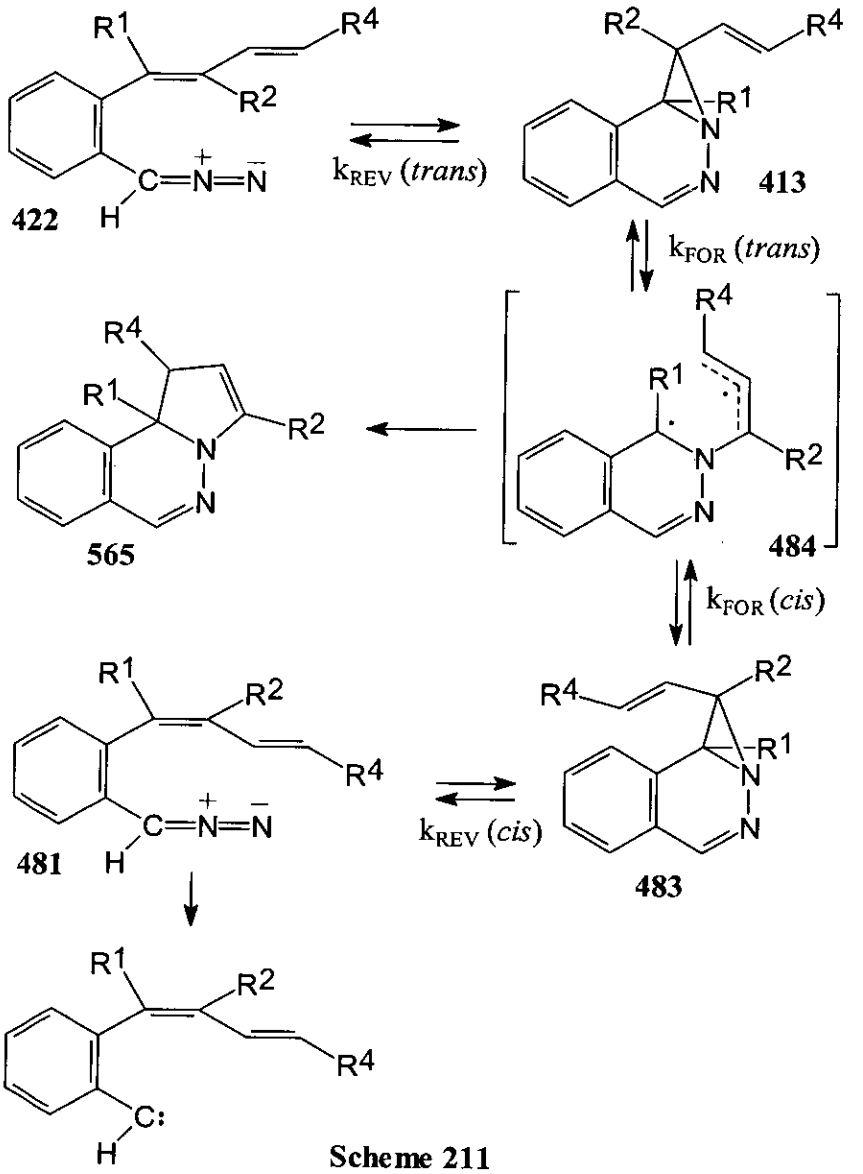
intermediate **484** derived from the initial 1,1-cycloaddition product is destabilised, compared to examples where both R^2 and R^4 are aromatic.

Where R^2 was a phenyl group, however, the reactivity of the diazoalkanes was fundamentally altered and, in all cases where R^4 was aromatic, the only products isolated were the phthalazines. The fact that no carbene-derived products were obtained from these reactions suggests that one or more of the steps in the proposed mechanism of phthalazine formation is more favourable where the triene is in the *trans* configuration than for the *cis* isomers.

It is most likely that this is due to differences between the *cis* and *trans* isomers in either the activation energy for the initial 1,1-cycloaddition, or the homolytic bond cleavage in **413** which generates the diradicals **484**. This is thought because the diradical intermediate is the same for both the *cis* and *trans* isomers of a particular analogue. Therefore, once the diradical has formed there is little reason why it should react to give the phthalazine where it derived from the *trans* isomer of the diazoalkane, and not react in this way if it derived from the *cis* isomer.

It is possible, however, that bond rotation in the diradical **484** is slow compared to reversion to the *endo*-vinylaziridine **483**. This would mean that the *endo*-vinylaziridine derived from *cis* diazoalkanes could be less able to adopt a transition state geometry in which ring closure to yield phthalazines is possible. Failure of the vinylaziridine to rearrange intramolecularly would ultimately lead to regeneration of the *cis* diazoalkane *via* a 1,1-cycloreversion and decomposition to the carbene. This could also possibly explain the poor yields of phthalazines obtained from reaction of the *cis* triene-conjugated diazoalkanes compared to those from the *trans* isomers. This is summarised in scheme **211**. It is proposed that the rate of attainment of a transition state **(484)** suitable for phthalazine formation is faster when the vinylaziridine is in the *exo*-configuration **(413)** than for the *endo* analogues **483**, *i.e.* k_{FOR} (*trans*) >> k_{FOR} (*cis*).

Where the terminal aromatic ring was replaced with a methyl group (diazoalkane **547**; R^1 = Me, R^2 = Ph, R^4 = Me) the favoured reaction pathway was decomposition to the carbene, yielding the intermolecularly derived azine **549**. Again, this observation is consistent with the theory concerning the stability of the putative diradical intermediate **484**. It is striking that making *either* R^2 or R^4 a non-aromatic group results in preclusion of phthalazine formation.



Scheme 211

EXPERIMENTAL

Contents **Page No.**

A. Symbols and Abbreviations

NMR	Nuclear magnetic resonance spectroscopy.
MHz	MegaHertz.
δ_H	Chemical shift, proton NMR.
δ_C	Chemical shift, carbon NMR.
J	Coupling constant (Hz).
br.	Broad.
s	Singlet.
d	Doublet.
t	Triplet.
q	Quartet.
m	Multiplet.
quat	Quaternary carbon atom.
ν	Wavenumber.
EI	Electron impact mass spectrometry.
FAB	Fast atom bombardment mass spectrometry.
m/z	Mass-to-charge ratio.
M^+	Molecular ion.
$[M+H]^+$	Molecular ion.
TLC	Thin-layer chromatography.
MPLC	Medium-pressure liquid chromatography.
DCM	Dichloromethane.
DME	1,2-Dimethoxyethane.
DMF	*N*,*N*-Dimethylformamide.
THF	Tetrahydrofuran.
LiHMDS	Lithium hexamethyldisilylazide.
$CDCl_3$	Deuteriochloroform.
d_6-DMSO	Deuteriated dimethylsulfoxide.
M	Moles per litre.

Mol	Moles.
Mmol	Millimoles.
w/v	Weight per volume.
p.s.i	Pounds per square inch.
mp	Melting point.
bp	Boiling point.
n-BuLi	*n*-Butyllithium.
COSY	Proton-proton correlation spectroscopy.
dec.	Decomposes.
lit.	Literature value.
DEPT	Distortionless enhancement polarisation transfer.

B. Instrumentation and General Techniques

Nuclear Magnetic Resonance Spectroscopy

^{1}H NMR spectra were obtained on a number of instruments. Routine diagnostic spectra were obtained on a Gemini 2000 (199.975 MHz) spectrometer while other ^{1}H spectra were variously obtained on Bruker WP200 (200.132 MHz), Bruker AC250 (250.13 MHz) or WP360 (360.130 MHz) instruments. ^{13}C NMR spectra were recorded at 62.90 MHz on a Bruker AC250 instrument or 90 MHz on a Bruker WP360 instument. ^{19}F NMR spectra were obtained at 235.360 MHz on the Bruker AC250 instrument.

Carbon multiplicities were determined by distortionless enhancement polarization transfer (DEPT) experiments ($\pi/2$ and $3\pi/4$). Labile protons bonded to heteroatoms in a compound were located by adding small amounts of deuteriated water to a deuteriochloroform solution and detecting signal loss due to deuterium-hydrogen exchange of the proton concerned. Irradiation and variable-temperature experiments were performed on the Bruker AC250 instrument and 2D spectra (^{1}H-^{1}H COSY and ^{1}H-^{13}C correlation) were obtained on the 360 MHz instrument. Spectra were

recorded from solutions in deuteriochloroform or d_6-DMSO, with chemical shifts (δ_H, δ_C) quoted relative to trimethylsilane (δ_H, δ_C = 0) in parts per million (ppm). Coupling constants (*J*) are quoted in Hz, with 200 MHz, 250 MHz and 360 MHz instruments giving an accuracy of 0.3 Hz per point. Values are quoted as recorded. The Bruker AC250 and WP360 instruments were operated by Mr. John R. A. Miller and Mr. Wesley Kerr. 2D HMBC, nOe and HSQC spectra were obtained by Dr. David Reed on the 360 MHz instrument.

Mass Spectrometry

High- and low-resolution electron impact and fast atom bombardment mass spectra were obtained by Mr. Alan Taylor and Mr. Harry MacKenzie on Kratos MS50TC instruments. Accurate mass measurements were provided to five decimal places.

Elemental Analyses

Microanalyses were performed by Mr. Tim Calder on a Perkin Elmer 240 CHN Elemental Analyser.

Infra-Red Spectroscopy

Solid samples were examined as nujol mulls and liquids/oils were analysed as neat films between sodium chloride plates, using a Perkin Elmer instrument.

Chromatography

Analytical thin-layer chromatography was performed on aluminium-backed plates coated with silica (0.2 mm, Merck Silica 60) impregnated with a UV fluorescent indicator or on pre-coated plastic plates (0.2 mm alumina, neutral (type E), Merck grade 60) impregnated with fluorescent indicator. Chromatograms were developed by viewing under long- or short-wave ultraviolet light to detect quenching of fluorescence.

Preparative dry-flash chromatography was performed on Fluka Kieselgel G, using the method of Harwood[140]. Elution was achieved using gradient elution with hexane and an incrementally increasing proportion of diethyl ether. Preparative flash column chromatography was performed using Merck Silica 60, 230-400 mesh, according to the method of Still[141]. Elution was achieved using an appropriate mixture of hexane and ether.

Medium-pressure liquid chromatography was carried out using either one or two glass columns (2.5 x 100 cm) packed with Merck Kieselgel 60 eluted with an appropriate hexane-ether mixture via a diaphragm pump (100 p.s.i maximum, *ex.* Metering Pumps Ltd.). The crude sample to be chromatographed was pre-adsorbed onto Kieselgel 60 and this was packed onto a short scrubber column (25 x 1.5 cm) to protect the main columns from excessive contamination. The apparatus was back-flushed with ethyl acetate after each sample run and forward-flushed with the appropriate mixture of hexane and ether prior to subsequent sample runs.

Solvents and Reagents

THF and DME were distilled from calcium hydride as required. Chloroform was dried by passage through a column of basic alumina. Dry ethanol was obtained by reaction with magnesium and distillation, as outlined in Vogel[142], and stored over dry 4 Å molecular sieves. Dry methanol was obtained by distillation and storage over 4 Å molecular sieves. *N,N*-Dimethylformamide (DMF) was dried over and distilled from phosphorus pentoxide and stored over 4 Å molecular sieves. HPLC Grade hexane and ethyl acetate were used as provided.

Diisopropylamine was distilled from potassium hydroxide pellets and stored over 4 Å molecular sieves. Thionyl chloride was purified as described in Vogel and stored over 4 Å molecular sieves. Cinnamaldehyde, crotonaldehyde and acrolein were distilled and stored over 4 Å molecular sieves. 2-Formylphenylboronic acid and *p*-nitrobenzoyl chloride were obtained from Aldrich and used as provided. 2-

Bromobenzylphosphonium bromide[88], diethyl 2-bromobenzylphosphonate[128] and diethyl perfluorobenzylphosphonate[90] were prepared previously by Munro, Blake and Bohill, respectively. All other phosphonium salts and phosphonates were commercially available.

Melting Points

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected.

Boiling Points

Small-scale distillations were performed using a Buchi Kugelrohr distillation apparatus, and the temperature quoted refers to the oven temperature.

Drying Agents

Magnesium sulfate was used unless otherwise stated.

I. Synthesis of Precursors

i. 1-(*o*-Bromophenyl)but-3-en-1-ol (271)

A solution of allyl bromide (6.70 g, 55 mmol) in dry ether (35 cm^3) was added dropwise to a suspension of magnesium turnings (1.3 g, 54 mmol) in dry ether (10 cm^3) under dry nitrogen. This solution was refluxed for 2.5 hrs and stirred at room temperature for a further 2 hrs. 2-Bromobenzaldehyde (6.30 g, 34 mmol) in dry ether (25 cm^3) was added dropwise and the suspension was stirred at room temperature overnight. Saturated aqueous ammonium chloride (30 cm^3) was added and the solution was stirred for 30 minutes upon which the layers were separated. The aqueous layer was extracted with ether and the combined organics were washed with water and dried. Removal of the solvent *in vacuo* gave a yellow oil which was distilled to give 1-(*o*-bromophenyl)but-3-en-1-ol (**271**) as a colourless oil (6.60 g, 29.2 mmol, 86 %), bp 110 °C / 1 mmHg (lit [126] 84 °C / 0.4 mmHg); δ_H (200 MHz, $CDCl_3$) 2.18-2.33 (1 H, m, H-2a), 2.30 (1 H, s, D_2O labile, OH), 2.38-2.61 (1 H, m, H-2b), 4.98-5.20 (3 H, m, H-4a, H-4b and H-1), 5.69-5.90 (1 H, m, H-3), 7.04 (1 H, ddd, 5.5, 5.5, 2.0, aromatic), 7.25-7.28 (1 H, m, aromatic), 7.41-7.49 (2 H, m, aromatic).

ii. Diethyl 1-(*o*-bromophenyl)ethylphosphonate (323)

To a solution of diethyl *o*-bromobenzylphosphonate (10.30 g, 33.6 mmol) in dry THF (75 cm^3), under nitrogen and with cooling in an ice-bath, lithium diisopropylamide (1.30 M in THF, 35 cm^3, 45.5 mmol) was slowly added. This solution was stirred for two hours at room temperature and a solution of methyl iodide (3.70 g, 26.0 mmol) in dry THF (10 cm^3) was added dropwise. The dark colour of the reaction mixture discharged quickly after this addition to give a pale red solution, which was stirred overnight at room temperature. Ammonium chloride solution (25 % w/v, 40 cm^3) was added and the aqueous layer was extracted with ether (2 x 50 cm^3) and the combined organic extract was washed with water (50 cm^3). Removal of the solvents *in vacuo* yielded a pale yellow oil which was purified

by bulb-to-bulb distillation to give diethyl 1-(*o*-bromophenyl)ethylphosphonate (**323**) as a colourless liquid (9.20 g, 28.7 mmol, 85 %), bp 230 °C/0.4 mmHg; Found: $[M+H]^+$, 321.0254 and 323.0237. $C_{12}H_{18}{}^{79}BrO_3P$ requires $[M+H]^+$, 321.0255 and $C_{12}H_{18}{}^{79}BrO_3P$ requires $[M+H]^+$, 323.0236; δ_H (250 MHz, $CDCl_3$) 1.07 (6 H, dt, $^4J_{P-CH3}$ 30.9, $^4J_{CH3-CH3}$ 7.0, 2 x CH_3CH_2OP), 1.39 (3 H, dd, $^3J_{PCCH3}$ 18.3, $^3J_{CH3-CH}$ 7.3, CH_3CHP,), 3.70 (3 H, m, CH_2 and CH), 3.97 (2 H, m, CH_2), 6.91-7.00 (1 H, m, aromatic), 7.12-7.25 (1 H, m, aromatic), 7.39-7.51 (2 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 15.85 (CH_3, d, J_{CCP} 5.2), 16.07 (CH_3, d, J_{CCOP} 5.7), 16.29 (CH_3, d, J_{CCOP} 5.8), 36.50 (CH, J_{P-CH} 139.8), 62.06 (CH_2, J_{POCH2} 20.7), 62.17 (CH_2, J_{POCH2} 20.7), 124.87 (quat, J_{CCP} 10.4), 127.55 (CH, aromatic, J_{C-P} 2.8), 128.30 (CH, aromatic, J_{C-P} 2.8), 129.59 (CH, aromatic, J_{C-P} 4.5), 132.64 (CH, aromatic, J_{C-P} 1.7), 137.77 (quat, C-Br, J_{CCCP} 4.8); *m/z* 323 (99 %, M+H, ^{81}Br), 321 (base peak, M+H, ^{79}Br), 267 (30 %), 265 (30 %), 241 (27 %, M-Br), 185 (59 %), 183 (50 %).

iii. (*E*)- and (*Z*)-2-Bromo-3-phenylbut-2-enal (434 and 435)

These compounds were prepared according to the method of Arnold *et. al.*[136] Phosphorus tribromide (54.0 g, 0.20 mol) was slowly added to an ice-cooled solution of DMF (12.4 g, 0.17 mol) in chloroform (100 cm^3), under a nitrogen atmosphere, *via* a dropping funnel. A solid was observed to form upon this addition and the resulting suspension was stirred for one hour with cooling. Phenylacetone (12.0 g, 0.09 mol) was added to this suspension and the resulting solution was stirred for 24 hours. The solvent was removed *in vacuo*, the residue was poured onto ice (*ca.* 500 g) and this mixture was neutralised with sodium bicarbonate. The aqueous mixture was extracted with DCM (3 x 75 cm^3), the combined extracts were washed with sodium bicarbonate solution (100 cm^3) and water (100 cm^3) and dried. Removal of the solvent *in vacuo* gave a dark oily residue, MPLC (silica, 3:2 hexane-ether) of which yielded, in order of elution; a) (*Z*)-3-bromo-2-phenylbut-2-enal **435** (5.4 g, 24.3 mmol, 27 %); δ_H (200 MHz, $CDCl_3$) 2.49 (3 H, s, CH_3), 7.04-7.43 (5 H, m, aromatic), 10.25 (1 H, s, CHO); and b) (*E*)-3-bromo-2-phenylbut-2-enal **434** (2.0 g, 9.0 mmol, 10 %); δ_H (200 MHz, $CDCl_3$) 2.97 (3 H, s, CH_3), 7.12-7.46 (5 H, m, aromatic), 10.09 (1 H, s, CHO).

iv. 2-Bromo-3-methylthiophene (390)

This compound was prepared by the method of Sharp[143]. *N*-Bromosuccinimide (35.6 g, 0.20 mol) was added portionwise to a well-stirred solution of 3-methylthiophene (20.0 g, 0.20 mol) in glacial acetic acid (25 cm^3), at such a rate that overheating of the reaction did not occur. Once all of the NBS had been added (*ca.* 1 hour) the solution was stirred for a further 15 minutes. Water (50 cm^3) was added and the crude product was separated, washed with sodium hydroxide (50 cm^3, 1 M), then with water (50 cm^3) and dried. Distillation of the crude product gave 2-bromo-3-methylthiophene (**390**) (27.0 g, 0.15 mol, 75 %) as a colourless liquid (bp 74 °C/15 mmHg (lit.[144] 61-63 °C/13 mmHg)

v. 2-Bromothienyl-3-methyltriphenylphosphonium Bromide (392)

A solution of 2-bromo-3-methylthiophene (20.0 g, 0.11 mol) and benzoyl peroxide (0.30 g, 1.2 mmol) in CCl_4 (75 cm^3) was heated to reflux under a nitrogen atmosphere. A mixture of *N*-bromosuccinimide (22.0 g, 0.12 mmol) and benzoyl peroxide (0.3 g, 1.2 mmol) was added portionwise to the boiling mixture over the course of an hour and the reaction was refluxed for a further 3 hours. Filtration of the solution followed by removal of the solvent *in vacuo* gave 2-bromo-3-bromomethylthiophene (**391**) as a dark brown oil which was not purified further, but was dissolved in dry THF (75 cm^3). To this solution was added triphenylphosphine (29.0 g, 0.11 mol) and the reaction was stirred at room temperature under a nitrogen atmosphere. After 10 minutes a precipitate was observed to form. After 64 hours the suspension was filtered to give a brown sludge which was washed with THF (2 x 50 cm^3) then recrystallised to give 2-bromothienyl-3-methyltriphenylphosphonium bromide (**392**) (27.8 g, 53.7 mmol, 49 % from monobromo compound) as large pale yellow crystals, mp 265-269 °C (ethanol) (lit.[145] 238-240 °C); δ_H (200 MHz, d_6-DMSO) 5.15 (2 H, d, J_{HCP} 14.5, CH_2), 7.63-8.19 (17 H, m, phenyl and thienyl H).

II. Synthesis of (*E,E*) Diene-Conjugated *ortho*-Bromobenzenes

i. (*E,E*)-2-(4-Phenylbuta-1,3-dienyl)bromobenzene (254)

(*E*)-Cinnamyltriphenylphosphonium bromide (8.82 g, 19.2 mmol) was suspended in THF (50 cm^3) under dry nitrogen and cooled to 0 °C. *n*-Butyllithium (1.6 M in hexanes, 12 cm^3) was added dropwise and the solution was stirred for 1 hr at 0 °C. 2-Bromobenzaldehyde (3.0 g, 16.2 mmol) was added dropwise at room temperature and the solution was stirred for one hour, then aqueous ammonium chloride (10 % w/v, 16 cm^3) was added and the layers were separated. The aqueous layer was extracted with ether (2 x 100 cm^3) and the combined organic layers were washed with water and dried. The solvent was removed under reduced pressure to give a yellow oil, flash column chromatography (silica, 9:1 hexane-ether) of which gave a mixture of (*E,E*)- and (*Z,E*)-2-(4-phenylbuta-1,3-dienyl)bromobenzene as a pale yellow oil (3.17 g, 69 %). The product was dissolved in hexane (100 cm^3) with a catalytic amount of iodine and heated at reflux for 2 hrs. The solvent was removed *in vacuo* and the residue was dissolved in DCM and treated with aqueous sodium dithionite (25 % w/v, 100 cm^3) then water (100 cm^3), and dried. The solvent was removed *in vacuo* and the residue recrystallised from hexane to give (*E,E*)-2-(4-phenylbuta-1,3-dienyl)bromobenzene (**254**) (2.91 g, 63 % overall) as a white solid, mp 110-111 °C; Found: M^+, 284.0198 and M^+, 286.0180. $C_{16}H_{13}{}^{79}Br$ requires M^+, 284.0201. $C_{16}H_{13}{}^{81}Br$ requires M^+, 286.0182. δ_H (200 MHz, $CDCl_3$) 6.71 (1 H, d, *J* 15.3, olefinic), 6.83-7.12 (4 H, m, olefinic and aromatic), 7.21-7.38 (4 H, m, aromatic), 7.44-7.64 (4 H, m, aromatic); δ_C (50 MHz, $CDCl_3$) 123.0 (quat), 123.1 (CH), 125.4 (CH), 125.6 (2 x CH, aromatic), 126.5 (CH), 126.9 (CH), 127.7 (2 x CH, aromatic), 128.1 (CH), 130.1 (CH), 130.8 (CH), 132.2 (CH), 133.0 (CH), 136.0 (quat), 136.1 (quat); *m/z* 286 (M^+, ^{81}Br, 31 %), 284 (M^+, ^{79}Br, 31 %), 205 (M^+-Br, 47 %).

ii. (*E*)-2-(Buta-1,3-dienyl)bromobenzene (269)

A solution of 1-(*o*-bromophenyl)but-3-en-1-ol (**271**) (5.23 g, 23 mmol), triphenylphosphine (7.25 g, 28 mmol), carbon tetrachloride (4.23 g, 27.5 mmol) and quinol (0.46 g, 4.1 mmol) in acetonitrile (50 cm^3) was heated at reflux under dry nitrogen for 15 minutes and allowed to cool to room temperature. Triethylamine (11.51 g, 114 mmol) was added and the solution was heated at reflux for a further 3 hrs. The solvents were removed in *vacuo* and the solid residue was extracted with hexane. The solvent was removed *in vacuo* and the residual oil dissolved in dry ether (150 cm^3). Potassium *tert*-butoxide (5.42 g, 48.4 mmol) was added and the suspension stirred overnight at room temperature. The reaction mixture was quenched with water (300 cm^3) and the layers were separated. The aqueous phase was extracted with ether (2 x 100 cm^3) and the combined organics were dried. Evaporation of the solvent *in vacuo* gave an oil (5.23 g) which was distilled at reduced pressure to give (*E*)-2-(buta-1,3-dienyl)bromobenzene (**269**) (3.41 g, 16.3 mmol, 71 %), bp 65 °C / 0.25 mmHg (lit. [126] 64 °C / 0.35 mmHg); δ_H (200 MHz, $CDCl_3$) 5.09-5.35 (2 H, m, olefinic), 6.40-7.05 (4 H, m, olefinic and aromatic), 7.15-7.27 (1 H, m, aromatic), 7.43-7.52 (2 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 118.70 (CH_2), 123.77 (quat), 126.36, 127.27, 128.62, 131.07, 132.02, 132.90 (CH), 136.60 (quat, C-Br), 137.01 (CH).

iii. (*E,E*)-2-(Penta-1,3-dienyl)bromobenzene (287)

To a stirred, ice-cooled suspension of 2-bromobenzylphosphonium bromide **285** (18.40 g, 35.9 mmol) in dry THF (75 cm^3) was added lithium diisopropylamide solution (45 cm^3, 1.2 M in THF), dropwise, under a nitrogen atmosphere. This solution was stirred at room temperature for 2 hours, after which a solution of distilled crotonaldehyde (2.5 g, 35.7 mmol) in dry THF (15 cm^3) was added dropwise. This solution was stirred overnight at room temperature, after which ammonium chloride solution (25 % w/v, 50 cm^3) was added. The layers were separated and the aqueous phase was extracted with ether (2 x 50 cm^3) and the combined organic layers were washed with water (2 x 25 cm^3) then dried. The

solvents were removed *in vacuo* and the residue purified by flash column chromatography (silica, 9:1 hexane-ether) to give a yellow oil. This was dissolved in hexane (150 cm^3) with a catalytic amount of iodine and refluxed for 3 hours. The solution was allowed to cool and sodium dithionite solution (25 % w/v, 50 cm^3) was added. The aqueous phase was extracted with ether (2 x 50 cm^3) and the combined organic layers were washed with water (50 cm^3). The solvents were removed *in vacuo* and the residue was passed through a short pad of silica as a solution in 9:1 hexane-ether to give (*E,E*)-2-(penta-1,3-dienyl)bromobenzene (**287**) as a yellow oil (4.14 g, 18.6 mmol, 52 %); Found: M^+, 222.0045. $C_{11}H_{11}{}^{79}Br$ requires M^+, 222.0044; δ_H (200 MHz, $CDCl_3$) 2.09 (3 H, dd, CH_3, *J* 6.8, 1.5), 6.13 (1 H, dq, *J* 15.0, 6.8), 6.42-6.62 (1 H, ddq, *J* 15.0, 8.9, 1.5, olefinic H-3), 6.87-7.16 (2 H, m, olefinic H-1 and H-2), 7.24-7.88 (4 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 18.25 (CH_3), 123.57 (quat), 126.19 (CH), 127.26 (CH), 128.13 (2 x CH), 131.53 (CH), 131.72 (CH), 131.91 (CH), 132.92 (CH), 137.24 (quat).

iv. (*E,E*)-2-(1-Methyl-4-phenylbuta-1,3-dienyl)bromobenzene (325)

(*E*)-Diethylcinnamyl phosphonate (10.13 g, 39.5 mmol) was dissolved in dry THF (50 cm^3) under a dry nitrogen atmosphere. *n*-Butyllithium solution (1.6 M in hexanes, 27 cm^3) was added dropwise with stirring and cooling (0 °C) and the solution was stirred for a further 30 minutes. 2-Bromoacetophenone (7.10 g, 35.7 mmol) in dry THF (15 cm^3) was added dropwise with cooling and the reaction mixture was stirred for a further hour, then overnight at room temperature. Aqueous ammonium chloride solution (25 % w/v, 50 cm^3) was added and the mixture was stirred for 1 hour. The layers were separated, the aqueous phase was extracted with ether (2 x 50 cm^3) and the combined organics were washed with aqueous ammonium chloride (25 % w/v, 50 cm^3) and water (50 cm^3), then dried. Removal of solvents *in vacuo* gave a yellow oil, which upon flash column chromatography (silica, 9:1 hexane-ether) gave (*E,E*)- and (*E,Z*)-2-(1-methyl-4-phenylbuta-1,3-dienyl)bromobenzene as a white oil (7.71 g, 25.8 mmol, 73 %). The (*E,E*):(*E,Z*) ratio was determined as 1:3 from ^1H NMR integral ratios; δ_H (200 MHz, $CDCl_3$) 2.17$^\$$ and 2.26* (3 H, s, CH_3), 6.11$^\$$ (1 H, d, *J* 10.9), 6.22* (1 H, ddd, *J* 10.9, 0.7, 0.7), 6.36-

6.56 (1 H, m), 6.59-6.67 (1 H, d, *J* 15.4), 7.10-7.69 (9 H, m, aromatic). * Denotes signals from major isomer, $ denotes minor isomer signals. Where no symbol is used, signals from both isomers coincide.

The isomer mixture was dissolved in hexane (150 cm^3) with iodine (50 mg) and the solution was heated at reflux for 2 hours, upon which the solvent was removed *in vacuo*. The residue was dissolved in DCM (50 cm^3) and washed with sodium dithionite solution (25 %, 2 x 25 cm^3) and water (2 x 25 cm^3). Removal of the solvent *in vacuo* followed by passage of a solution of the residual oil in 95:5 hexane-ether (100 cm^3) through a short silica pad yielded (*E,E*)-2-(1-methyl-4-phenylbuta-1,3-dienyl)bromobenzene (**325**) as a white oil in quantitative yield; Found: M^+, 298.0359 and M^+, 300.0340. $C_{17}H_{15}{}^{79}Br$ requires M^+, 298.0357. $C_{17}H_{15}{}^{81}Br$ requires M^+, 300.0380; δ_H (200 MHz, $CDCl_3$) 2.14 (3 H, d, *J* 1.6, CH_3), 6.11 (1 H, d, *J* 10.9, olefinic H-2), 6.52 (1 H, d, *J* 15.3, olefinic H-4), 6.99-7.67 (10 H, m, 9 x aromatic and 1 x olefinic H).

v. (*E,E*)-2-(1-Methylpenta-1,3-dienyl)bromobenzene (337)

To an ice-cooled solution of diethyl 1-(*o*-bromophenyl)ethylphosphonate (**323**) (4.0 g, 12.4 mmol) in dry THF (50 cm^3) under a nitrogen atmosphere was added lithium diisopropylamide solution (17.0 cm^3, 0.88 M in THF). This solution was stirred at room temperature for 4 hours, after which crotonaldehyde (0.96 g, 13.7 mmol) in dry THF (10 cm^3) was added. This solution was stirred overnight and ammonium chloride solution (25 %, 40 cm^3) was added. The aqueous layer was extracted with ether (2 x 50 cm^3) and the combined extracts washed with water (40 cm^3) and dried. The solvents were removed *in vacuo* to give a yellow oil which was purified by flash column chromatography (silica, hexane-ether, 9:1) to give (*Z,E*) and (*E,E*)-2-(1,4-dimethylbuta-1,3-dienyl)bromobenzene as a colourless oil. The product was dissolved in hexane (50 cm^3) and a catalytic amount of iodine was added. The solution was heated at reflux for 3 hours, after which the solvent was removed *in vacuo* and the residue was dissolved in DCM (50 cm^3). This solution was washed with sodium dithionite solution (25 % w/v, 50 cm^3) and water (2 x 50 cm^3) then

dried, and the solvent was removed *in vacuo*. A solution of the residue in 9:1 hexane-ether was passed through a silica pad and removal of the solvent *in vacuo* gave (*E,E*)-2-(1-methylpenta-1,3-dienyl)bromobenzene (**337**) as a pale yellow oil (1.90 g, 8.0 mmol, 65 %) bp 130 °C / 0.03 mmHg; Found: M^+, 236.0201. $C_{12}H_{13}{}^{79}Br$ requires M^+, 236.0201; δ_H (250 MHz, $CDCl_3$) 1.84 (3 H, ddd, *J* 6.7, 1.1, 0.6, CH_3CH), 2.09 (3 H, t, *J* 0.5, CH_3), 5.77 (1 H, dq, *J* 14.9, 6.8, *CH*=CHMe), 5.70-5.84 (1 H, m, olefinic), 6.31-6.46 (1 H, m, olefinic), 7.05-7.28 (3 H, m, aromatic), 7.52-7.58 (1 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 17.82 (CH_3), 18.43 (CH_3), 122.16 (quat CCH_3), 127.07 (CH), 127.49 (CH), 127.95 (CH), 129.85 (2 x CH), 130.44 (CH), 132.63 (CH), 135.16 (quat), 146.00 (quat, C-Br).

vi. (*E*)-2-(1-Methylbuta-1,3-dienyl)bromobenzene (342)

To a solution of diethyl 1-(*o*-bromophenyl)ethylphosphonate (**323**) (1.18 g, 3.7 mmol) in dry THF (20 cm^3), at 0 °C and under nitrogen, was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 4.2 cm^3, 4.2 mmol). This solution was stirred for 2 hours at room temperature, after which distilled acrolein (0.25 g, 4.5 mmol) in dry THF (5.0 cm^3) was added. This solution was stirred at room temperature for 3 hours, after which ammonium chloride solution (25 % w/v, 20 cm^3) was added. The aqueous layer was extracted with DCM (2 x 50 cm^3) and the combined extracts were washed with water (40 cm^3) and dried. The solvents were removed *in vacuo* to give a yellow oil, which after flash column chromatography yielded (*E*)-2-(1-methylbuta-1,3-dienyl)bromobenzene (**432**) as a yellow oil (0.25 g, 1.1 mmol, 31 %); Found: M^+, 222.0040 and M^+, 224.0030. $C_{11}H_{11}{}^{79}Br$ requires M^+, 222.0044. $C_{11}H_{11}{}^{81}Br$ requires M^+, 224.0025; δ_H (200 MHz, $CDCl_3$) 2.12 (3 H, d, CH_3, *J* 1.4), 5.18-5.32 (2 H, m, olefinic), 6.02 (1 H, ddq, *J* 11.0, 0.8, 1.4, olefinic H-2), 6.71 (1 H, ddd, *J* 16.8, 11.0, 10.2, olefinic H-3), 7.06-7.40 (3 H, m, aromatic), 7.55 (1 H, ddd, *J* 7.8, 1.3, 0.4, aromatic); δ_C (63 MHz, $CDCl_3$) 17.95 (CH_3), 117.84 (CH_2), 121.97 (quat), 127.12 (CH), 128.18 (CH), 129.73 (CH), 130.50 (CH), 132.74 (2 x CH), 138.42 (quat), 145.72 (quat). A subsequent I_2-catalysed isomerisation reaction was found not to cause any changes in the chromatographic or spectroscopic characteristics of this compound.

vii. (*E,E*)-2-(2-Methyl-4-phenylbuta-1,3-dienyl)bromobenzene (371)

Lithium bis(trimethylsilyl)amide (1.0 M, 32.0 cm^3, 32.0 mmol) was slowly added to a suspension of *o*-bromobenzyl triphenylphosphonium bromide (10.0 g, 19.5 mmol) in THF (100 cm^3) under a nitrogen atmosphere and with ice-bath cooling. The mixture was stirred at room temperature for 2 hours, after which a solution of benzylideneacetone (2.8 g, 19.2 mmol) in THF (10 cm^3) was added. The solution was stirred at 40 °C for 2 hours then at room temperature for 72 hours. Saturated ammonium chloride solution (75 cm^3) was added and the layers were separated. The aqueous phase was extracted with ether (3 x 50 cm^3) and the combined organic extracts were washed with water (2 x 50 cm^3), dried and the solvents were removed *in vacuo*. Dry-flash column chromatography (silica, hexane) gave (*E,E*)- and (*E,Z*)-2-(2-methyl-4-phenylbuta-1,3-dienyl)bromobenzene as a colourless solid (2.56 g, 8.6 mmol, 45 %). This was dissolved in hexane (150 cm^3) along with iodine (cat. amount) and the solution was heated to reflux for 3 hours, after which the solvent was removed *in vacuo* and the residue was taken up in DCM (50 cm^3). This solution was washed with sodium dithionite solution (2 x 50 cm^3, 25 %), water (2 x 50 cm^3) and dried. Removal of the solvent *in vacuo* gave (*E,E*)-2-(2-methyl-4-phenylbuta-1,3-dienyl)bromobenzene (**371**) (2.50 g, 8.36 mmol, 97 %) mp 98-99 °C (hexane); Found: M^+, 300.0341. $C_{17}H_{15}{}^{81}Br$ requires M^+, 300.0338; δ_H ($CDCl_3$, 250 MHz) 2.06 (3 H, d, *J* 1.2, CH_3), 6.57-6.81 (2 H, m, *H*C=C*H*), 7.03-7.67 (10 H, m, aromatic and olefinic H); δ_C (63 MHz, $CDCl_3$) 13.9 (CH_3), 124.4 (quat, C-CH_3), 126.4 (2 x CH, aromatic), 126.6, 127.3, 128.1, 128.3 (CH), 128.5 (2 x CH, aromatic), 128.7, 130.9, 131.2, 133.2 (CH), 136.7, 137.2, 137.6 (quat).

viii. (*E,E*)-2-Bromo-3-(4-phenylbuta-1,3-dienyl)thiophene (393)

n-Butyllithium (22.0 cm^3, 1.6 M in hexane, 35.2 mmol) was added to a solution of diisopropylamine (4.0 g, 39.6 mmol) in dry THF (10 cm^3) with ice-cooling, under nitrogen, and stirred for 1 hour at room temperature. This solution was added to a suspension of 2-bromo-3-thienylmethyltriphenylphosphonium bromide (**392**) (12.0

g, 23.2 mmol) in dry THF (100 cm^3) at 0 °C under nitrogen. The resulting orange solution was stirred for 1 hour at 0 °C, after which cinnamaldehyde (3.5 g, 26.5 mmol) in dry THF (20 cm^3) was added. This solution was stirred for 2 hours at room temperature, after which the reaction was quenched with ammonium chloride solution (50 cm^3, 25 %, w/v). The aqueous phase was extracted with ether (2 x 75 cm^3) and the combined extracts were washed with water, dried, and the solvents were removed *in vacuo*. The brown oil obtained was purified by dry-flash column chromatography (silica, hexane) to give (*E,E*)- and (*Z,E*)-2-bromo-3-(4-phenylbuta-1,3-dienyl)thiophene as a pale yellow solid. The mixture of isomers was dissolved in hexane along with a catalytic amount of iodine and the solution was refluxed for 4 hours, until TLC analysis showed only one spot, corresponding to the (*E,E*) isomer. The solvent was removed *in vacuo* and the residue was treated with sodium dithionite solution (50 cm^3, 10 % w/w) and DCM (100 cm^3). The organic phase was washed with sodium dithionite solution (50 cm^3) and water (50 cm^3), dried and the solvent was removed. The residue was crystallised to give (*E,E*)-2-bromo-3-(4-phenylbuta-1,3-dienyl)thiophene (**393**) as straw-coloured needles (4.20 g, 14.4 mmol, 62 %), mp 114-115 °C (hexane-ethanol); Found 57.65 % C, 3.78 % H, M^+, 289.9764 and M^+, 291.9745. $C_{14}H_{11}BrS$ requires 57.74 % C, 3.78 % H, M^+ (^{79}Br) 289.9765 and M^+ (^{81}Br), 291.9746; δ_H (360 MHz, $CDCl_3$) 6.74 (2 H, d, *J* 15.2, olefinic H-1 and H-4), 6.87 (1 H, dd, *J* 15.3, 10.3, olefinic), 7.03 (1 H, dd, *J* 15.4, 10.4, olefinic), 7.21 (1 H, d, *J* 5.8, thienyl), 7.28 (1 H, d, *J* 5.8, thienyl), 7.30-7.54 (5 H, m, aromatic); δ_C (91 MHz, $CDCl_3$) 111.64 (quat), 125.03, 125.29, 126.53 (CH), 126.95 (2 x CH, aromatic), 128.20 (CH), 129.18 (2 x CH, aromatic), 129.48, 131.58, 133.92 (CH), 137.66 (quat), 138.79 (quat).

ix. (*E,E*)- and (*Z,E*)-2-Bromo-3-(penta-1,3-dienyl)thiophene (402)

n-Butyllithium (22.0 cm^3, 1.6 M in hexane, 35.2 mmol) was added to an ice-cooled solution of diisopropylamine (3.9 g, 38.6 mmol) in THF (10 cm^3) and the resulting solution was stirred under nitrogen at room temperature for 1 hour. The LDA solution was then added to a cooled (0 °C) suspension of 2-bromothienyl-3-methyltriphenylphosphonium bromide (**392**) (8.50 g, 16.4 mmol) in THF (100 cm^3)

and the resulting dark mixture was stirred at 0 °C for 90 minutes. A solution of crotonaldehyde (2.5 g, 35.7 mmol) in THF (10 cm^3) was then added and the mixture was stirred at room temperature for 2 hours, after which ammonium chloride solution (50 cm^3, 25 % w/w) was added. The organic layer was washed with water (2 x 50 cm^3), dried, and the solvent was removed *in vacuo*. Flash column chromatography (silica, hexane) gave 2-bromo-3-(penta-1,3-dienyl)thiophene (**402**) as a pale yellow oil (2.8 g, 12.2 mmol, 74 %) as an inseparable, approximately 1:1, mixture of (*E,E*) and (*Z,E*) isomers; Found: M^+, 227.9608 and M^+, 229.9589. $C_9H_9{}^{79}BrS$ requires M^+, 227.9608. $C_9H_9{}^{81}BrS$ requires M^+, 229.9589; δ_H (250 MHz, $CDCl_3$) 1.80-1.84 (3 H, m, CH_3 *E* and *Z*), 5.80-5.95 (1 H, m, =C*H*CH_3 *E* and *Z*), 6.06-6.67 (3 H, m, olefinic *E* and *Z*), 7.07-7.25 (2 H, m, thienyl *E* and *Z*); δ_C (63 MHz, $CDCl_3$) 18.3* (CH_3), 18.4 (CH_3), 110.0* (quat), 111.4 (quat), 119.4 (CH), 121.8* (CH), 124.4* (CH), 125.1 (CH), 125.7* (CH), 127.7 (CH), 128.1 (CH), 131.0* (CH), 131.0 (CH), 131.1* (CH), 131.6* (CH), 133.1 (CH), 137.7 (quat C-Br), 138.3* (quat C-Br). (* Denotes major isomer signals). An attempted I_2/hexane/reflux isomerisation was found to cause extensive (> 80 %) decomposition after 1 hour, so the mixed-isomer product was used in the next stage without further manipulation.

III. Synthesis of (*E,Z*)-Bromodienes

i. (*E,Z*)- and (*Z,Z*)-4-Bromo-1,3-diphenylpenta-1,3-diene (538)

This compound was prepared by the method of Sharp[137]. *n*-Butyllithium (2.5 M in hexane, 2.0 cm^3, 5.0 mmol) was slowly added to an ice-cooled suspension of benzyltriphenylphosphonium bromide (2.0 g, 4.6 mmol) in THF (30 cm^3) and the suspension was stirred for 1 hour, then allowed to warm to room temperature. A solution of (*E*)-2-bromo-3-phenylbut-2-enal **434** (1.0 g, 4.5 mmol) in THF (10 cm^3) was added and the solution stirred for a further 2 hours. Ammonium chloride solution was added (25 % w/v, 25 cm^3) and the aqueous phase was extracted with ether (2 x 30 cm^3). The combined organic extracts were dried and the solvents were removed *in vacuo* to give a yellow oil which was purified by flash column chromatography (silica, hexane) to give 4-bromo-1,3-diphenylpenta-1,3-diene **538**

(1.20 g, 4.0 mmol, 89 %) as a yellow oil, found to be a mixture of isomers (approximate (*E,Z*):(*Z,Z*) ratio 3:4 by ^{1}H NMR). δ_H (200 MHz, $CDCl_3$) 2.24* (3 H, d, *J* 0.9, CH_3), 2.72 (3 H, s, CH_3), 6.00 (1 H, d, *J* 15.8, H-4), 6.12* (1 H, dd, *J* 12.1, 1.0, H-4), 6.53* (1 H, d, *J* 12.1, H-5), 7.17-7.50 (10 H, m, Ar-H and (*E,Z*) H-5) (* denotes major isomer signals).

ii. (*Z*)-4-Bromo-3-phenylpenta-1,3-diene (553)

To an ice-cooled suspension of methyltriphenylphosphonium bromide (1.6 g, 4.6 mmol) in dry THF was added *n*-butyllithium (1.6 M in hexane, 3.0 cm^3, 4.8 mmol). This mixture was stirred at 0 °C for 2 hours and (*E*)-2-bromo-3-phenylbut-2-enal **434** (1.0 g, 4.4 mmol) in dry THF was added. After 3 hours stirring at room temperature ammonium chloride solution (sat., 40 cm^3) was added. The aqueous phase was extracted with ether (2 x 40 cm^3) and the combined organics were washed with water, dried and the solvents were removed *in vacuo*. Flash-column chromatography (silica, hexane) of the oily residue gave (*Z*)-4-bromo-3-phenylpenta-1,3-diene **553** as a pale-yellow, waxy solid (0.85 g, 3.8 mmol, 86 %); δ_H (250 MHz, $CDCl_3$) 2.61 (3 H, s, CH_3), 4.71 (1 H, dd, *J* 16.9, 1.5, olefinic H-4a), 5.20 (1 H, ddd, *J* 11.1, 1.4, 0.5, olefinic H-4b), 6.87 (1 H, dd, *J* 17.0, 10.6, olefinic H-3), 7.10-7.14 (2 H, m, aromatic), 7.30-7.43 (3 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 25.0 (CH_3), 118.4 (CH_2), 124.0 (quat), 127.0 (CH), 128.0 (2 x CH, aromatic), 129.3 (2 x CH, aromatic), 133.2 (CH), 140.2 (quat), 140.4 (quat).

iii. (*E,Z*)- and (*Z,Z*)-5-Bromo-4-phenylhexa-2,4-diene (544)

To a cooled (0 °C) suspension of ethyltriphenylphosphonium bromide (1.75 g, 4.7 mmol) in dry THF (40 cm^3) was added *n*-butyllithium (2.0 cm^3, 2.5 M in hexane). The yellow solution was stirred for 2 hours under nitrogen, with cooling, after which a solution of *E*-3-bromo-2-phenylbut-2-enal **434** (1.0 g, 4.4 mmol) in dry THF (10 cm^3) was added. The reaction was stirred at room temperature for 3 hours and ammonium chloride solution (25 % w/v, 40 cm^3) was added. The aqueous phase was extracted with ether (2 x 25 cm^3) and the combined organic fractions were

washed with water (40 cm^3) and dried. Removal of the solvents *in vacuo* followed by flash column chromatography (silica, hexane) gave an approximately 1:1 mixture of (*E,Z*)- and (*Z,Z*)-5-bromo-4-phenylhexa-2,4-diene **544** as a yellow liquid (0.9 g, 3.8 mmol, 86 %); δ_H (250 MHz, $CDCl_3$) 1.76 (3 H, d, *J* 6.6, CH_3CH), 2.53 (3 H, dd, *J* 7.0, 1.8, CH_3CH), 2.29 (3 H, s, CH_3), 2.43 (3 H, d, *J* 1.1, CH_3), 5.15 (1 H, dq, *J* 15.2, 6.6, olefinic H-4, (*Z,E*)), 5.64 (1 H, dq, *J* 11.0, 7.0, H-4), 5.99 (1 H, dq, *J* 11.1, 1.7, olefinic H-3), 6.52 (1 H, dq, *J* 15.2, 1.7, olefinic H-3), 7.06-7.46 (5 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 14.6 (CH_3), 18.5 (CH_3), 25.6 (CH_3), 26.7 (CH_3), 127.0 (CH), 127.8 (2 x CH, aromatic), 127.8* (2 x CH, aromatic), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.4 (2 x CH, aromatic), 128.7* (2 x CH, aromatic), 128.9 (CH), 129.2 (CH), 129.3 (CH), 132.9 (quat), 137.2 (quat), 138.6 (quat), 140.6 (quat), 141.4 (quat), 141.9 (quat); *m/z* (EI+) 238 (18 %), 236 (19 %), 173 (base peak), 157 (38 %, M-Br), 142 (38 %), 129 (54 %). This compound was found to be too unstable to store overnight, even in a freezer, and had to be used immediately in the ensuing Suzuki reaction.

iv. (*E,Z*)-4-Bromo-3-phenyl-1-(pentafluorophenyl)penta-1,3-diene

A solution of diethyl perfluorobenzylphosphonate (0.68 g, 2.0 mmol) in dry THF (40 cm^3) was cooled to 0 °C under dry nitrogen and *n*-butyllithium (0.8 cm^3, 2.5 M in hexane, 2.0 mmol) was added dropwise. This solution was stirred at 0 °C for 2 hours, upon which (*E*)-2-bromo-3-phenylbut-2-enal **434** (0.40 g, 1.8 mmol) in dry THF (5 cm^3) was added. The reaction was stirred at room temperature for 2 hours, then quenched with ammonium chloride solution (40 cm^3, 25 % w/v). The aqueous phase was extracted with ether (2 x 25 cm^3) and the combined organic layers were washed with water (25 cm^3), dried and the solvents were removed *in vacuo*. Flash column chromatography (silica, 9:1 hexane-ether) gave (*E,Z*)-4-bromo-3-phenyl-1-(pentafluorophenyl)penta-1,3-diene as a white solid (0.35 g, 0.90 mmol, 45 %), mp 64-66 °C (hexane); Found: M^+, 387.9887 and M^+, 389.9868. $C_{17}H_{10}{}^{79}BrF_5$ requires M^+, 387.9886. $C_{17}H_{10}{}^{81}BrF_5$ requires M^+, 389.9867. δ_H (250 MHz, $CDCl_3$) 2.69 (3 H, s, CH_3), 5.88 (1 H, d, *J* 16.2, olefinic H-4), 7.11-7.16 (2 H, m, 2 x Ar-H), 7.16-7.47 (3 H, m, 3 x Ar-H), 7.58 (1 H, d, *J* 16.2, H-5); δ_C (63 MHz, $CDCl_3$) 25.37

(CH_3), 112.38 (quat, C-$(CF)_5$), 116.81 (CH, C-4), 127.61 (CH, Ar), 128.05 (quat), 128.39 (2 x CH, Ar), 129.30 (2 x CH, Ar), 135.59 (CH, C*H*-C_6F_5), 139.46 (quat), 140.18 (quat), 5 x quat C-F unobserved; δ_F (235 MHz, $CDCl_3$) -163.26 – -163.50 (2 F, m, Ar-F), -156.55 (1 F, t, *J* 20.6, *para*-F), -142.86 – -143.00 (2 F, m, Ar-F).

IV. Synthesis of (*E,E*)-Bromodienes

i. (*E,E*)-4-Bromo-1,3-diphenylpenta-1,3-diene (441)

To an ice-cooled suspension of benzyltriphenylphosphonium bromide (6.1 g, 14.0 mmol) in THF (40 cm^3) was added *n*-butyllithium (1.6 M in hexane, 9.4 cm^3, 15.0 mmol). This mixture was stirred at 0 °C under nitrogen for 1 hour, after which (*Z*)-3-bromo-2-phenylbut-2-enal **435** (2.0 g, 8.9 mmol) in dry THF (10 cm^3) was added. This solution was stirred at room temperature for 2 hours, after which ammonium chloride solution was added (sat., 40 cm^3). The aqueous layer was extracted with ether (2 x 40 cm^3) and the combined extracts were washed with water (2 x 25 cm^3), dried, and the solvent was removed *in vacuo*. Flash column chromatography (silica, hexane) of the residue gave (*E,E*)-4-bromo-1,3-diphenylpenta-1,3-diene **441** (1.94 g, 6.5 mmol, 73 %) as a colourless solid, mp 51-53 °C (hexane), lit. [137] 53-55 °C; δ_H (200 MHz, $CDCl_3$) 2.25 (3 H, s, CH_3), 6.00 (1 H, d, *J* 15.7, olefinic H), 7.06 (10 H, m, aromatic), 7.59 (1 H, d, *J* 15.7, olefinic H).

ii. (*E*)-4-Bromo-3-phenylpenta-1,3-diene

To a cooled (0 °C) suspension of methyltriphenylphosphonium bromide (2.65 g, 7.4 mmol) in THF (50 cm^3) was added *n*-butyllithium (2.5 M, 3.2 cm^3, 8.0 mmol), dropwise. This solution was stirred for 1 hour, then the cooling was removed and (*Z*)-3-bromo-2-phenylbut-2-enal **435** (1.66 g, 7.4 mmol) in dry THF (10 cm^3) was added. This solution was stirred for 2 hours at room temperature, then quenched with ammonium chloride solution (25 %, 50 cm^3). The aqueous layer was extracted with ether (2 x 50 cm^3) and the organic extracts washed with water (50 cm^3) and dried. Removal of the solvent *in vacuo* gave a brown solid which upon flash column

chromatography (silica, hexane) gave (*E*)-4-bromo-3-phenylpenta-1,3-diene as a yellow oil (0.92 g, 4.1 mmol, 55 %) bp 80 °C / 0.05 mmHg; Found: M^+, 222.0044. $C_{11}H_{11}{}^{79}Br$ requires M^+, 222.0044; δ_H (250 MHz, $CDCl_3$) 2.19 (3 H, dd, CH_3, *J* 1.1, 0.6), 4.69 (1 H, ddq, *J* 17.1, 1.5, 0.7, H-5a, *cis* H-4), 5.22 (1 H, ddq, *J* 10.6, 1.5, 0.7, olefinic H-5b, *trans* H-4), 7.06-7.17 (3 H, m, aromatic and olefinic H-4), 7.29-7.41 (3 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 27.05 (CH_3), 119.48 (CH_2), 122.90 (quat), 127.26 (CH), 128.26 (2 x CH, aromatic), 129.40 (2 x CH, aromatic), 137.59 (quat), 138.04 (CH), 138.95 (quat); *m/z* (EI+) 224 (12 %, ^{81}Br M^+), 222 (13 %, ^{79}Br M^+), 143 (64 %, M-Br), 128 (base peak).

iii. (*E,E*)-4-Bromo-3-phenyl-1-(pentafluorophenyl)penta-1,3-diene

To an ice-cooled solution of diethyl 2,3,4,5,6-pentafluorobenzyl phosphonate (1.56 g, 4.9 mmol) in dry THF (30 cm^3) was added *n*-butyllithium (2.0 cm^3, 2.5 M in hexane, 5.0 mmol). This solution was stirred at 0 °C for an hour, then warmed to room temperature. A solution of (*Z*)-2-bromo-3-phenylbutenal **435** (1.0 g, 4.44 mmol) in THF (10 cm^3) was added and the solution was stirred for 2 hours. Saturated ammonium chloride solution (30 cm^3) was added and the organic layer was separated. The aqueous phase was extracted with ether (2 x 30 cm^3) and the combined organic extracts were washed with water (20 cm^3), dried and the solvents were removed *in vacuo*. Flash column chromatography (silica, hexane) gave (*E,E*)-4-bromo-3-phenyl-1-(pentafluorophenyl)penta-1,3-diene as a colourless oil which solidified on cooling (1.03 g, 2.7 mmol, 61 %), mp 85-87 °C (hexane); Found: M^+, 387.9891 and M^+, 389.9866. $C_{17}H_{10}{}^{79}BrF_5$ requires M^+, 387.9886. $C_{17}H_{10}{}^{81}BrF_5$ requires M^+, 389.9866; δ_H (200 MHz, $CDCl_3$) 2.26 (3 H, s, CH_3), 5.86 (1 H, d, *J* 16.2, olefinic H-4), 7.11-7.25 (2 H, m, Ar-H), 7.34-7.48 (3 H, m, Ar-H), 7.86 (1 H, d, *J* 16.2, H-5); δ_C (63 MHz, $CDCl_3$) 27.47 (CH_3), 112.38 (quat *C*-CF), 117.83 (CH, C-4), 127.03 (quat, C-Me), 127.84 (CH, Ar-H), 128.67 (2 x CH, Ar-H), 129.38 (2 x CH, Ar-H), 136.69 (quat), 138.45 (CH, t, J_{CCF} 8.0, *C*H-C_6F_5), 138.90 (quat), 5 x quat C-F unobserved; δ_F (235.4 MHz, $CDCl_3$) -142.68 – -142.82 (m, 2 x F), -156.67 (1 F, t, *J* 20.8), -163.41 – -163.64 (m, 2 x F).

iv. (*E,E*)-4-Bromo-3-phenyl-1-(*p*-methoxyphenyl)penta-1,3-diene (474)

n-Butyllithium (3.70 cm^3, 2.5 M in hexane) was added dropwise to an ice-cooled solution of diethyl (4-methoxybenzyl)phosphonate (2 g, 7.80 mmol) in dry THF (40 cm^3) under nitrogen and this solution was stirred at 0 °C for one hour. A solution of (*Z*)-3-bromo-2-phenylbut-2-enal **435** (1.80 g, 8.0 mmol) in dry THF (10 cm^3) was added and the solution was allowed to reach room temperature and stirred for 2 hours. Ammonium chloride solution (40 cm^3, 25 % w/w) was added, the aqueous layer was extracted with ether (2 x 40 cm^3) and the combined extracts were washed with water (2 x 40 cm^3) and dried. Removal of the solvents gave a yellow oil, flash column chromatography (silica, hexane) of this residue yielding (*E,E*)-4-bromo-3-phenyl-1-(*p*-methoxyphenyl)penta-1,3-diene **474** as a pale yellow oil (0.41 g, 1.25 mmol, 16 %); Found: M^+, 328.0463 and M^+, 330.0446. $C_{18}H_{17}{}^{79}BrO$ requires M^+, 328.0463. $C_{18}H_{17}{}^{81}BrO$ requires M^+, 330.0444; δ_H (250 MHz, $CDCl_3$) 2.21 (3 H, s, CH_3), 3.79 (3 H, s, CH_3-O), 5.92 (1 H, d, *J* 16.0, olefinic), 6.82 (2 H, d, *J* 9.0, aromatic), 7.13-7.17 (2 H, m, aromatic), 7.25-7.46 (6 H, m, aromatic and olefinic); δ_C (63 MHz, $CDCl_3$) 27.1 (CH_3), 55.1 (CH_3-O), 113.9 (2 x CH, aromatic), 122.1 (quat), 127.3 (CH), 127.8 (2 x CH, aromatic), 128.3 (2 x CH, aromatic), 128.5 (CH), 129.5 (2 x CH, aromatic), 129.9 (quat), 133.7 (CH), 138.1, 138.9, 159.3 (quat); *m/z* 330 (M^+, ^{81}Br, 12 %), 328 (M^+, ^{81}Br, 11 %), 249 (M^+-Br, 17 %).

V. Synthesis of (*E,E*) Diene-Conjugated *ortho*-Benzaldehydes

i. (*E,E*)-2-(4-Phenylbuta-1,3-dienyl)benzaldehyde (257)

(*E,E*)-2-(4-Phenylbuta-1,3-dienyl)bromobenzene (**255**) (2.0 g, 7.0 mmol) was dissolved in THF (20 cm^3) under dry nitrogen and cooled to –78 °C. *n*-Butyllithium (1.6 M in hexanes, 4.8 cm^3) was added dropwise and the solution was stirred for 15 minutes. DMF (0.62 g, 8.5 mmol) in dry THF (7 cm^3) was added dropwise at –78 °C and the solution was stirred overnight at room temperature. Aqueous ammonium chloride (25 % w/v, 40 cm^3) was added and the aqueous layer was extracted with DCM (2 x 40 cm^3). The combined organics were washed with aqueous ammonium

chloride (25 % w/v, 40 cm^3) and water (40 cm^3), dried, and the solvent was removed *in vacuo* to yield a yellow oil. Wet flash column chromatography (silica, 3:1 hexane-ether) afforded (*E,E*)-2-(4-phenylbuta-1,3-dienyl)benzaldehyde (**257**) (1.11 g, 68 %) as a pale yellow solid, mp 97-98.5 °C (hexane), Found 87.11 % C, 6.02 % H, M^+, 234.1045. $C_{17}H_{14}O$ requires 87.16 % C, 6.10 % H, M^+, 234.1045; δ_H (200 MHz, $CDCl_3$) 6.65 (1 H, d, *J* 14.5, olefinic H-4), 6.80-7.05 (2 H, m, olefinic), 7.15-7.63 (9 H, aromatic and olefinic), 7.65 (1 H, dd, *J* 7.6, 1.1, aromatic), 10.21 (1 H, s, CHO); δ_C (63 MHz, $CDCl_3$) 126.5 (2 x CH, aromatic), 126.5 (CH), 126.5 (quat), 127.3 (CH), 127.8 (CH), 128.1 (CH), 128.5 (2 x CH, aromatic), 128.8 (CH), 132.3 (CH), 133.4 (CH), 134.1 (CH), 134.5 (CH), 136.8 (quat), 139.4 (quat), 192.5 (CH, CHO); *m/z* 234 (M^+, 77%), 216 (16 %), 206 (35 %), 132 (77 %).

ii. (*E*)-2-(Buta-1,3-dienyl)benzaldehyde

(*E*)-2-(Buta-1,3-dienyl)bromobenzene (**269**) (2.80 g, 13.4 mmol) was dissolved in dry THF (50 cm^3) under dry nitrogen and the solution was cooled to -78 °C. *n*-Butyllithium (1.6 M in hexanes, 9.2 cm^3) was added dropwise with stirring. After *ca.* 10 minutes, DMF (1.19 g, 16.3 mmol) in dry THF (5 cm^3) was added dropwise and the solution was stirred overnight at room temperature. The reaction was hydrolysed by addition of aqueous ammonium chloride (25 % w/v, 50 cm^3) and stirred for 30 minutes. The layers were separated, the aqueous phase was extracted with ether (2 x 50 cm^3) and the solvent removed *in vacuo*. Flash column chromatography of the residual oil, (silica, 9:1 hexane-ether) gave (*E*)-2-(buta-1,3-dienyl)benzaldehyde (1.37 g, 8.7 mmol, 65 %) as a pale yellow solid, mp 71-73 °C (hexane); Found: M^+, 158.0732. $C_{11}H_{10}O$ requires M^+, 158.0732; δ_H (200 MHz, $CDCl_3$) 5.26-5.51 (2 H, m, $=CH_2$), 6.51-6.82 (2 H, m, olefinic), 7.15-7.65 (4 H, m, 3 x aromatic and 1 x olefinic), 7.79-7.83 (1 H, dd, *J* 6.5 and 1.1, aromatic), 10.27 (1 H, s, CHO); δ_C (63 MHz, $CDCl_3$) 119.39 (CH_2), 126.74, 127.44, 128.30, 131.85 (CH), 132.48 (quat), 133.44, 134.49, 136.80 (CH), 139.34 (quat, *C*-CHO), 192.29 (CHO); ν_{max} (nujol)/cm^{-1} 1695.5 (CHO), 1594.5 (C=C).

iii. (*E,E*)-2-(Penta-1,3-dienyl)benzaldehyde

A solution of (*E,E*)-2-(penta-1,3-dienyl)bromobenzene (**287**) (1.75 g, 7.8 mmol) in dry THF (40 cm^3) was cooled in a cardice-acetone bath under a nitrogen atmosphere and *n*-butyllithium (3.4 cm^3, 2.5 M in hexane, 8.6 mmol) was added dropwise. This solution was stirred at low temperature for 30 minutes, after which dry DMF (0.57 g, 7.8 mmol) in dry THF (10 cm^3) was added dropwise. This solution was stirred for 3 hours at room temperature, following which ammonium chloride solution (25 % w/v, 40 cm^3) was added. The aqueous phase was extracted with ether (2 x 50 cm^3) and the combined organic layers were washed with water (2 x 25 cm^3) and dried. The solvents were removed *in vacuo* to give a yellow oil. Flash column chromatography (silica, 4:1 hexane-ether) gave (*E,E*)-2-(penta-1,3-dienyl)benzaldehyde (1.23 g, 7.15 mmol, 91 %), mp 80-82 °C (dec) (hexane); Found: M^+, 172.0884. $C_{12}H_{12}O$ requires M^+, 172.0888; δ_H (250 MHz, $CDCl_3$) 2.09 (3 H, dd, *J* 6.8, 1.5, CH_3), 5.92 (1 H, ddq, *J* 15.0, 1.6, 6.8, olefinic H-4), 6.22-6.37 (1 H, ddq, *J* 15.0, 10.4, 1.6, olefinic H-3), 6.70 (1 H, dd, *J* 15.5, 10.4, olefinic H-2), 7.25-7.81 (5 H, m, 4 x aromatic and 1 x olefinic), 10.26 (1 H, s, CHO); δ_C (63 MHz, $CDCl_3$) 18.29 (CH_3), 125.04 (CH), 126.61 (CH), 126.95 (CH), 131.56 (CH), 131.70 (CH), 132.32 (quat, aromatic), 132.49 (CH), 133.44 (CH), 134.55 (CH), 140.14 (quat, *C*-CHO), 192.38 (CHO).

iv. (*E,E*)-2-(1-Methyl-4-phenylbuta-1,3-dienyl)benzaldehyde

(*E,E*)-2-(1-Methyl-4-phenylbuta-1,3-dienyl)bromobenzene (**325**) (1.25 g, 4.2 mmol) was dissolved in dry THF (25 cm^3) under a dry nitrogen atmosphere. *n*-Butyllithium solution (1.6 M in hexanes, 3.0 cm^3) was added dropwise with cooling (-78 °C) and stirring. After 10 minutes stirring at –78 °C dry DMF (0.38 g, 5.2 mmol) in dry THF (3 cm^3) was added dropwise and the solution was stirred overnight at room temperature. Aqueous ammonium chloride (25 % w/v, 20 cm^3) was added and the layers were separated after stirring for 30 minutes. The aqueous phase was extracted with ether (2 x 20 cm^3) and the combined organics were washed with aqueous ammonium chloride (25 % w/v, 20 cm^3) and water (20 cm^3) then dried. The solvent was removed *in vacuo* to give a yellow oil. Wet flash column chromatography

(silica, 9:1 hexane-ether) gave (*E,E*)-2-(1-methyl-4-phenylbuta-1,3-dienyl)benzaldehyde as a pale yellow oil (0.36 g, 1.5 mmol, 36 %); Found: M^+, 248.1204. $C_{18}H_{16}O$ requires M^+, 248.1201; δ_H (250 MHz, $CDCl_3$) 2.31 (3 H, d, *J* 1.2, CH_3), 6.09-6.15 (1 H, m, olefinic, H-2), 6.63 (1 H, d, *J* 15.5, olefinic H-4), 7.15 (1 H, dd, *J* 15.5, 11.0, olefinic H-3), 7.21-7.60 (8 H, m, aromatic), 7.92-7.95 (1 H, m, aromatic), 10.12 (1 H, d, *J* 0.7, CHO); δ_C (63 MHz, $CDCl_3$) 19.1 (CH_3), 124.3 (CH), 126.4 (2 x CH, aromatic), 127.1, 127.7, 128.0 (CH), 128.6 (3 x CH), 133.2, 133.6 (CH), 133.7, 134.0 (quat), 134.3 (CH), 137.1 (quat), 148.7 (quat, *C*-CHO), 192.1 (CH, CHO).

v. (*E,E*)-2-(1-Methylpenta-1,3-dienyl)benzaldehyde

A solution of (*E,E*)-2-(1-methylpenta-1,3-dienyl)bromobenzene (**337**) (1.70 g, 7.2 mmol) in dry THF (40 cm^3) was cooled in a cardice-acetone bath under a nitrogen atmosphere. *tert*-Butyllithium (1.5 M in pentane, 5.3 cm^3, 7.9 mmol) was added dropwise with stirring and after 15 minutes DMF (0.63 g, 8.6 mmol) in dry THF (5 cm^3) was added to the cooled solution. The mixture was stirred for 3 hours at room temperature, after which ammonium chloride solution (25 % w/v, 40 cm^3) was added. The layers were separated and the aqueous phase was extracted with DCM (3 x 50 cm^3). The combined organic layers were washed with water (50 cm^3), dried and the solvents were removed *in vacuo* to give a yellow oil. Flash column chromatography (silica, hexane-ether, 4:1) gave (*E,E*)-2-(1-Methylpenta-1,3-dienyl)benzaldehyde as a yellow oil, bp 180 °C / 0.03 mmHg (0.90 g, 4.8 mmol, 67 %); Found: M^+, 186.1043. $C_{13}H_{14}O$ requires M^+, 186.1045; δ_H (250 MHz, $CDCl_3$) 1.84 (3 H, ddd, *J* 6.8, 1.1, 0.5, CH_3CH=), 2.18 (3 H, dd, *J* 1.3, 0.5, CH_3), 5.75-5.91 (2 H, m, olefinic), 6.36-6.48 (1 H, m, olefinic), 7.20-7.56 (3 H, m, aromatic), 7.88-7.92 (1 H, m, aromatic), 10.77 (d, 1 H, *J* 0.7, CHO); δ_C (63 MHz, $CDCl_3$) 18.44 (CH_3), 18.78 (CH_3), 126.83 (CH), 127.30 (CH), 127.72 (CH), 128.07 (quat), 128.60 (CH), 130.57 (quat), 131.97 (CH), 133.16 (CH), 133.64 (CH), 149.13 (quat, *C*-CHO), 192.32 (CH, CHO); ν_{max} (thin film)/cm^{-1} 1686.0 (C=O).

vi. (*E*)-2-(1-Methylbuta-1,3-dienyl)benzaldehyde

A solution of (*E*)-2-(1-methylbuta-1,3-dienyl)bromobenzene (**342**) (0.20 g, 0.9 mmol) in THF (20 cm^3) was cooled in a cardice-acetone bath under a nitrogen atmosphere. *n*-Butyllithium (2.5 M in hexane, 0.4 cm^3, 1.0 mmol) was added dropwise and the solution was stirred for 15 minutes at low temperature. Dry DMF (0.08 g, 1.1 mmol) in dry THF (5 cm^3) was added and the solution was stirred for 2 hours at room temperature. Ammonium chloride solution (25 % w/v, 10 cm^3) was added and the aqueous phase was extracted with DCM (2 x 30 cm^3). The combined organic extracts were washed with water (30 cm^3), dried and the solvents were removed *in vacuo*, leaving a yellow oil. Flash column chromatography (silica, 4:1 hexane-ether) yielded (*E*)-2-(1-methylbuta-1,3-dienyl)benzaldehyde as a pale yellow oil (0.13 g, 0.76 mmol, 81 %); Found: M^+, 172.0887. $C_{12}H_{12}O$ requires M^+, 172.0888; δ_H (200 MHz, $CDCl_3$) 2.20 (3 H, d, *J* 1.4, CH_3), 5.23-5.33 (2 H, m, olefinic), 5.93-5.99 (1 H, m, olefinic), 6.66-6.84 (1 H, m, olefinic), 7.17-7.94 (4 H, m, aromatic), 10.1 (1 H, d, *J* 0.8, CHO); δ_C (63 MHz, $CDCl_3$) 19.07 (CH_3), 119.11 (CH_2), 127.18 (CH), 127.85 (CH), 128.58 (CH), 132.25 (CH), 133.30 (CH), 133.55 (quat), 133.68 (CH), 134.14 (CH), 148.66 (quat *C*-CHO), 192.10 (CH, *C*HO).

vii. (*E,E*)-2-(2-Methyl-4-phenylbuta-1,3-dienyl)benzaldehyde

To a cooled (-78 °C) solution of (*E,E*)-2-(2-methyl-4-phenylbuta-1,3-dienyl)bromobenzene (**371**) (1.0 g, 3.34 mmol) in THF (30 cm^3) was added *n*-butyllithium (1.6 M in hexanes, 2.5 cm^3, 4.0 mmol). The solution was stirred for 10 minutes, dry DMF (0.3 g, 4.1 mmol) was added and the solution was allowed to warm to room temperature, then stirred for 1 hour. Saturated ammonium chloride solution (25 cm^3) was added and the layers were separated. The aqueous layer was extracted with ether (2 x 25 cm^3) and the combined organic extracts were washed with water (2 x 25 cm^3), dried, and the solvents were removed *in vacuo*. Flash column chromatography (silica, hexane then 9:1 hexane-ether) gave (*E,E*)-2-(2-methyl-4-phenylbuta-1,3-dienyl)benzaldehyde as a yellow oil (0.55 g, 2.2 mmol, 67 %); Found: M^+, 248.1203. $C_{18}H_{16}O$ requires M^+, 248.1201; δ_H ($CDCl_3$, 250 MHz)

1.95 (3 H, d, *J* 1.2, CH_3), 6.70 (1 H, d, *J* 16.3, olefinic H-3), 7.03-7.94 (11 H, m, aryl and olefinic CH), 10.22 (1 H, s, CHO); δ_C ($CDCl_3$, 63 MHz) 14.1 (CH_3), 126.6 (2 x Ar CH), 127.4 (CH), 127.7 (CH), 128.1 (CH), 128.7 (2 x Ar CH), 129.1 (CH), 129.3 (CH), 130.8 (CH), 131.8 (CH), 133.8 (quat), 137.2 (quat), 139.0 (quat), 140.8 (quat), 192.4 (CHO); ν_{max} (neat) 1693.9 (C=O), 1594.1 (C=C).

viii. (*E,E*)-2-Formyl-3-(4-phenylbuta-1,3-dienyl)thiophene

n-Butyllithium (10 cm^3, 1.6 M in hexane, 16.0 mmol) was added dropwise to a cooled (-78 °C) solution of (*E,E*)-2-bromo-3-(4-phenylbuta-1,3-dienyl)thiophene (**393**) (3.3 g, 11.3 mmol) in THF (70 cm^3) under a nitrogen atmosphere. This solution was stirred at –78 °C for 15 minutes, after which DMF (1.2 g, 16.4 mmol) was added and the solution was allowed to warm to room temperature. After 2 hours of stirring, ammonium chloride solution (40 cm^3, 25 % w/w) was added and the aqueous phase was extracted with ether (2 x 50 cm^3). The combined organics were washed with water (2 x 25 cm^3), dried, and the solvents were removed *in vacuo*. Crystallisation of the bright yellow solid residue gave (*E,E*)-2-formyl-3-(4-phenylbuta-1,3-dienyl)thiophene as large, bright yellow needles (2.15 g, 9.0 mmol, 80 %), mp 115-116.5 °C (ethanol); Found: M^+, 240.0609. $C_{15}H_{12}OS$ requires M^+, 240.0609; δ_H (250 MHz, $CDCl_3$) 6.70-6.82 (1 H, m, olefinic H), 6.91-7.05 (2 H, m, olefinic H), 7.18-7.47 (7 H, m, olefinic and aromatic H), 7.60-7.63 (1 H, m, thienyl H), 10.14 (1 H, d, *J* 1.0, CHO); δ_C (63 MHz, $CDCl_3$) 122.8, 126.4 (CH), 126.6 (2 x aromatic CH), 128.1, 128.2 (CH), 128.6 (2 x aromatic CH), 134.2, 134.9, 135.7 (CH), 136.5, 136.9 (quat), 146.6 (quat *C*-CHO), 181.8 (CHO); ν_{max} (nujol) 1645.0 cm^{-1} (C=O).

ix. (*E,E*)- and (*Z,E*)-2-Formyl-3-(penta-1,3-dienyl)thiophene

Under nitrogen, *n*-butyllithium (7.2 cm^3, 1.6 M in hexane, 11.5 mmol) was slowly added to a cooled (-78 °C) solution of (*E,E*) and (*Z,E*)-2-bromo-3-(penta-1,3-dienyl)thiophene (**402**) (2.60 g, 11.4 mmol) in dry THF (75 cm^3). This solution was stirred at -78 °C for 15 minutes, after which dry DMF (1.0 g, 13.7 mmol) was added

and the mixture was allowed to warm to room temperature. After 2 hours, ammonium chloride solution (50 cm^3, 25 % w/w) was added and the organic layer was separated. The aqueous phase was extracted with ether (2 x 50 cm^3) and the combined organics were washed with water (2 x 50 cm^3), dried and the solvents were removed *in vacuo*. Flash column chromatography (silica, 0-10 % hexane-ether) afforded (*E,E*)- and (*Z,E*)-2-formyl-3-(penta-1,3-dienyl)thiophene [3:2 (*E,E*):(*Z,E*) ratio from NMR integral] as a red oil (1.71 g, 9.6 mmol, 85 %), bp 110 °C (oven) / 0.05 mmHg; Found: M^+, 178.0452. $C_{10}H_{10}OS$ requires M^+, 178.0452; δ_H (250 MHz, Cl_3) 1.76-1.84 (3 H, m, CH_3), 5.87-6.02 (1 H, m, =C*H*CH_3), 6.18-6.28 (1 H, m, olefinic), 6.35-6.51 (2 H, m, olefinic), 6.76* (1 H, dd, *J* 15.5, 10.2, olefinic H-2), 6.96* (1 H, d, *J* 15.5, olefinic H-1), 7.14$^{\$}$ (1 H, d, *J* 5.0, thienyl), 7.28* (1 H, d, *J* 5.2, thienyl), 7.57* (1 H, dd, *J* 5.2, 0.6, thienyl), 7.65$^{\$}$ (1 H, d, *J* 5.0, thienyl), 9.94$^{\$}$ (1 H, d, *J* 1.1, CHO), 10.08* (1 H, d, *J* 0.9, CHO); δ_C (63 MHz, $CDCl_3$) 19.0 (CH_3), 118.4$^{\$}$, 120.6*, 126.9*, 127.8$^{\$}$, 130.8$^{\$}$, 131.8*, 134.4$^{\$}$, 134.6*, 134.7*, 135.2$^{\$}$, 135.7 (CH, olefinic and thienyl), 137.1*, 138.6$^{\$}$, 147.2$^{\$}$, 147.8* (quat), 182.4*, 183.5$^{\$}$ (CHO); ν_{max} (film) 1652.1 cm^{-1} (C=O). *Denotes major (*E,E*) isomer, $^{\$}$ denotes minor (*Z,E*) isomer. Where no symbol is present, signals from both isomers coincide.

VI. Synthesis of (Z,E) 1,2,4-Trisubstituted Diene-Conjugated *ortho*-Benzaldehydes

i. (*Z,E*)- and (*Z,Z*)-2-(1-Methyl-2,4-diphenylbuta-1,3-dienyl) benzaldehyde (539)

A mixture of (*E,Z*) and (*Z,Z*)-4-bromo-1,3-diphenylpenta-1,3-diene **538** (0.76 g, 2.5 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.14 g, 0.13 mmol, 5 mol %) in dry DME (15 cm^3) was stirred in the darkness and under nitrogen for 1 hour, after which sodium carbonate (0.28 g, 0.26 mmol), 2-formylphenylboronic acid (0.39 g, 0.26 mmol) and water (8 cm^3) were added. The mixture was heated at reflux for 30 minutes and stirred at room temperature overnight. The solvent was removed *in vacuo* and DCM (10 cm^3) was added to the aqueous residue, the aqueous layer being

further extracted with DCM (2 x 10 cm^3). The extracts were washed with water (20 cm^3), dried, and passed through a short alumina pad. Removal of the solvent *in vacuo* afforded a yellow oil, which upon flash column chromatography (silica, 9:1 hexane-ether) yielded (*Z,E*)- and (*Z,Z*)-2-(1-methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde **539** as an inseparable, 1:1.2 (from ^1H NMR) mixture of (*Z,E*) and (*Z,Z*) isomers (0.65 g, 2.0 mmol, 80 %), mp 74-77.5 °C (hexane); δ_H(250 MHz, $CDCl_3$) 2.02* (3 H, d, *J* 1.3, CH_3), 2.45$^{\$}$ (3 H, s, CH_3), 6.21$^{\$}$ (1 H, d, *J* 15.9, olefinic H-3), 6.50* (1 H, dq, *J* 12.0, 1.4, olefinic H-3), 6.70* (1 H, d, *J* 12.0, olefinic H-4), 6.93-7.78 (14 H, m, aromatic), 7.59$^{\$}$ (1 H, d, *J* 15.9, olefinic H-4), 10.10* (1 H, d, *J* 0.7, CHO), 10.15$^{\$}$ (1 H, d, *J* 0.7, CHO); δ_C(63 MHz, $CDCl_3$) 21.8$^{\$}$ (CH_3), 24.2* (CH_3), 126.3 (CH), 126.4* (2 x CH, phenyl), 126.7 (CH), 126.9 (CH), 127.0 (CH), 127.2 (CH), 127.5* (2 x CH, phenyl), 127.6 (CH), 127.6$^{\$}$ (2 x CH, phenyl), 127.9 (CH), 128.0* (2 x CH, phenyl), 128.0* (2 x CH, phenyl), 128.5$^{\$}$ (2 x CH, phenyl), 129.4$^{\$}$ (2 x CH, phenyl), 129.8 (CH), 130.0 (CH), 130.1 (CH), 130.2$^{\$}$ (2 x CH, phenyl), 131.7 (CH), 132.1 (quat), 132.5 (quat), 133.2 (CH), 133.2 (CH), 133.3 (CH), 133.4 (quat), 133.6 (CH), 137.0 (quat), 137.3 (quat), 139.0 (quat), 139.3 (quat), 139.6 (quat), 147.6 (quat), 148.1 (quat), 191.7$^{\$}$ (CH, CHO), 191.8* (CH, CHO). * Denotes major (*Z,Z*) isomer signals, $^{\$}$ denotes minor (*Z,E*) isomer signals. Where no symbol is used, assignment of the signal was not possible.

ii. (*Z*)-2-(1-Methyl-2-phenylbuta-1,3-dienyl)benzaldehyde

To a solution of (*Z*)-4-bromo-3-phenylpenta-1,3-diene **553** (0.7 g, 3.14 mmol) in dry DME (15 cm^3) was added tetrakis(triphenylphosphine) palladium(0) (0.17 g, 0.16 mmol, 5 mol %) and the mixture was stirred for 15 minutes, in the dark and under nitrogen. Sodium carbonate (0.34 g, 3.2 mmol), 2-formylphenylboronic acid (0.48 g, 3.2 mmol) and water (10 cm^3) were added and the mixture was heated at reflux for 15 minutes and stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and DCM (20 cm^3) and water (10 cm^3) were added to the residue. The aqueous phase was extracted with DCM (2 x 20 cm^3) and the combined extracts were washed with water (30 cm^3), dried, and the solvent was removed *in vacuo* to give a dark oil. Flash-column chromatography (silica, 7:3 hexane-ether) gave (*Z*)-2-(1-

methyl-2-phenylbuta-1,3-dienyl)benzaldehyde as a pale yellow solid (0.65 g, 2.6 mmol, 83 %), mp 89-90.5 °C (dec) (hexane); δ_H (250 MHz, $CDCl_3$) 1.92 (3 H, d, *J* 0.4, CH_3), 4.61 (1 H, ddd, *J* 17.1, 1.5, 0.7, olefinic H-4a), 4.92 (1 H, ddd, *J* 10.6, 1.5, 0.7, olefinic H-4b), 6.22 (1 H, dd, *J* 17.1, 10.6, olefinic H-3), 7.19-7.24 (2 H, m, aromatic), 7.30-7.49 (5 H, m, aromatic), 7.64 (1 H, ddd, *J* 7.5, 7.5, 1.5, aromatic), 7.99 (1 H, ddd, *J* 7.7, 1.4, 0.5, aromatic), 10.20 (1 H, d, *J* 0.8, CHO); δ_C (63 MHz, $CDCl_3$) 24.1 (CH_3), 117.5 (CH_2), 126.9 (CH), 127.5 (CH), 127.7 (CH), 128.2 (2 x CH, aromatic), 129.6 (2 x CH, aromatic), 129.6 (CH), 133.3 (quat), 133.4 (quat), 134.1 (CH), 136.1 (CH), 138.4 (quat), 140.5 (quat), 147.0 (quat), 191.8 (CH, CHO).

iii. (*Z,E*)- and (*Z,Z*)-2-(1-Methyl-2-phenylpenta-1,3-dienyl) benzaldehyde (545)

A mixture of (*E,Z*)- and (*Z,Z*)-5-bromo-4-phenylhexa-2,4-diene (**544**) (0.80 g, 3.4 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.20 g, 0.17 mmol, 5 mol %) in dry DME (10 cm^3) was stirred, in the dark and under nitrogen, for 1 hour. 2-Formylphenylboronic acid (0.6 g, 4.0 mmol), sodium carbonate (0.45 g, 4.2 mmol) and water (8 cm^3) were added and the mixture was heated at reflux for 15 minutes, then stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and water (20 cm^3) was added to the residue. This aqueous solution was extracted with DCM (3 x 25 cm^3) and the combined extracts were washed with water (25 cm^3), dried, passed through a short alumina pad, and the solvent was removed *in vacuo*. Flash column chromatography (silica, 9:1 hexane-ether) of the residue gave a 1:1 mixture of (*Z,E*)- and (*Z,Z*)-2-(1-methyl-2-phenylpenta-1,3-dienyl)benzaldehyde **545** as a pale yellow oil (0.31 g, 1.1 mmol, 34 %); Found: M^+, 262.1356. $C_{19}H_{18}O$ requires M^+, 262.1358; δ_H (250 MHz, $CDCl_3$) 1.04 (3 H, ddd, *J* 6.8, 0.8, 0.4, C-4 CH_3), 1.51 (3 H, ddd, *J* 6.7, 0.8, 0.8, C-4 CH_3), 1.87 (3 H, s, C-1 CH_3), 2.06 (3 H, d, *J* 0.4, C-1 CH_3), 5.08 (1 H, dq, *J* 15.4, 6.7, olefinic H-4), 5.27 (1 H, dq, *J* 11.5, 6.8, olefinic H-4), 5.69 (1 H, dqq, *J* 11.6, 0.8, 0.4, olefinic H-3), 5.89 (1 H, dq, *J* 15.4, 0.6, olefinic H-3), 7.19-8.03 (9 H, aromatic), 10.19 (1 H, d, *J* 0.8, CHO), 10.21 (1 H, d, *J* 0.8, CHO); δ_C (63 MHz, $CDCl_3$) 15.1 (CH_3), 18.6 (CH_3), 21.6 (CH_3), 23.6 (CH_3), 126.2, 126.5, 126.8, 127.3, 127.5, 127.5, 127.6, 128.1, 129.5, 129.8, 129.9,

130.1, 130.2, 130.4, 131.0 (CH, aromatic and olefinic), 131.6, 132.5, 132.9 (quat), 133.3$ (CH), 133.4* (CH, aromatic *C*HCCHO), 134.2 (quat), 137.9, 139.6, 140.5, 147.8* (quat, *C*CHO), 148.5 (quat, *C*CHO), 191.6* (CH, CHO), 191.9$ (CH, CHO).

iv. (*Z,E*)-2-[1-Methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl]benzaldehyde

A mixture of (*E,Z*)-4-bromo-3-phenyl-1-(pentafluorophenyl)penta-1,3-diene (0.26 g, 0.67 mmol) and tetrakis(triphenylphosphine) palladium (0) (40 mg, 0.035 mmol, 5 mol %) in dry DME (10 cm^3) was stirred in the dark under dry nitrogen for 1 hour. 2-Formylphenylboronic acid (0.10 g, 0.67 mmol), sodium carbonate (0.08 g, 0.75 mmol) and water (4 cm^3) were added and the mixture was heated at reflux for 1 hour, then stirred at room temperature for 2 hours. The DME was removed *in vacuo* and DCM (25 cm^3) and water (10 cm^3) were added. The aqueous layer was further extracted with DCM (2 x 20 cm^3) and the combined extracts were washed with water (2 x 10 cm^3), dried, and passed through a short pad of alumina. Removal of the solvent *in vacuo* followed by flash column chromatography (silica, 7:3 hexane-ether) gave (*Z,E*)-2-[1-methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl]benzaldehyde as a pale yellow solid (0.25 g, 0.60 mmol, 90 %) mp 127-128.5 °C (hexane); Found 69.56 % C, 3.65 % H, M^+, 414.1044. $C_{24}H_{15}F_5O$ requires 69.38 % C, 3.65 % H, M^+, 414.1043. δ_H (250 MHz, $CDCl_3$) 2.40 (3 H, s, CH_3), 6.04 (1 H, d, *J* 16.3, olefinic H-3), 6.88-6.92 (2 H, m, olefinic and aromatic), 7.05-7.18 (4 H, m, aromatic), 7.17-7.24 (1 H, m, aromatic), 7.39 (1 H, td, *J* 7.5, 1.5, aromatic), 7.66 (1 H, dd, *J* 7.7, 1.3, aromatic), 7.87 (1 H, d, *J* 16.3, =C*H*C_6F_5), 10.09 (1 H, s, CHO); δ_C (63 MHz, $CDCl_3$) 21.8 (CH_3), 112.5 (m, quat), 116.9 (CH), 126.8 (CH), 127.0 (CH), 127.9 (2 x CH, aromatic), 128.4 (CH), 129.8 (CH), 130.1 (2 x CH, aromatic), 132.4 (quat), 133.4 (CH), 131.5-131.6 (CH, =C*H*C_6F_5), 137.7 (2 x quat), 139.2 (quat), 147.2 (quat), 191.5 (CH, CHO), 5 x C-F quat carbons not observed; δ_F (235 MHz, $CDCl_3$) -163.59 – -163.36 (2 x F, *meta* F), -156.88 (1 x F, dd, J_{FCF} 20.9, *para* F), -142.98 (2 x F, dd, J_{FCF} 21.6, J_{FCF} 7.8, *ortho* F).

VII. Synthesis of (*E,E*) 1,2,4-Trisubstituted Diene-Conjugated *ortho*-Benzaldehydes

i. (*E,E*)- and (*Z,E*)-2-(1-Methyl-2,4-diphenylbuta-1,3-dienyl) benzaldehyde (442)

A mixture of (*Z,E*) and (*E,E*)-4-bromo-1,3-diphenylpenta-1,3-diene **441** (0.76 g, 2.5 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.14 g, 0.13 mmol, 5 mol %) in dry DME (15 cm^3) was stirred in the darkness and under nitrogen for 1 hour, after which sodium carbonate (0.28 g, 0.26 mmol), 2-formylphenylboronic acid (0.39 g, 0.26 mmol) and water (8 cm^3) were added. The mixture was heated at reflux for 30 minutes and stirred at room temperature overnight. The solvent was removed *in vacuo* and DCM (10 cm^3) was added to the aqueous residue, the aqueous layer being further extracted with DCM (2 x 10 cm^3). The extracts were washed with water (20 cm^3), dried, and passed through a short alumina pad. Removal of the solvent *in vacuo* afforded a yellow oil, which upon flash column chromatography (silica, 9:1 hexane-ether) yielded (*E,E*) and (*E,Z*)-2-(1-methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde **442** as an inseparable, 4:1 (from ^1H NMR) mixture of (*E,E*) and (*E,Z*) isomers (0.65 g, 2.0 mmol, 80 %), mp 57-58 °C (hexane), lit.[137] 61-62 °C; δ_H (250 MHz, $CDCl_3$) 1.98* (3 H, s, CH_3), 2.14$ (3 H, d, *J* 1.5, CH_3), 5.96* (1 H, d, *J* 15.9, olefinic H-4), 5.98$ (1 H, d, *J* 12.0, olefinic H-4), 6.21$ (1 H, d, *J* 12.0, olefinic H-3), 6.67* (1 H, dd, *J* 15.8, 0.3, olefinic H-3), 6.97-7.55 (12 H, m, aromatic), 7.70* (1 H, dt, *J* 1.5, 6.0, aromatic), 7.88-7.92$ (1 H, m, aromatic), 8.06* (1 H, ddd, *J* 7.8, 1.5, 0.5, aromatic), 10.19$ (1 H, d, *J* 0.8, CHO), 10.26* (1 H, d, *J* 0.8, CHO); δ_C (63 MHz, $CDCl_3$) 23.7$ (CH_3), 24.4* (CH_3), 126.2* (2 x CH, aromatic), 126.5$ (CH), 126.9$ (CH), 127.1* (CH), 127.3* (CH), 127.6* (CH), 127.7$ (2 x CH, aromatic), 127.8* (CH), 128.2* (2 x CH, aromatic), 128.4* (2 x CH, aromatic), 128.5* (CH), 129.0$ (CH), 129.6* (2 x CH, aromatic), 129.9* (CH), 130.1$ (CH), 131.4$ (CH), 132.2* (CH), 133.1$ (quat), 133.4$ (quat), 133.5* (quat), 133.6$ (CH), 133.8* (quat), 134.2* (CH), 136.7$ (quat), 137.1* (quat), 138.0$ (quat), 138.8* (quat), 139.0$ (quat), 140.3* (quat), 147.0* (quat, *C*-CHO), 148.0$ (quat, *C*-CHO), 191.8 (CH, CHO).

ii. (*E*)-2-(1-Methyl-2-phenylbuta-1,3-dienyl)benzaldehyde

In the dark and under nitrogen a mixture of (*E*)-4-bromo-3-phenylpenta-1,3-diene (0.70 g, 3.2 mmol) and tetrakistriphenylphosphine palladium (0) (0.18 g, 5 mol % catalyst) in DME (10 cm^3) was stirred for 1 hour at room temperature. 2-Formylphenylboronic acid (0.46 g, 3.1 mmol), sodium carbonate (0.34 g, 3.2 mmol) and water (12 cm^3) were added and the mixture was refluxed for 3 hours. The solvents were removed *in vacuo* and water (20 cm^3) was added to the residue, followed by DCM (20 cm^3). The aqueous layer was extracted twice more with DCM (20 cm^3) and the combined organic layers were washed with water (20 cm^3), dried and the solvents removed *in vacuo*. Flash column chromatography (silica, hexane-ether, 9:1) of the residual brown oil gave (*E*)-2-(1-methyl-2-phenylbuta-1,3-dienyl)benzaldehyde as a pale yellow solid (0.44 g, 1.8 mmol, 58 %), mp 79-80 °C (dec); Found: M^+, 248.1201. $C_{18}H_{16}O$ requires M^+, 248.1201; δ_H (250 MHz, $CDCl_3$) 2.32 (3 H, s, CH_3), 4.83 (1 H, ddd, *J* 15.4, 1.6, 0.4, olefinic H-4a), 5.29 (1 H, ddd, *J* 10.7, 1.6, 0.5, olefinic H-4b), 6.83-7.40 (9 H, m, aromatic and olefinic H-3), 7.62-7.66 (1 H, m, aromatic), 10.09 (1 H, d, *J* 0.8, CHO); δ_C (63 MHz, $CDCl_3$) 21.6 (CH_3), 118.6 (CH_2), 126.3 (CH), 126.7 (CH), 127.6 (3 x CH, aromatic), 130.0 (CH), 130.2 (2 x CH, aromatic), 132.4 (quat), 133.0 (quat), 133.3 (CH), 134.6 (CH), 138.6 (quat), 139.8 (quat), 148.1 (quat), 191.7 (CH, CHO); ν_{max} (nujol)/cm^{-1} 1692.41 (CHO).

iii. (*E,E*)-2-[1-Methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl]benzaldehyde

A solution of (*E,E*)-4-bromo-3-phenyl-1-(pentafluorophenyl)penta-1,3-diene (1.0 g, 2.57 mmol) and tetrakis(triphenylphosphine) palladium (0) (0.15 g, 0.13 mmol, 5 % cat) in dry DME (15 cm^3) was stirred in the dark, under nitrogen, for 1 hour. 2-Formyl phenylboronic acid (0.43 g, 2.83 mmol), sodium carbonate (0.28 g, 2.64 mmol) and water (7 cm^3) were added and the mixture was heated to reflux for 30 minutes, then stirred at room temperature for 4 hours. The solvent was removed *in*

vacuo and the aqueous residue was extracted with DCM (3 x 30 cm^3). The combined organic extracts were washed with water (20 cm^3), dried and the solvent was removed *in vacuo*. Flash column chromatography (silica, gradient elution 0-10 % hexane-ether) of the residue gave (*E,E*)-2-[1-methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl]benzaldehyde as a colourless oil (0.86 g, 2.08 mmol, 81 %); Found: M^+, 414.1039. $C_{24}H_{15}F_5O$ requires M^+, 414.1043; δ_H (250 MHz, $CDCl_3$) 2.00 (3 H, s, CH_3), 5.80 (1 H, d, *J* 16.2, H-3), 6.93 (1 H, d, *J* 16.3, H-4), 7.25-7.55 (7 H, m, Ar-H), 7.69 (1 H, dt, *J* 7.5, 1.5, Ar-H), 8.01-8.05 (1 H, m, Ar-H), 10.20 (1 H, d, *J* 0.6, CHO); δ_C (63 MHz, $CDCl_3$) 24.38 (CH_3), 112.47 (m, quat *C*-CF), 115.65 (CH), 127.5 (CH), 128.0 (CH), 128.5 (CH), 128.6 (2 x CH, aromatic), 129.5 (CH), 129.5 (2 x CH, aromatic), 133.5 (quat), 134.2 (CH), 136.8 (CH, olefinic C-4), 137.4 (quat), 138.2 (quat), 140.1 (quat), 145.9 (quat, C-*C*HO), 191.4 (CH, CHO), 5 x quat C-F unobserved.

iv. (*E,E*)-2-[1-Methyl-2-phenyl-4-(*p*-methoxyphenyl)buta-1,3-dienyl]benzaldehyde

A solution of (*E,E*)-4-bromo-3-phenyl-1-(*p*-methoxyphenyl)penta-1,3-diene (0.4 g, 1.2 mmol) and tetrakistriphenylphosphine palladium (90 mg, 0.08 mmol, 7 mol %) in dry DME (20 cm^3) was stirred for 1 hour in the dark and under nitrogen. 2-Formyl phenylboronic acid (0.19 g, 1.3 mmol), sodium carbonate (0.15 g, 1.4 mmol) and water (8 cm^3) were added and the mixture was heated to reflux for 10 minutes and stirred overnight at room temperature. The solvent was removed *in vacuo* and water (20 cm^3) and DCM (40 cm^3) were added. The organic layer was separated and the aqueous phase was extracted with DCM (2 x 40 cm^3). The combined organic extracts were washed with water, dried and the solvent was removed *in vacuo*. The residue was dissolved in DCM (30 cm^3) and passed through an alumina pad. Flash column chromatography (silica, hexane-ether 10 %) gave (*E,E*)-2-[1-methyl-2-phenyl-4-(*p*-methoxyphenyl)buta-1,3-dienyl]benzaldehyde as a yellow oil (0.41 g, 1.16 mmol, 95 %); Found: $[M+H]^+$, 355.1698. $C_{25}H_{23}O_2$ requires $[M+H]^+$, 355.1698; δ_H (250 MHz, $CDCl_3$) 1.95 (3 H, s, CH_3-C), 3.72 (3 H, s, CH_3-O), 5.88 (1 H, d, *J* 5.8, H-4), 6.51 (1 H, dd, *J* 15.9, 0.4, H-3), 6.68 (2 H, d, *J* 8.8), 6.95 (2 H, dd,

J 8.8, 0.4), 7.25-7.53 (7 H, m, Ar-H), 7.68 (1 H, dt, *J* 7.5, 1.5, Ar-H), 8.04 (1 H, ddd, *J* 7.8, 1.5, 0.5), 10.24 (1 H, d, *J* 0.8, CHO); δ_C (63 MHz, $CDCl_3$) 24.33 (CH_3-C), 55.06 (CH_3-O), 113.7 (2 x CH, aromatic), 126.59, 126.99 (CH), 127.45 (2 x CH, aromatic), 127.51, 127.66 (CH), 128.34 (2 x CH, aromatic), 129.61 (2 x CH, aromatic), 129.95, 131.77 (CH), 132.44, 133.58 (quat), 134.17 (CH), 139.05, 140.47, 147.27, 158.94 (quat), 191.96 (CHO).

VIII. Synthesis of Diene-Conjugated *ortho*-Benzaldoximes

i. (*E,E*)-2-(4-Phenylbuta-1,3-dienyl)benzaldoxime (258)

(*E,E*)-2-(4-Phenylbuta-1,3-dienyl)benzaldehyde (**257**) (1.0 g, 4 mmol) was dissolved in ethanol (30 cm^3) and heated to *ca.* 35 °C. Sodium acetate (0.34 g, 4.14 mmol) in water (10 cm^3) was added to hydroxylamine hydrochloride (0.29 g, 4.17 mmol) in water (10 cm^3). This solution was added to the warmed aldehyde solution, upon which a light yellow solid was obtained. Partial removal of ethanol *in vacuo* and overnight refrigeration of the solution gave a pale yellow solid. This was recrystallised to give (*E,E*)-2-(4-phenylbuta-1,3-dienyl)benzaldoxime (**258**) as a white solid (0.61 g, 2.5 mmol, 65 %), mp 150-151.5 °C (cyclohexane-ethanol), lit. [94]150-152 °C; Found: $(M+H)^+$, 250.1226. $C_{17}H_{15}NO$ requires $(M+H)^+$, 250.1232; δ_H (200 MHz, $CDCl_3$) 6.64 (1 H, d, *J* 15.0, olefinic), 6.72-7.10 (3 H, m, olefinic), 7.16-7.40 (7 H, m, aromatic), 7.55 (2 H, dd, *J* 16.5, 7.1, aromatic), 7.68 (1 H, br. s, OH), 8.44 (1 H, s, CH=N); δ_C (63 MHz, $CDCl_3$/d_6-DMSO) 125.9 (CH), 126.1 (2 x CH), 127.2 (2 x CH), 127.5 (CH), 128.4 (3 x CH), 128.9 (CH), 129.3 (CH), 129.9 (quat), 131.7 (CH), 133.2 (CH), 136.1 (quat), 136.8 (quat), 148.0 (CH, CH=N); *m/z* (EI+) 250 (M+H, 100 %), 232 (M-OH, 74 %), 146 (13 %), 117 (9 %).

ii. (*E*)-2-(Buta-1,3-dienyl)benzaldoxime (273)

(*E*)-2-(Buta-1,3-dienyl)benzaldehyde (1.0 g, 6.3 mmol) was dissolved in ethanol (30 cm^3) and heated to *ca.* 35 °C. Sodium acetate (0.54 g, 6.6 mmol) in water (10 cm^3) was added to hydroxylamine hydrochloride (0.46 g, 6.6 mmol) in water (10 cm^3).

This solution was added to the warmed aldehyde solution and stirred at *ca.* 35 °C for 2 hours. Partial removal of ethanol *in vacuo* and overnight refrigeration of the solution gave a pale brown solid. This was recrystallised to give (*E*)-2-(buta-1,3-dienyl)benzaldoxime (**273**) as silver flakes (0.87 g, 5.1 mmol, 80 %), mp 148-150 °C (dec) (cyclohexane-ethanol); Found: $[M+H]^+$, 174.0915. $C_{11}H_{12}NO$ requires $[M+H]^+$, 174.0919; δ_H (250 MHz, $CDCl_3$) 5.19-5.52 (2 H, m, olefinic H-4a and b), 6.46-6.81 (2 H, m, olefinic H-2 and H-3), 6.93 (1 H, d, *J* 15.2, olefinic H-1), 7.14-7.40 (2 H, m, aromatic), 7.51-7.55 (1 H, m, aromatic), 7.66 (1 H, dd, *J* 7.7, 1.5, aromatic), 8.49 (1 H, s, CH=N), 8.76 (1 H, br. s, D_2O labile, OH); δ_C (63 MHz, $CDCl_3$) 118.7 ($=CH_2$), 126.5 (CH), 127.2 (CH), 127.6 (CH), 129.0 (CH), 129.0 (quat.), 129.8 (CH), 133.1 (CH), 136.5 (quat.), 136.8 (CH), 148.9 (CH=N); *m/z* (EI+) 174 (M+H, base peak), 156 (M-OH, 16 %).

iii. (*E,E*)-2-(Penta-1,3-dienyl)benzaldoxime (288)

A solution of (*E,E*)-2-(penta-1,3-dienyl)benzaldehyde (1.20 g, 7.0 mmol) in ethanol (50 cm^3) was warmed to approximately 40 °C and a solution of hydroxylamine hydrochloride (0.53 g, 7.70 mmol) and sodium acetate (0.63 g, 7.70 mmol) in water (10 cm^3) was added. This solution was stirred for 3 hours at 40 °C, after which the majority of the ethanol was removed *in vacuo*. The remaining solution was stored in a refrigerator overnight upon which a solid formed. This solid was recovered and the mother liquor was concentrated further and again stored in the cold to obtain a further crop of solid. The combined solids were recrystallised to give (*E,E*)-2-(penta-1,3-dienyl)benzaldoxime (**288**) as a cream coloured solid (0.98 g, 5.2 mmol, 74 %) mp 87.5-89 °C (ethanol); Found 76.83 % C, 6.99 % C, 7.48 % N, M^+, 187.0990. $C_{12}H_{13}NO$ requires 76.98 % C, 6.99 % H, 7.48 % N, M^+, 187.0997; δ_H (250 MHz, $CDCl_3$) 1.82 (3 H, dd, *J* 6.8, 1.5, CH_3), 5.87 (1 H, ddq, *J* 15.0, 0.6, 6.8, olefinic H-4), 6.25 (1 H, ddq, *J* 15.1, 9.8, 1.6, olefinic H-3), 6.62 (1 H, dd, *J* 15.5, 9.8, olefinic H-2), 6.75 (1 H, d, *J* 15.5, olefinic H-1), 7.20-7.88 (4 H, m, aromatic), 8.48 (1 H, s, *H*C=N), 8.75 (1 H, br. s, O*H*); δ_C (63 MHz, $CDCl_3$) 18.27 (CH_3), 125.82 (CH), 126.24 (CH), 127.04 (CH), 127.08 (CH), 128.76 (quat), 129.73 (CH),

131.57 (CH), 131.64 (CH), 132.90 (CH), 137.04 (quat), 148.96 (CH, HC=N); *m/z* 187 (M^+, 44 %), 170 (M^+-OH, 53 %), 146 (base peak).

iv. (*E,E*)-2-(1-Methyl-4-phenylbuta-1,3-dienyl)benzaldoxime

(E,E)-2-(1-Methyl-4-phenylbuta-1,3-dienyl)benzaldehyde (0.22 g, 0.9 mmol) was dissolved in ethanol (10 cm^3) and heated to *ca.* 35 °C. Sodium acetate (0.08 g, 1.0 mmol) in water (3 cm^3) was added to hydroxylamine hydrochloride (0.07 g, 1.0 mmol) in water (3 cm^3). This solution was added to the warmed aldehyde solution and stirred at room temperature for 1 hr. Partial removal of ethanol *in vacuo* and overnight refrigeration of the solution gave a white solid. Recrystallisation gave (*E,E*)-2-(1-methyl-4-phenylbuta-1,3-dienyl)benzaldoxime as a white solid (0.17 g, 0.65 mmol, 73 %), mp 99-100 °C (cyclohexane-ethanol); Found: $(M+H)^+$, 264.1377. $C_{18}H_{18}NO$ requires $(M+H)^+$, 264.1388; δ_H (250 MHz, $CDCl_3$) 2.21 (3 H, d, *J* 1.3, CH_3), 6.14 (1 H, dq, *J* 11.0, 1.3, olefinic H-2), 6.60 (1 H, d, *J* 15.5, olefinic H-4), 7.12 (1 H, dd, *J* 15.5, 11.0, olefinic H-3), 7.14-7.57 (8 H, m, aromatic), 7.79-7.85 (1 H, m, aromatic), 8.17 (1 H, br. s, D_2O labile, OH), 8.28 (1 H, s, CH=N); δ_C (63 MHz, $CDCl_3$) 19.2 (CH_3), 124.6 (CH), 126.1 (CH), 126.3 (2 x CH, aromatic), 127.1 (CH), 127.5 (CH), 128.3 (CH), 128.5 (2 x CH, aromatic), 128.8 (quat), 129.6 (CH), 131.7 (CH), 133.4 (CH), 135.8 (quat), 137.3 (quat), 145.2 (quat), 149.4 (CH, CH=N).

v. (*E,E*)-2-(1-Methylpenta-1,3-dienyl)benzaldoxime

Sodium acetate (0.39 g, 4.7 mmol) and hydroxylamine hydrochloride (0.33 g, 4.7 mmol) were dissolved in the minimum amount of water and this solution was added to (*E,E*)-2-(1-methylpenta-1,3-dienyl)benzaldehyde (0.84 g, 4.5 mmol) in ethanol (30 cm^3), with stirring. The mixture was warmed to *ca.* 35 °C and stirred at this temperature for 3 hours. The solvents were removed and the residue dissolved in DCM (75 cm^3) and the organic solution washed with water (2 x 40 cm^3) and dried. Removal of the solvents gave an oily residue which was purified by dry-flash column chromatography (silica, hexane-ether, gradient elution, 0-50 %) to give (*E,E*)-2-(1-methylpenta-1,3-dienyl)benzaldoxime as a white solid (0.66 g, 3.3 mmol, 73 %), mp

95-96 °C; Found: M^+, 201.1150. $C_{13}H_{15}NO$ requires M^+, 201.1154; δ_H (250 MHz, $CDCl_3$) 1.84 (3 H, ddd, C*H*$_3$CH=, *J* 6.7, 1.0, 0.5), 2.09 (3 H, t, *J* 0.6, CH_3), 5.78 (1 H, dq, *J* 15.0, 6.7, CH=C*H*CH$_3$), 5.92 (1 H, d, *J* 10.9, olefinic H-2), 6.40 (1 H, ddq, *J* 15.0, 10.9, 1.6, olefinic H-3), 7.20-7.38 (3 H, m, aromatic), 7.78-7.81 (1 H, m, aromatic), 8.29 (s, 1 H, C*H*=N), 9.16 (1 H, br. s, NO*H*); δ_C (63 MHz, $CDCl_3$) 18.38 (CH_3), 18.87 (CH_3), 125.97 (CH), 126.83 (CH), 127.45 (CH), 128.38 (CH), 128.78 (quat), 129.52 (CH), 130.89 (CH), 131.55 (CH), 132.30 (quat), 145.53 (quat *C*-CH=N), 149.60 (CH, H*C*=N).

vi. (*E*)-2-(1-Methylbuta-1,3-dienyl)benzaldoxime

A solution of sodium acetate (0.055 g, 0.66 mmol) in water (1 cm^3) was added to a solution of hydroxylamine hydrochloride (0.05 g, 0.7 mmol) in water (1 cm^3). This mixture was added to a solution of (*E*)-2-(1-methylbuta-1,3-dienyl)benzaldehyde (0.10 g, 0.58 mmol) in ethanol (10 cm^3) which was warmed to 40 °C. This solution was stirred with warming for 2 hours. The solvents were removed *in vacuo* and the residue was dissolved in DCM (20 cm^3). The organic solution was washed with water (2 x 10 cm^3) and the aqueous washings were extracted with DCM (2 x 20 cm^3). The combined organic extracts were washed with water (20 cm^3), dried and the solvent was removed *in vacuo*. Dry-flash column chromatography (silica, hexane-ether, gradient elution) gave (*E*)-2-(1-methylbuta-1,3-dienyl)benzaldoxime as a yellow oil which did not solidify (0.09 g, 0.48 mmol, 73 %); Found: M^+, 187.0990. $C_{12}H_{13}NO$ requires M^+, 187.0997; δ_H (250 MHz, $CDCl_3$) 2.10 (3 H, d, *J* 1.4, CH_3), 5.19-5.30 (2 H, m, olefinic =CH_2), 5.95 (1 H, dq, *J* 10.1, 1.4, olefinic H-2), 6.69 (1 H, ddd, *J* 16.8, 10.9, 10.2, C*H*=CH_2 H-3), 7.17-7.43 (4 H, m, aromatic), 7.77-7.81 (1 H, m, C*H*=N), 8.24 (1 H, br. S, O*H*); δ_C (63 MHz, $CDCl_3$) 19.13 (CH_3), 118.25 (CH_2), 125.95 (CH), 127.08 (CH), 128.29 (CH), 128.79 (quat), 129.55 (CH), 131.81 (CH), 132.51 (CH), 135.88 (quat), 145.10 (quat), 149.48 (CH, *C*H=N).

vii. (*E,E*)-2-(2-Methyl-4-phenylbuta-1,3-dienyl)benzaldoxime

A solution of sodium acetate (0.22 g, 3.33 mmol) in water (2 cm^3) was added to a solution of hydroxylamine hydrochloride (0.19 g, 2.73 mmol) in water (2 cm^3). This solution was added to a warmed (*ca.* 40 °C) solution of (*E,E*)-2-(2-methyl-4-phenylbuta-1,3-dienyl)benzaldehyde (0.65 g, 2.62 mmol) in ethanol (20 cm^3). The warm solution was stirred under a nitrogen atmosphere for 2 hours then concentrated to *ca.* half volume. The resulting suspension was filtered and the solid residue was recrystallised from ethanol to give (*E,E*)-2-(2-methyl-4-phenylbuta-1,3-dienyl)benzaldoxime (0.60 g, 2.28 mmol, 87 %) as colourless rhomboids, mp 112-114 °C; Found: M^+, 263.1312. $C_{18}H_{17}NO$ requires M^+, 263.1310; δ_H (250 MHz, $CDCl_3$) 1.94 (3 H, d, *J* 1.1, CH_3), 6.68 (1 H, d, *J* 16.1, trans =C*H*Ph), 6.75 (1 H, s, -C*H*=CMe), 7.02 (1 H, dd, *J* 16.1, 0.6, trans C*H*=CHPh), 7.22-7.51 (8 H, m, Ar-H), 7.78-7.81 (1 H, m, Ar-H), 8.35 (1 H, s, CH=N), 8.90 (1 H, br. s, OH); δ_C (63 MHz, $CDCl_3$) 13.9 (CH_3), 126.0 (CH), 126.4 (2 x Ar CH), 127.1, 127.4 (CH), 128.5 (2 x Ar CH), 128.7, 129.0, 129.3 (CH), 130.0 (quat), 130.1, 132.9 (CH), 137.2, 137.3, 137.9 (quat), 149.2 (CH=N); ν_{max}/cm^{-1} (nujol) 3281.7 (OH), 1716.0 (C=N).

viii. (*E,E*)-2-Carbaldoxime-3-(4-phenylbuta-1,3-dienyl)thiophene (394)

A solution of sodium acetate (0.34 g, 4.2 mmol) in water (2 cm^3) was added to a solution of hydroxylamine hydrochloride (0.30 g, 4.3 mmol) in water (2 cm^3) and this mixture was immediately added to a warmed (*ca.* 40 °C) solution of 2-formyl-3-(4-phenylbuta-1,3-dienyl)thiophene (0.98 g, 4.1 mmol) in methanol (100 cm^3). This mixture was stirred for 3 hours, after which the solution was concentrated to *ca.* ¼ volume *in vacuo*, giving a yellow precipitate. This was isolated at the pump and crystallised to give a pale yellow solid. The mother liquor was concentrated to give a second batch of *syn-* and *anti*-(*E,E*)-2-carbaldoxime-3-(4-phenylbuta-1,3-dienyl)thiophene (**394**) (0.85 g, 3.3 mmol, 81 %), mp 159-160.5 °C (ethanol); Found: M^+, 255.0718. $C_{15}H_{13}NOS$ requires M^+, 255.0718; δ_H (360 MHz, $CDCl_3/d_6$-DMSO) 6.34* (1 H, d, *J* 15.2, olefinic), 6.36$ (1 H, d, *J* 15.2, olefinic), 6.49-6.51 (1 H, m, olefinic), 6.53-6.70 (2 H, m, olefinic), 6.89-7.13 (7 H, m, aromatic), 7.61$ (1 H, s,

CH=N), 7.61* (1 H, s, CH=N), 10.74* (1 H, s, OH), 11.46$ (1 H, br. s, OH); δ_C (63 MHz, $CDCl_3/d_6$-DMSO) 124.07$ (CH), 124.22* (CH), 124.37$ (CH), 125.44* (CH), 126.60* (2 x CH aromatic), 127.94* (CH), 128.90* (2 x CH aromatic), 129.20* (CH), 129.27 (CH), 129.90 (CH), 131.33* (CH), 131.87 (CH), 131.92 (CH), 133.62* (CH), 133.73 (CH), 137.23* (quat), 137.92 (CH=N), 139.17* (quat), 140.25* (quat), 142.11* (CH=N); ν_{max}/cm^{-1} (nujol) 3313.6 (OH), 1710.1 (C=N), 1458.2 (C=C).

* Denotes major isomer signals. $ Denotes minor isomer. Where there is no symbol, signals from both isomers coincide.

ix. (*E,E*)- and (*Z,E*)-2-Carbaldoxime-3-(penta-1,3-dienyl)thiophene (403)

Sodium acetate (0.43 g, 5.2 mmol) in water (3 cm^3) was added to hydroxylamine hydrochloride (0.37 g, 5.3 mmol) in water (3 cm^3) and this mixture was added to a solution of (*E,E*)- and (*Z,E*)-2-carbaldehyde-3-(penta-1,3-dienyl)thiophene (0.90 g, 5.1 mmol) in ethanol (40 cm^3). The reaction mixture was stirred at *ca.* 40 °C under nitrogen for 90 minutes. The solvent was removed *in vacuo* and the product was extracted into DCM (2 x 40 cm^3), the combined extracts being washed with water (40 cm^3) and dried. Removal of the solvent *in vacuo* and flash column chromatography (silica, 30 % hexane-ether) gave *syn*- and *anti*-(*E,E*)- and (*Z,E*)-2-carbaldoxime-3-(penta-1,3-dienyl)thiophene (**403**) as an oil which could not be crystallised (0.84 g, 4.4 mmol, 84 %); Found: M^+, 193.0563. $C_{10}H_{11}NOS$ requires M^+, 193.0561; δ_H (250 MHz, $CDCl_3$) 1.65-1.73 (3 H, m, CH_3), 5.68-5.85 (1 H, m, C*H*CH_3), 6.05-6.36 (2 H, m, olefinic), 6.46-6.64 (1 H, m, olefinic), 6.95-7.48 (2 H, m, thienyl), 7.63$ (1 H, d, *J* 0.8, CH=N), 7.78* (1 H, s, CH=N), OH unobserved due to broadening; δ_C (63 MHz, $CDCl_3$) 18.8 (CH_3), 120.1$, 121.6*, 124.3* (CH, olefinic), 125.5*, 126.7$ (quat), 128.3$, 128.3$, 129.7$, 130.1*, 132.0*, 132.1*, 132.6*, 133.1$, 133.8$ (CH, olefinic and thienyl), 138.6*, 139.6$ (CH=N), 140.5$, 141.2* (quat). * Denotes major isomer, $ denotes minor isomer. No symbol is used where signals coincide.

IX. Synthesis of Diene-Conjugated Benzyl- and Thienylbenzamides

i. (*E,E*)-*N*-[2-(4-Phenylbuta-1,3-dienyl)benzyl]benzamide (262)

A mixture of (*E,E*)-2-(4-phenylbuta-1,3-dienyl)benzaldoxime (**258**) (0.4 g, 1.6 mmol), ammonium acetate (0.136 g, 1.8 mmol), zinc dust (0.79 g, 0.012 g-atom), conc. aqueous ammonia (0.88 s.g., 12 cm^3) and ethanol (4 cm^3) was heated at reflux overnight. The solvents were removed *in vacuo* and the solid residue was stirred with aqueous potassium hydroxide (33 %, 20 cm^3) for 1 hour. Ether (20 cm^3) was added and the mixture was filtered through a celite pad. The ether layer was separated, dried and the ether removed *in vacuo* to yield (*E,E*)-2-(4-phenylbuta-1,3-dienyl)benzylamine (**261**) (0.28 g crude) as a white solid. δ_H (200 MHz, $CDCl_3$) 1.38 (2 H, br. s, NH_2), 3.89 (2 H, s, CH_2), 6.61 (1 H, d, *J* 15.7, olefinic H-4), 6.83-7.55 (12 H, m, olefinic and aromatic). No purification of the amine was attempted and it was immediately taken on to the next stage.

Sodium carbonate (0.435 g, 4.1 mmol) was added to a solution of crude (*E,E*)-2-(4-phenylbuta-1,3-dienyl)benzylamine (**261**) (0.26 g) in DCM (10 cm^3) and benzoyl chloride (0.24 g, 1.7 mmol) was added dropwise with stirring. The solution was refluxed for 3 hours and stirred overnight at room temperature under dry nitrogen. Water (5 cm^3) was added and the mixture stirred for 1 hour, upon which aqueous sodium hydroxide (5 M, 10 cm^3) was added and the solution was stirred for a further 30 minutes. The layers were separated, the aqueous phase was extracted with DCM (10 cm^3) and the combined organics were washed with water (2 x 20 cm^3) and dried. The solvent was removed *in vacuo* to yield an off-white solid. Recrystallisation by adding a few drops of hexane to a hot ethanolic solution of the crude product gave (*E,E*)-*N*-[2-(4-phenylbuta-1,3-dienyl)benzyl]benzamide (**262**) as white needles (0.27 g, 0.8 mmol, 50 % based on oxime), mp 174-175 °C (ethanol-hexane), lit.[94] 174.5-175.5 °C; Found: M^+, 339.1619. $C_{24}H_{21}NO$ requires M^+, 339.1623; δ_H (200 MHz, d_6-DMSO) 4.65 (2 H, d, *J* 5.5, CH_2), 6.72 (1 H, d, *J* 14.4, olefinic), 6.88-7.65 (15 H, m, olefinic and aromatic), 7.94 (2 H, m, aromatic), 8.88 (1 H, br. t, *J* 5.5, D_2O labile, NH); δ_C (63 MHz, d_6-DMSO) 39.2 (CH_2), 123.3 (CH), 124.5 (2 x CH), 125.5 (CH),

125.6 (3 x CH), 125.8 (CH), 126.3 (2 x CH), 126.8 (2 x CH), 126.9 (CH), 127.7 (CH), 127.8 (CH), 129.1 (CH), 129.3 (CH), 131.0 (CH), 132.7 (quat), 133.7 (quat), 134.4 (quat), 135.2 (quat), 164.8 (quat, C=O).

ii. (*E*)-*N*-[2-(Buta-1,3-dienyl)benzyl]benzamide (274)

(*E*)-2-(Buta-1,3-dienyl)benzaldoxime (**273**) (1.0 g, 5.78 mmol), ammonium acetate (0.53 g, 6.9 mmol) and zinc powder (2.45 g, 38 mmol), conc. aqueous ammonia solution (0.88 s.g., 40 cm^3) and ethanol (15 cm^3) were heated to reflux for 4 hours under a dry nitrogen atmosphere. The solvents were removed *in vacuo* and the residue was stirred with aqueous potassium hydroxide (33 % w/v, 40 cm^3) for 1 hour. The suspension was filtered through a celite pad the layers separated and the aqueous phase extracted with ether (2 x 30 cm^3). The combined organics were washed with water, dried and the solvent was removed *in vacuo* to yield (*E*)-2-(buta-1,3-dienyl)benzylamine an orange-red oil (0.6 g) which was taken through to the next stage without purification. δ_H (200 MHz, $CDCl_3$) 1.21 (2 H, br. s, NH_2), 3.86 (2 H, s, CH_2), 5.17-5.49 (2 H, m, $=CH_2$), 6.48-6.82 (3 H, m, olefinic), 7.12-7.30 (3 H, m, aromatic), 7.42-7.51 (1 H, m, aromatic); *m/z* (EI+) 160 (32 %, M+H), 143 (70 %, M-NH_2), 91 (base peak)

Sodium carbonate (1.5 g, 14 mmol) was added to a solution of (*E*)-2-(buta-1,3-dienyl)benzylamine (0.57 g, 3.6 mmol) in DCM (25 cm^3). Benzoyl chloride (0.72 g, 5.1 mmol) was added dropwise with stirring and the solution was heated at reflux for 3 hrs under dry nitrogen. Water (10 cm^3) was added and the mixture stirred for 1 hr, upon which aqueous sodium hydroxide (5 M, 10 cm^3) was added and the solution was stirred for a further 30 minutes. The layers were separated, the aqueous phase was extracted with DCM (10 cm^3) and the combined organics were washed with water (2 x 20 cm^3) and dried. The solvent was removed *in vacuo* at room temperature to yield an orange-red oil, dry flash column chromatography (silica, 1:1 hexane-ether) of which furnished white needles of (*E*)-*N*-[2-(buta-1,3-dienyl)benzyl]benzamide (**274**) (0.79 g, 0.30 mmol, 83 %), mp 134-135 °C (hexane-ethanol); Found: $[M+H]^+$, 264.1389. $C_{18}H_{18}NO$ requires $[M+H]^+$, 264.1388; δ_H (250

MHz, $CDCl_3$) 4.70 (2 H, d, *J* 5.2, CH_2N), 5.16-5.21, (2 H, dd, *J* 10.0, 1.5, olefinic), 6.18 (1 H, br. s, NH), 6.44-6.59 (3 H, m, olefinic), 7.20-7.51 (6 H, m, aromatic), 7.56-7.60 (1 H, dd, *J* 7.8, 1.5, aromatic), 7.71-7.76 (2 H, m, aromatic), δ_C (63 MHz, $CDCl_3$) 42.2 (CH_2N), 118.3 (=CH_2), 125.9 (CH), 126.8 (2 x CH, aromatic), 127.7, 128.1 (CH), 128.4 (2 x CH, aromatic), 129.0, 129.5, 131.4, 132.1 (CH), 134.2, 134.8, 136.2 (quat), 137.0 (CH), 167.0 (quat, C=O).

iii. (*E,E*)-*N*-[2-(Penta-1,3-dienyl)benzyl]benzamide (289)

A mixture of (*E,E*)-2-(penta-1,3-dienyl)benzaldoxime (**288**) (0.50 g, 2.6 mmol), ammonium acetate (0.23 g, 3.0 mmol), zinc dust (1.30 g, 0.02 g-atom), ammonia solution (20 cm^3, 0.88 s.g.) and ethanol (7 cm^3) was heated to reflux for 45 minutes. After cooling to room temperature the solvents were removed *in vacuo* and potassium hydroxide solution (33 % w/v, 25 cm^3) was added to the residue and this mixture was stirred for 15 minutes, after which ether (40 cm^3) was added and the mixture was filtered through a celite pad. The aqueous layer was extracted with ether (2 x 50 cm^3) and the combined organics were washed with water (2 x 10 cm^3) and dried. Removal of the solvent *in vacuo* gave (*E,E*)-2-(penta-1,3-dienyl)benzylamine (**298**) as a red oil (0.27 g), which was taken onto the next stage without further purification. Found: M^+, 173.1209. $C_{12}H_{15}N$ requires M^+, 173.1205; δ_H (250 MHz, $CDCl_3$) 1.43 (2 H, br. s, NH_2), 1.82 (3 H, dd, *J* 6.8, 1.6, CH_3), 3.90 (2 H, s, CH_2N), 5.85 (1 H, dq, *J* 15.0, 6.8, =C*H*CH_3), 6.21-6.32 (1 H, m, C*H*=$CHCH_3$), 6.68-6.71 (2 H, m, Ar-C*H*=C*H*-), 7.15-7.28 (3 H, m, Ar-H), 7.47-7.52 (1 H, m, Ar-H); δ_C (63 MHz, $CDCl_3$) 18.24 (CH_3), 44.2 (CH_2), 125.4, 126.1, 127.1, 127.2, 128.0, 130.6, 131.3, 131.9 (aromatic and olefinic CH), 135.7, 140.1 (aromatic quat); ν_{max}/cm^{-1} (film) 3372.8, 3303.2 (NH_2), 1480.1, 1447.8 (C=C).

The oil obtained above was dissolved in DCM (15 cm^3) and sodium carbonate (0.65 g, 6.10 mmol) and benzoyl chloride (0.30 g, 2.14 mmol) were added. This mixture was heated to reflux for 3 hours. After cooling, water (5 cm^3) was added, followed 30 minutes later by sodium hydroxide solution (5 M, 20 cm^3). This mixture was stirred for a further 30 minutes, then the layers were separated and the aqueous layer

was extracted with DCM (2 x 50 cm^3) and the combined organic extracts were washed with water (20 cm^3) and dried. The solvent was removed *in vacuo* leaving an oily residue. Dry-flash column chromatography (silica, hexane-ether, gradient elution) gave (*E,E*)-*N*-[2-(penta-1,3-dienyl)benzyl]benzamide (**289**) as a white solid (0.47 g, 1.7 mmol, 65 % from oxime), mp 140-141 °C (ethanol-hexane); Found: M^+, 277.1462. $C_{19}H_{19}NO$ requires M^+, 277.1467; δ_H (250 MHz, $CDCl_3$) 1.79 (3 H, dd, *J* 6.7, 1.5, CH_3), 4.65 (2 H, d, *J* 5.2, CH_2), 5.83 (1 H, dq, *J* 15.1, 6.8, olefinic H-4), 6.23 (1 H, m, olefinic H-3), 6.39 (1 H, br. t, NH), 6.68 (2 H, m, olefinic H-2 and H-1), 7.15–7.55 (7 H, m, aromatic), 7.71–7.76 (2 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 18.18 (CH_3), 42.18 (CH_2), 125.50 (CH), 125.70 (CH), 126.80 (2 x CH), 127.17 (CH), 128.00 (CH), 128.35 (2 x CH), 129.45 (CH), 131.04 (CH), 131.27 (CH), 131.77 (CH), 131.82 (CH), 134.20 (quat), 134.3 (quat), 136.61 (quat), 167.03 (quat, C=O).

iv. (*E,E*)-*N*-[2-(Penta-1,3-dienyl)benzyl]-*o*-toluamide (299)

A mixture of (*E,E*)-2-(penta-1,3-dienyl)benzylamine (**298**) (0.8 g, 4.6 mmol), sodium carbonate (0.53 g, 5.0 mmol) and *o*-toluoyl chloride (0.77 g, 5.0 mmol) in DCM (25 cm^3) was heated to reflux under nitrogen for 3 hours. Water (15 cm^3) was added to the cool solution and this was stirred for 30 minutes, after which sodium hydroxide solution (5 M, 10 cm^3) was added. After a further 30 minutes stirring the phases were separated and the aqueous layer was extracted with DCM (3 x 30 cm^3) and the combined extracts were washed with water (30 cm^3). Dry-flash column chromatography (silica, hexane-ether, gradient elution) gave (*E,E*)-*N*-[2-(penta-1,3-dienyl)benzyl]-*o*-toluamide (**299**) as a white solid (1.10 g, 3.6 mmol, 78 %), mp 138-139 °C (ethanol-hexane); Found: M^+, 291.1621. $C_{20}H_{21}NO$ requires M^+, 291.1623; δ_H (250 MHz, d_6-DMSO) 1.77 (3 H, dd, CH_3CH=, *J* 6.8, 1.5, CH_3), 2.30 (3 H, s, Ar-CH_3), 4.48 (2 H, d, *J* 5.8, CH_2-N), 5.88 (1 H, dq, *J* 15.1, 6.8, olefinic H-1), 6.20-6.31 (1 H, m, olefinic), 6.71-6.80 (1 H, m, olefinic), 7.16-7.34 (8 H, m, aromatic), 7.55-7.58 (1 H, m, aromatic), 8.70 (1 H, br. t, *J* 5.7, NH); δ_C (63 MHz, d_6-DMSO) 18.57 (CH_3), 19.72 (CH_3), 41.02 (CH_2), 125.27, 125.91, 126.74, 127.39, 127.43, 127.79, 129.22, 129.78, 130.85, 131.01, 131.26, 132.59 (CH), 135.59, 135.95, 136.15, 137.23 (quat), 169.42 (quat, C=O).

v. (*E,E*)-*N*-[2-(1-Methyl-4-phenylbuta-1,3-dienyl)benzyl]benzamide (326)

(*E,E*)-2-(1-Methyl-4-phenylbuta-1,3-dienyl)benzaldoxime (0.16 g, 0.38 mmol), ammonium acetate (0.06 g, 0.72 mmol) and zinc powder (0.32 g, 5.0 x 10^{-3} g-atom), conc. aqueous ammonia solution (0.88 s.g., 5 cm^3) and ethanol (3 cm^3) were heated to reflux for 3.5 hours under a dry nitrogen atmosphere. The solvents were removed *in vacuo* and the residue was stirred with aqueous potassium hydroxide (33 % w/v, 10 cm^3) for 1 hour. The suspension was filtered through a celite pad the layers separated and the aqueous phase extracted with ether (2 x 20 cm^3). The combined organics were washed with water, dried and the solvent was removed *in vacuo* to yield (*E,E*)-2-(1-methyl-4-phenylbuta-1,3-dienyl)benzylamine as an off-white solid (0.12 g) which was taken through to the next stage without purification. δ_H (200 MHz, $CDCl_3$) 1.15 (2 H, br. s, NH_2), 2.13 (3 H, s, CH_3), 3.79 (2 H, s, CH_2), 6.09 (1 H, d, *J* 11.3, olefinic), 6.48 (1 H, d, *J* 16.0, olefinic), 7.00-7.40 (9 H, m, aromatic and olefinic); δ_C (63 MHz, $CDCl_3$) 19.2 (CH_3), 44.1 (CH_2), 124.9 (CH), 126.2 (2 x CH, phenyl), 126.6 (CH), 127.2 (CH), 127.3 (CH), 127.8 (CH), 128.3 (CH), 128.5 (2 x CH, phenyl), 129.4 (CH), 132.4 (CH), 137.4 (quat), 138.0 (quat), 140.1 (quat), 144.1 (quat).

Sodium carbonate (0.22 g, 2.0 mmol) was added to a solution of 2-(1-methyl-4-phenylbuta-1,3-dienyl)benzylamine (0.11 g, 0.44 mmol) in DCM (10 cm^3). Benzoyl chloride (0.1 g, 0.7 mmol) was added dropwise with stirring and the solution was refluxed for 3 hrs under dry nitrogen. Water (10 cm^3) was added and the mixture stirred for 1 hr, upon which aqueous sodium hydroxide (5 M, 10 cm^3) was added and the solution was stirred for a further 30 minutes. The layers were separated, the aqueous phase was extracted with DCM (10 cm^3) and the combined organics washed with water (2 x 20 cm^3). The solvent was removed *in vacuo* at room temperature to give a pale red solid which was recrystallised from ether-hexane to give (*E,E*)-*N*-[2-[(1-methyl-4-phenylbuta-1,3-dienyl)benzyl]benzamide (**326**) as a white solid (0.09 g, 0.26 mmol, 67 % from oxime), mp 136-137 °C (ether-hexane); Found: $(M+H)^+$, 354.1866. $C_{25}H_{24}NO$ requires $(M+H)^+$, 354.1858; δ_H (250 MHz, $CDCl_3$) 2.22 (3 H,

d, *J* 1.0, CH_3), 4.67 (2 H, d, *J* 5.5, CH_2), 6.18 (1 H, dq, *J* 11.0, olefinic H-2), 6.55 (1 H, d, *J* 15.5, olefinic H-4), 6.63 (1 H, br. t, *J* 5.2, NH), 7.13 (1 H, dd, *J* 15.5, 11.0, olefinic H-3), 7.20-7.50 (12 H, m, aromatic), 7.75-7.8 (2 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 18.9 (CH_3), 41.9 (CH_2), 124.6 (CH), 126.2 (2 x CH, aromatic), 126.8 (2 x CH, aromatic), 127.2 (CH), 127.3 (CH), 127.4 (CH), 128.3 (2 x CH, aromatic), 128.4 (CH), 128.5 (2 x CH, aromatic), 128.6 (CH), 130.0 (CH), 131.3 (CH), 132.9 (CH), 134.2 (quat.), 134.6 (quat.), 137.2 (quat.), 137.6 (quat.), 144.6 (quat.), 167.0 (quat.).

vi. (*E,E*)-*N*-[2-(1-Methylpenta-1,3-dienyl)benzyl]benzamide (338)

A mixture of (*E,E*)-2-(1-methylpenta-1,3-dienyl)benzaldoxime (0.60 g, 3.0 mmol), zinc dust (1.27 g, 0.02 g-atom), ammonium acetate (0.28 g, 3.7 mmol), ammonia solution (21 cm^3, 0.88 s.g.) and ethanol (8 cm^3) was heated to reflux for 30 minutes, under a nitrogen atmosphere. Once cool, the solvents were removed *in vacuo* and the residue treated with potassium hydroxide solution (33 % w/v, 40 cm^3). Ether (50 cm^3) was added and the mixture was filtered through a celite pad. The aqueous phase was extracted with DCM (3 x 50 cm^3), washed with water (20 cm^3), dried and then the solvents were removed *in vacuo*. (*E,E*)-2-(1-Methylpenta-1,3-dienyl)benzylamine was obtained as a white oil (0.35 g); δ_H (250 MHz, $CDCl_3$) 1.82 (3 H, dd, *J* 6.8, 1.4, CH_3CH=), 1.94 (2 H, br. s, NH_2), 2.06 (3 H, s, CH_3), 3.75 (2 H, s, CH_2), 5.71 (1 H, dq, *J* 15.0, 6.8, olefinic H-4), 5.92 (1 H, d, *J* 10.8, olefinic H-2), 6.39 (1 H, ddq, *J* 15.0, 11.1, 1.7, olefinic H-3), 7.07-7.38 (4 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 13.51 (CH_3), 18.85 (CH_3), 44.04 (CH_2), 126.54 (CH), 126.93 (CH), 127.55 (CH), 127.68 (CH), 128.42 (CH), 129.16 (CH), 129.75 (CH), 134.40 (quat), 140.00 (quat), 144.37 (quat). This was used in the next stage without further purification.

The crude product from the section above (0.35 g) was dissolved in DCM (15 cm^3) and sodium carbonate (0.77 g, 7.3 mmol) and benzoyl chloride (0.39 g, 2.8 mmol) were added. This mixture was heated to reflux under nitrogen for 3 hours. Once cool, water (5 cm^3), then sodium hydroxide solution (5 M, 20 cm^3) were added and

the solution was stirred for 30 minutes. The aqueous layer was extracted with DCM (2 x 50 cm^3) and the combined organics were washed with water and dried. The solvents were removed *in vacuo* to yield a light-brown oil. Dry-flash column chromatography (silica, hexane-ether, gradient elution, 0-50 %) gave (*E,E*)-*N*-[2-(1-methylpenta-1,3-dienyl)benzyl]benzamide (**338**) as a white solid (0.32 g, 1.1 mmol, 37 % from oxime) mp 125-127 °C (ethanol-hexane); Found: M^+, 291.1620. $C_{20}H_{21}NO$ requires M^+, 291.1623; δ_H (250 MHz, $CDCl_3$) 1.82 (3 H, ddd, *J* 6.7, 0.5, 0.5, CH_3CH=), 2.08 (3 H, s, CH_3), 4.63 (2 H, d, *J* 5.5, CH_2), 5.70 (1 H, dq, *J* 15.2, 6.7, olefinic H-4), 5.96 (1 H, d, *J* 10.9, olefinic H-2), 6.33-6.45 (2 H, m, olefinic H-3 and NH), 7.13-7.51 (7 H, m, aromatic), 7.69-7.77 (2 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 18.38 (CH_3), 18.66 (CH_3), 42.14 (CH_2), 126.79 (2 x CH, aromatic), 127.09 (CH), 127.43 (2 x CH), 128.43 (2 x CH, aromatic), 128.64 (CH), 128.74 (CH), 129.80 (CH), 130.36 (CH), 131.35 (CH), 134.13 (quat), 134.28 (quat), 134.57 (quat), 145.00 (quat), 167.07 (quat C=O).

vii. (*E*)-*N*-[2-(1-Methylbuta-1,3-dienyl)benzyl]benzamide (343)

A mixture of (*E*)-2-(1-methylbuta-1,3-dienyl)benzaldoxime (0.09 g, 0.45 mmol), zinc dust, (0.3 g, 4.6 g-atom), ammonium acetate (0.05 g, 3.9 mmol), ammonia solution (5.0 cm^3, 0.88 s.g.) and ethanol (2.0 cm^3) was heated to reflux under a nitrogen atmosphere for 45 minutes. Once cool, the solvents were removed *in vacuo* and potassium hydroxide solution (33 % w/v, 3 cm^3) was added to the solid grey residue and the mixture was stirred for 30 minutes. Ether (10 cm^3) was added and the mixture was filtered through a celite pad. The aqueous layer was extracted with ether (2 x 10 cm^3), the combined extracts were dried and the solvent was removed *in vacuo* to leave an oil. This oil was dissolved in DCM (15 cm^3) and sodium carbonate (0.3 g, 2.8 mmol) and benzoyl chloride (0.12 g, 0.85 mmol) were added. This mixture was heated to reflux for 3 hours and stirred at room temperature overnight. Water (5.0 cm^3) was added, followed 30 minutes later by sodium hydroxide solution (5 M, 5 cm^3). The aqueous layer was extracted with DCM (2 x 15 cm^3) and the combined extracts were washed with water (15 cm^3) and dried. Removal of the solvent *in vacuo* gave an oil which was purified by dry-flash column

chromatography (silica, hexane-ether, gradient elution, 0-50 %) to give (*E*)-*N*-[2-(1-methylbuta-1,3-dienyl)benzyl]benzamide (**343**) (0.10 g, 0.36 mmol, 80 % from oxime) mp 110-111 °C (ethanol-hexane); Found: $[M+H]^+$, 278.1545. $C_{19}H_{20}NO$ requires $[M+H]^+$, 278.1545; δ_H (250 MHz, $CDCl_3$) 2.09 (3 H, d, *J* 1.4, CH_3), 4.60 (2 H, d, *J* 5.5, CH_2), 5.16-5.25 (2 H, m, olefinic H-4a and H-4b), 5.99 (1 H, ddq, *J* 11.0, 1.4, olefinic H-2), 6.69 (1 H, ddd, *J* 16.6, 11.0, 10.4, olefinic H-3), 6.79 (1 H, br. t, NH), 7.12-7.49 (7 H, m, aromatic), 7.71-7.77 (2 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 18.66 (CH_3), 41.75 (CH_2), 119.56 (CH_2), 126.74 (2 x CH), 127.10 (CH), 127.18 (CH), 128.24 (3 x CH), 128.33 (CH), 130.12 (CH), 131.16 (CH), 132.47 (CH), 134.09 (quat), 134.49 (quat), 137.43 (quat), 144.33 (quat), 167.07 (quat, C=O).

viii. (*E,E*)-*N*-[2-(2-Methyl-4-phenylbuta-1,3-dienyl)benzyl]benzamide (372)

A solution of (*E,E*)-2-(2-methyl-4-phenylbuta-1,3-dienyl)benzaldoxime (0.54 g, 2.05 mmol), zinc dust (1.8 g, 0.028 g-atom) and ammonium acetate (0.30 g, 3.9 mmol) in ethanol (12 cm^3) and ammonia solution (0.88 s.g., 30 cm^3) was heated at reflux under nitrogen for 2 hours. The solution was allowed to cool and the solvents were removed *in vacuo*. The residue was stirred with potassium hydroxide solution (33 % w/w, 15 cm^3) for 30 minutes, ether (40 cm^3) was added and the mixture was filtered through a celite pad. The aqueous phase was extracted with ether (2 x 40 cm^3) and the combined extracts were washed with water (25 cm^3), dried, and the solvents were removed *in vacuo*. (*E,E*)-2-(2-Methyl-4-phenylbuta-1,3-dienyl)benzylamine was obtained as a red oil (0.49 g, 1.98 mmol, 97 %) which was benzoylated without further purification; Found: M^+, 249.1520. $C_{18}H_{19}N$ requires M^+, 249.1518; δ_H (250 MHz, $CDCl_3$) 1.48 (2 H, br.s, NH_2), 2.00 (3 H, d, *J* 1.2, CH_3), 3.86 (2 H, s, CH_2N), 6.67 (1 H, d, *J* 16.1, *trans* CH=C*H*Ph), 6.77 (1 H, s, C*H*=CMe), 7.04 (1 H, dd, *J* 16.1, 0.8, *trans* C*H*=CHPh), 7.13-7.51 (9 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 13.8 (CH_3), 42.1 (CH_2), 126.3 (2 x CH), 127.3 (2 x CH), 128.1 (CH), 128.5 (3 x CH), 129.8 (2 x CH), 133.3 (CH), 135.9, 136.7, 137.3, 141.5 (quat); ν_{max} (neat) 3375.4, 3304.2 cm^{-1} (NH_2); 1596.6, 1493.3 cm^{-1} (C=C).

A solution of crude (*E,E*)-2-(2-methyl-4-phenylbuta-1,3-dienyl)benzylamine (0.44 g), sodium carbonate (0.29 g, 2.72 mmol) and benzoyl chloride (0.33 g, 2.37 mmol) in DCM (25 cm^3) was heated to reflux under nitrogen for 2 hours then stirred overnight at room temperature. Water (10 cm^3) was added and the solution was stirred for 15 minutes, after which potassium hydroxide solution (10 cm^3, 33 % w/w) was added and the solution was stirred for a further 15 minutes. The aqueous phase was extracted with DCM (2 x 30 cm^3), the combined extracts were washed with water (2 x 25 cm^3), dried, then the solvent was removed *in vacuo* to give a beige oil. Flash column chromatography (silica, 25-50 % hexane-ether) gave a white foam which crystallised from hexane-ethanol to give (*E,E*)-*N*-[2-(2-methyl-4-phenylbuta-1,3-dienyl)benzyl]benzamide (**372**) as a white solid (0.35 g, 0.99 mmol, 48 % from oxime) mp 113-113.5 °C (ethanol); Found 84.78 % C, 6.62 % H, 3.96 % N, M^+, 353.1774. $C_{25}H_{23}NO$ requires 84.96 % C, 6.62 % H, 3.96 % N, M^+, 353.1780; δ_H (250 MHz, $CDCl_3$) 1.98 (3 H, d, *J* 1.2, CH_3), 4.64 (2 H, d, *J* 5.5, CH_2N), 6.51 (1 H, br. t, NH), 6.65 (1 H, d, *J* 16.1, *trans* =CHPh), 6.76 (1 H, s, C*H*=CMe), 7.01 (1 H, dd, *J* 16.1, 0.7, *trans* C*H*=CHPh), 7.21-7.66 (12 H, m, Ar-H), 7.72-7.77 (2 H, m, Ar-H); δ_C (63 MHz, $CDCl_3$) 13.8 (CH_3), 42.1 (CH_2), 126.3 (2 x CH), 126.7 (2 x CH), 127.1 (CH), 127.2 (CH), 127.3 (CH), 128.3 (2 x CH), 128.4 (2 x CH), 128.5 (2 x CH), 129.5 (CH), 129.9 (CH), 131.3 (CH), 133.0 (CH), 134.2 (quat), 136.1 (quat), 136.5 (quat), 137.1 (quat), 137.2 (quat), 167.1 (quat, C=O); *m/z* 353 (1 %, M^+), 249 (1 %, M-COPh), 232 (3 %, M-H_2NCOPh), 105 (16 %), 86 (base peak).

ix. (*E,E*)-*N*-Benzoyl-2-aminomethyl-3-(4-phenylbuta-1,3-dienyl)thiophene (395)

A mixture of (*E,E*)-2-carbaldoxime-3-(4-phenylbuta-1,3-dienyl)thiophene (**394**) (0.77 g, 3.0 mmol), zinc dust (1.3 g, 0.02 g-atom), aqueous ammonia solution (40 cm^3, 0.88 s.g.), ammonium acetate (3.9 mmol) and ethanol (30 cm^3) was heated at reflux under nitrogen for 90 minutes. The solvents were removed *in vacuo* and the residue was stirred with potassium hydroxide solution (40 cm^3, 33 % w/w) for 15 minutes. Ether was added and the mixture was filtered through a celite pad. The aqueous phase was extracted with ether (2 x 50 cm^3), washed with potassium

hydroxide solution (30 cm^3, 33 % w/w) and dried. The solvent was removed *in vacuo*, affording (*E,E*)-2-aminomethyl-3-(4-phenylbuta-1,3-dienyl)thiophene as a yellow solid (0.58 g, 2.4 mmol, 80 %); Found 241.0926. $C_{15}H_{15}NS$ requires 241.0925; δ_H (250 MHz, $CDCl_3$) 1.56 (2 H, br. s, NH_2), 4.09 (2 H, s, CH_2), 6.60-6.82 (3 H, m, olefinic), 6.94 (1 H, ddd, *J* 15.3, 9.1, 0.9, olefinic), 7.14 (1 H, dd, *J* 5.3, 0.4), 7.22 (1 H, d, *J* 5.4), 7.23-7.45 (5 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 39.0 (CH_2), 123.1, 124.5, 125.2 (CH), 126.1 (2 x CH, aromatic), 127.3 (CH), 128.5 (2 x CH, aromatic), 129.2, 129.3, 132.2 (CH), 134.6, 137.2, 142.9 (quat). Further purification of this compound was not attempted and the crude product was used immediately in the next stage. Neither ^1H nor ^{13}C NMR spectroscopy showed any impurities and all signals in the ^1H NMR spectrum integrated correctly.

A solution of (*E,E*)-2-aminomethyl-3-(4-phenylbuta-1,3-dienyl)thiophene (0.53 g, 2.2 mmol), benzoyl chloride (0.40 g, 2.8 mmol) and sodium carbonate (0.30 g, 2.8 mmol) in DCM (40 cm^3) was heated at reflux under nitrogen for 1 hour and stirred at room temperature overnight. Water (20 cm^3) was added followed after 15 minutes by sodium hydroxide solution (20 cm^3, 5 M). The aqueous phase was extracted with DCM (2 x 40 cm^3) and the extracts were washed with water, dried, and the solvent was removed *in vacuo*, yielding a yellow solid. Crystallisation furnished beige needles and concentration of the mother liquor gave a second crop of (*E,E*)-*N*-benzoyl-2-aminomethyl-3-(4-phenylbuta-1,3-dienyl)thiophene (**395**) (0.68 g, 2.0 mmol, 91 %), mp 188.5-190 °C (ethanol); Found: M^+, 345.1187. $C_{22}H_{19}NOS$ requires M^+, 345.1187; δ_H (250 MHz, d_6-DMSO) 4.72 (2 H, d, *J* 5.8, CH_2), 6.64 (1 H, d, *J* 15.4, olefinic), 6.75-7.06 (3 H, m, olefinic), 7.16-7.51 (10 H, m, aromatic), 7.91-8.11 (2 H, m, aromatic), 9.05 (1 H, br. t, *J* 5.8, NH); δ_C (63 MHz, d_6-DMSO) 34.1 (CH_2), 122.3, 123.0, 123.5 (CH), 124.3 (2 x CH), 125.6 (3 x CH), 126.3, 126.8 (2 x CH), 127.6, 127.7, 129.4, 130.2 (CH), 132.4, 134.0, 135.3, 136.8 (quat), 164.6 (quat, C=O); ν_{max}/cm^{-1} (nujol) 1541.5 (C=C), 1641.7 (C=O), 3326.8 (NH).

x. (*E,E*)-*N*-Benzoyl-2-aminomethyl-3-(penta-1,3-dienyl)thiophene (404)

A mixture of (*E,E*)- and (*Z,E*)-2-carbaldoxime-3-(penta-1,3-dienyl)thiophene (**403**) (0.73 g, 3.8 mmol), zinc dust (1.7 g, 0.026 g-atom), ammonium acetate (0.38 g, 4.9 mmol), aqueous ammonia solution (45 cm^3, 0.88 s.g.) and ethanol (30 cm^3) was heated at reflux under nitrogen for 30 minutes, at which point TLC analysis (silica, 1:1 hexane-ether) showed no spots with $R_f < 0$. The solvent was removed *in vacuo* and potassium hydroxide solution (40 cm^3, 33 % w/w) was added to the residue, followed by ether (40 cm^3). The mixture was filtered through a celite pad and the aqueous layer was extracted with ether (2 x 40 cm^3), washed with potassium hydroxide solution (40 cm^3, 33 % w/w) and dried. Removal of the solvent *in vacuo* gave (*E,E*)- and (*Z,E*)-2-aminomethyl-3-(penta-1,3-dienyl)thiophene as a yellow oil (0.58 g, 3.2 mmol, 86 %) which was used in the next stage without further purification; Found: M^+, 197.0770. $C_{10}H_{13}NS$ requires M^+, 179.0769; δ_H (250 MHz, $CDCl_3$) 1.69 (2 H, br. s, NH_2), 1.80-1.85 (3 H, m, (*E,E*)/(*Z,E*) CH_3), 3.99$^\$$ (2 H, s, CH_2), 4.06* (2 H, s, CH_2), 5.74-5.94 (1 H, m, (*E,E*)/(*Z,E*) $CHCH_3$), 6.12-6.63 (3 H, m, (*E,E*)/(*Z,E*) olefinic), 7.05-7.18 (2 H, m, (*E,E*)/(*Z,E*) thienyl H); δ_C (63 MHz, $CDCl_3$) 18.8* (CH_3), 18.9$^\$$ (CH_3), 39.5* (CH_2), 40.1$^\$$ (CH_2), 120.4$^\$$, 122.2*, 122.7$^\$$, 123.5*, 125.8*, 128.6$^\$$, 129.5$^\$$, 130.1*, 130.3*, 130.9$^\$$, 132.3*, 132.6$^\$$ (CH), 134.5$^\$$, 135.3*, 142.4*, 143.7$^\$$ (quat); ν_{max}/cm^{-1} (film) 3371.8, 3297.8 (NH_2).
(* Denotes major isomer signals, $^\$$ denotes minor isomer.)

To a mixture of (*E,E*)- and (*Z,E*)-2-aminomethyl-3-(penta-1,3-dienyl)thiophene (0.53 g, 3.0 mmol) and sodium carbonate (0.40 g, 3.8 mmol) in DCM (25 cm^3) was added benzoyl chloride (0.56 g, 4.0 mmol). The reaction mixture was heated at reflux under nitrogen for 1 hour, then stirred overnight at room temperature. Water (5 cm^3) was added, followed after 10 minutes by potassium hydroxide solution (10 cm^3, 33 % w/v) and the aqueous layer was extracted with DCM (2 x 40 cm^3). The combined extracts were washed with water (40 cm^3), dried, and the solvent was removed *in vacuo* to leave a dark brown oil. Dry-flash column chromatography (silica, 0-50 % hexane-ether) gave a yellow solid, a mixture of (*E,E*)- and (*Z,E*)-*N*-benzoyl-2-

aminomethyl-3-(penta-1,3-dienyl)thiophene. This was dissolved in DCM (30 cm^3) and heated at reflux under nitrogen with a catalytic amount of iodine for 35 minutes, when TLC analysis showed almost complete absence of a slightly lower-running spot, assumed to be due to the (*Z,E*) isomer. Saturated sodium metabisulfite solution (40 cm^3) was added and the organic layer was washed with water (2 x 20 cm^3), dried, and the solvent removed *in vacuo*. Dry-flash column chromatography (silica, 2:3 hexane-ether) gave (*E,E*)-*N*-benzoyl-2-aminomethyl-3-(penta-1,3-dienyl)thiophene (**404**) as a white solid (0.19 g, 0.7 mmol, 22 %), mp 89-90.5 °C (hexane-ethanol); Found: M^+, 283.1031. $C_{17}H_{17}NOS$ requires M^+, 283.1031; δ_H (250 MHz, $CDCl_3$) 1.79 (3 H, dd, *J* 6.7, 1.4, CH_3), 4.76 (2 H, d, *J* 5.3, CH_2), 5.79 (1 H, dq, *J* 15.3, 6.7, olefinic H-4), 6.17 (1 H, ddq, *J* 15.4, 9.2, 1.4, olefinic H-3), 6.45-6.63 (3 H, m, NH and 2 x olefinic H), 7.12-7.41 (2 H, m, aromatic), 7.43-7.50 (3 H, m, aromatic), 7.73-7.77 (2 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 18.8 (CH_3), 37.0 (CH_2), 121.8, 124.8, 125.8 (CH), 127.5, 129.0, 131.1 (2 x CH), 132.0, 132.3 (CH), 134.5, 135.0, 137.7 (quat), 167.6 (quat, C=O).

X. Synthesis of (*E,E*) Triene-Conjugated Tosylhydrazones

i. (*E,E*)-2-(4-Phenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (496)

To a solution of (*E,E*)-2-(4-phenylbuta-1,3-dienyl)benzaldehyde **257** (2.3 g, 9.8 mmol) in ethanol (20 cm^3) was added *p*-tosylhydrazide (1.92 g, 10.3 mmol) in ethanol (20 cm^3). This solution was stirred at *ca.* 40 °C, in the dark and under nitrogen, for 2 hours, after which the solution was concentrated to *ca.* ½ volume *in vacuo*. The precipitate was isolated and the mother liquor was further concentrated to give a second crop of white solid. Crystallisation gave (*E,E*)-2-(4-phenylbuta-1,3-dienyl)benzaldehyde tosylhydrazone **496** as white needles (3.52 g, 8.8 mmol, 89 %), mp 140.5-142 °C (ethanol); Found; 71.41 % C, 5.27 % H, 6.80 % N; $[M+H]^+$, 403.1471. $C_{24}H_{23}N_2O_2S$ requires 71.61 % C, 5.51 % H, 6.96 % N; $[M+H]^+$, 403.1480; δ_H (250 MHz, $CDCl_3$) 2.31 (3 H, s, CH_3), 6.62-7.49 (14 H, m, aromatic and olefinic), 7.68 (1 H, dd, *J* 7.8, 1.3, aromatic), 7.90-7.94 (2 H, m, aromatic), 8.21 (1 H, s, CH=N), 8.77 (1 H, s, NH); δ_C (63 MHz, $CDCl_3$) 21.34 (CH_3), 126.11 (CH),

126.35 (2 x CH, aromatic), 127.24, 127.46, 127.60 (CH), 127.76 (2 x CH, aromatic), 128.50 (2 x CH, aromatic), 128.74 (CH), 128.98 (quat), 129.54 (2 x CH, aromatic), 129.92 (CH), 129.98, 132.57, 133.62 (CH), 135.01, 136.82, 136.91 (quat), 144.09 (quat, C-SO_2), 146.70 (CH=N); *m/z* (FAB) 403 (11 %, M+H), 217 (52 %, M-HNHN*p*-Ts), 91 (base peak).

ii. (*E*)-2-(Buta-1,3-dienyl)benzaldehyde Tosylhydrazone (506)

To a solution of (*E*)-2-(buta-1,3-dienyl)benzaldehyde (1.0 g, 6.3 mmol) in ethanol (15 cm^3) was added a solution of *p*-tosylhydrazide (1.30 g, 7.0 mmol) in ethanol (15 cm^3). The mixture was warmed to *ca.* 40 °C and stirred, under nitrogen and in the dark, for 2 hours. Concentration of the mixture *in vacuo* gave a precipitate which was isolated at the pump, with a second crop of solid being collected from the mother liquor upon further concentration. Recrystallisation gave (*E*)-2-(buta-1,3-dienyl)benzaldehyde tosylhydrazone **506** as white needles (1.70 g, 5.2 mmol, 82 %) mp 102-104.5 °C (dec.) (ethanol); Found; 66.06 % C, 5.38 % H, 8.51 % H; M^+, 326.1089. $C_{18}H_{18}N_2O_2S$ requires; 66.23 % C, 5.56 % H, 8.58 % H; M^+, 326.1089; δ_H (250 MHz, $CDCl_3$) 2.38 (3 H, s, CH_3), 5.19 (1 H, ddd, *J* 8.4, 2.0, 1.0, olefinic H-4a), 5.33 (1 H, ddd, *J* 13.7, 1.9, 0.9, olefinic H-4b), 6.40-6.62 (2 H, m, olefinic H-2 and H-3), 6.90 (1 H, d, *J* 14.6, olefinic H-1), 7.16-7.32 (4 H, m, aromatic), 7.40-7.45 (1 H, m, aromatic), 7.66 (1 H, dd, *J* 7.7, 1.5, aromatic), 7.88 (2 H, ddd, *J* 8.2, 1.1, 1.0, aromatic), 8.10 (1 H, s, CH=N), 8.47 (1 H, s, D_2O labile, NH); δ_C (63 MHz, $CDCl_3$) 21.45 (CH_3), 118.63 (CH_2), 126.43, 127.42, 127.56 (CH), 127.84 (2 x CH), 129.05 (CH), 129.58 (2 x CH), 129.99 (CH), 130.06 (quat), 133.14 (CH), 135.05 (quat), 136.71 (quat), 138.89 (CH), 144.16 (quat), 146.52 (CH, HC=N); *m/z* (FAB) 327 $(M+H)^+$.

iii. (*E,E*)-2-(Penta-1,3-dienyl)benzaldehyde Tosylhydrazone (505)

To a solution of (*E,E*)-2-(penta-1,3-dienyl)benzaldehyde (0.85 g, 4.9 mmol) in ethanol (20 cm^3) was added a solution of *p*-tosylhydrazide (0.95 g, 5.1 mmol) in ethanol (10 cm^3). This solution was stirred at *ca.* 40 °C, under nitrogen and in the

dark, for 3 hours. The solvent was removed *in vacuo* to give a yellow solid, flash column chromatography (silica, 40 % hexane-ether) of which gave (*E,E*)-2-(penta-1,3-dienyl)benzaldehyde tosylhydrazone **505** as a white solid (1.30 g, 3.8 mmol, 78 %), mp 128.5-130 °C (ethanol); Found: M^+, 340.1244. $C_{19}H_{20}N_2O_2S$ requires M^+, 340.1246. δ_H (250 MHz, $CDCl_3$) 1.82 (3 H, dd, *J* 6.8, 1.4, =CHC*H*$_3$), 2.40 (3 H, s, CH_3), 5.84 (1 H, dq, *J* 15.0, 6.8, =C*H*CH_3), 6.20 (1 H, ddq, *J* 15.0, 10.1, 1.5, C*H*=$CHCH_3$), 6.52 (1 H, dd, *J* 15.5, 10.2, olefinic H-2), 6.73 (1 H, d, *J* 15.5, olefinic H-1), 7.19 (1 H, dt, *J* 1.4, 6.1, aromatic), 7.25-7.39 (4 H, m, aromatic), 7.67 (1 H, dd, *J* 7.8, 1.5, aromatic) 7.84-7.94 (2 H, m, aromatic), 8.06 (1 H, s, CH=N), NH not observed; δ_C (63 MHz, $CDCl_3$) 18.3 (CH_3), 21.5 (CH_3), 125.7, 126.4, 127.0, 127.4 (CH, aromatic and olefinic), 127.9 (2 x CH, aromatic, *meta*-SO_2), 129.6 (2 x CH, aromatic, *ortho*-SO_2), 129.7, 130.1, 131.6, 131.8, 133.3 (CH, aromatic and olefinic), 135.1, 137.4 (quat), 144.2 (quat, C-SO_2), 146.6 (CH=N).

iv. (*E,E*)-2-(1-Methylpenta-1,3-dienyl)benzaldehyde Tosylhydrazone (512)

To a solution of (*E,E*)-2-(1-methylpenta-1,3-dienyl)benzaldehyde (0.40 g, 2.2 mmol) in methanol (15 cm^3) was added a solution of *p*-tosylhydrazide (0.41 g, 2.2 mmol) in methanol (10 cm^3). The reaction mixture was stirred at *ca.* 40 °C, in the dark and under nitrogen, for 2 hours. The solvent was partially removed *in vacuo*, the precipitated solid was collected and the filtrate was further concentrated to obtain further crops of the crude product. Crystallisation of the combined crops gave (*E,E*)-2-(1-methylpenta-1,3-dienyl)benzaldehyde tosylhydrazone **512** as a white crystalline solid (0.65 g, 1.8 mmol, 82 %) mp 135-136.5 °C (hexane-ethanol); Found: $[M+H]^+$, 355.1481. $C_{20}H_{23}N_2O_2S$ requires $[M+H]^+$, 355.1480; δ_H (250 MHz, $CDCl_3$) 1.80 (3 H, ddd, *J* 6.9, 1.0, 0.5, =CHC*H*$_3$), 1.99 (3 H, t, *J* 0.5, CH_3C=), 2.40 (3 H, s, Ar-CH_3), 5.65 (1 H, dq, *J* 15.0, 6.8, =C*H*CH_3), 5.73 (1 H, dd, *J* 10.8, 0.6, CH_3C=C*H*), 6.33 (1 H, ddq, *J* 15.0, 11.0, 1.6, C*H*=$CHCH_3$), 7.13-7.33 (5 H, m, aromatic), 7.73-7.88 (3 H, m, aromatic), 7.96 (1 H, s, CH=N), NH not observed; δ_C (63 MHz, $CDCl_3$) 18.37 (CH_3), 18.8 (CH_3), 21.5 (CH_3), 126.3, 126.7, 127.3 (CH), 127.8 (2 x CH, aromatic), 128.1 (CH), 129.5 (2 x CH, aromatic), 129.8 (CH), 129.9 (quat), 131.1, 131.7 (CH),

132.0, 135.2, 144.0, 145.7 (quat), 147.4 (CH, CH=N); *m/z* (FAB, thio matrix) 355 (M+H), 169 (base peak, M-HNHN*p*Ts).

v. (*E,E*)-2-(2-Methyl-4-phenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (518)

A solution of *p*-tosylhydrazide (0.39 g, 2.10 mmol) in ethanol (15 cm^3) was added to a solution of (*E,E*)-2-(2-methyl-4-phenylbuta-1,3-dienyl)benzaldehyde (0.50 g, 2.02 mmol) in ethanol (15 cm^3) along with a few drops of conc. HCl solution. The solution was stirred at *ca.* 40 °C, in the dark and under nitrogen, for 2 hours. Concentration of the solution *in vacuo* to *ca.* ½ volume, followed by filtration and crystallisation of the solid residue from methanol afforded (*E,E*)-2-(2-methyl-4-phenylbuta-1,3-dienyl)benzaldehyde tosylhydrazone **518** as colourless needles (640 mg, 1.54 mmol, 76 %) mp 156-157 °C (methanol); Found 72.09 % C, 5.82 % H, 6.75 % N, $[M+H]^+$, 417.1636. $C_{25}H_{25}N_2O_2S$ requires 71.85 % C, 5.81 % H, 6.73 % N, $[M+H]^+$, 417.1637; δ_H (250 MHz, d_6-DMSO) 1.76 (3 H, s, CH_3), 2.34 (3 H, s, CH_3-Ar), 6.73 (1 H, d, *J* 16.0, olefinic), 6.84 (1 H, s, olefinic), 7.12-7.78 (14 H, m, aromatic and olefinic H), 8.06 (1 H, s, CH=N), 11.43 (1 H, br. s, NH); δ_C (63 MHz, d_6-DMSO) 13.8 (CH_3), 21.1 (CH_3), 125.5 (CH), 126.5 (2 x Ar-CH), 127.3 (2 x Ar-CH), 127.5, 127.7, 128.6 (CH), 128.9 (2 x Ar-CH), 129.2, 129.7 (CH), 129.8 (2 x Ar-CH), 130.1 (CH), 131.5 (quat.), 133.0 (CH), 136.2, 137.1, 137.2, 137.7 (quat.), 143.6 (quat, C-SO_2), 146.0 (CH, CH=N).

vi. (*E,E*)-2-Formyl-3-(4-phenylbuta-1,3-dienyl)thiophene Tosylhydrazone

A solution of *p*-tosylhydrazide (0.47 g, 2.5 mmol) in methanol (5 cm^3) was added to a solution of (*E,E*)-2-formyl-3-(4-phenylbuta-1,3-dienyl)thiophene (0.6 g, 2.5 mmol) in methanol (100 cm^3) and a few drops of conc. HCl solution were added. This solution was warmed to *ca.* 45 °C and stirred, under nitrogen and with shielding from daylight, for 3 hours. The solvent was removed *in vacuo* to give a red foam, which, upon flash column chromatography (silica, 50 % hexane-ether) yielded a yellow solid which was crystallised to give (*E,E*)-2-formyl-3-(4-phenylbuta-1,3-

dienyl)thiophene tosylhydrazone (0.86 g, 2.1 mmol, 84 %), mp 168-169.5 °C (ethanol); Found; 64.24 % C, 4.79 % H, 6.61 % N; $[M+H]^+$, 409.1045 (FAB+, NOBA matrix). $C_{22}H_{21}N_2O_2S_2$ requires; 64.68 % C, 4.94 % H, 6.86 % N; $[M+H]^+$, 409.1045; δ_H (200 MHz, d_6-DMSO) 2.39 (3 H, s, CH_3), 6.77-7.18 (4 H, m, olefinic), 7.26-7.62 (9 H, m, aromatic), 7.81 (2 H, d, *J* 7.8, $SO_2C_6H_4$ *ortho*), 8.36 (1 H, s, CH=N), NH not observed; δ_C (63 MHz, d_6-DMSO) 21.1 (CH_3), 123.8, 126.0 (CH), 126.54, 127.4 (2 x CH, aromatic), 128.0 (CH), 128.9 (3 x CH, aromatic), 129.3, 129.7, 132.3 (CH), 133.0 (quat), 133.9 (CH), 136.1, 136.9, 140.5, 140.8 (quat), 143.6 (CH, CH=N).

viii. (*E,E*)- and (*Z,E*)-2-Formyl-3-(penta-1,3-dienyl)thiophene Tosylhydrazone (526)

A solution of *p*-tosylhydrazide (0.59 g, 3.2 mmol) in methanol (5 cm^3) was added to a warmed (*ca.* 40 °C) solution of (*E,E*)- and (*Z,E*)-2-formyl-3-(penta-1,3-dienyl)thiophene (0.56 g, 3.1 mmol) in methanol (50 cm^3) along with a few drops of conc. HCl solution. This solution was stirred at 40 °C, under nitrogen and in darkness, for 3 hours, after which the solvent was removed *in vacuo* to leave a dark red oil. Flash column chromatography (silica, 2:3 hexane-ether) gave *syn*- and *anti*-(*E,E*)- and (*Z,E*)-2-formyl-3-(penta-1,3-dienyl)thiophene tosylhydrazone **526** as a yellow solid (0.91 g, 2.6 mmol, 85 %), mp 60-64 °C (ethanol); Found: M^+, 346.0809. $C_{17}H_{18}N_2O_2S_2$ requires M^+, 346.0801; δ_H (250 MHz, d_6-DMSO) 1.73 (3 H, m, CH_3), 2.34 (3 H, s, CH_3), 5.83-5.96 (1 H, m, olefinic H-4), 6.14-6.32 (2 H, m, olefinic), 6.58$^\$$ (1 H, d, *J* 15.6, olefinic), 6.78* (1 H, dd, *J* 15.5, 10.1, olefinic), 7.08$^\$$ (1 H, d, *J* 5.2, thienyl), 7.32* (1 H, d, *J* 5.3, thienyl), 7.37-7.41 (2 H, m, aromatic), 7.51* (1 H, d, *J* 5.3, thienyl), 7.57$^\$$ (1 H, d, *J* 5.1, thienyl), 7.73 (2 H, dd, *J* 8.3, 3.2, aromatic), 8.06$^\$$ (1 H, s, CH=N), 8.25* (1 H, s, CH=N), 11.31$^\$$ (1 H, s, NH), 11.34* (1 H, s, NH); δ_C (63 MHz, d_6-DMSO) 19.1, 21.9 (CH_3), 119.5, 121.7, 126.7 (CH), 128.1 (2 x CH, aromatic), 128.4, 129.1, 129.4, 130.0 (CH, aromatic and olefinic), 130.5 (2 x CH, aromatic), 132.6, 132.9, 133.1, 134.3 (CH), 134.8 (quat), 136.8 (2 x quat), 140.3, 141.4 (quat), 141.8 (CH, CH=N), 141.9 (CH, CH=N), 144.4 (2 x quat).

XI. Synthesis of (*Z*,*E*)-1,2,4-Trisubstituted Triene-Conjugated Tosylhydrazones

i. (*Z*,*E*) and (*Z*,*Z*)-2-(1-Methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (540)

A solution of *p*-tosylhydrazide (0.35 g, 1.9 mmol) in ethanol (10 cm^3) was added to a solution of (*Z*,*E*) and (*Z*,*Z*)-2-(1-methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde **539** (0.60 g, 0.19 mmol) in ethanol (10 cm^3). This solution was stirred in the dark, under nitrogen and at *ca.* 40 °C, for 2 hours. The solvent was removed *in vacuo* to leave a viscous pale-yellow oil, flash column chromatography (silica, 3:2 hexane-ether) of which yielded (*Z*,*E*) and (*Z*,*Z*)-2-(1-methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde tosylhydrazone **540** (1:1.2 (*Z*,*E*):(*Z*,*Z*) by ^1H NMR) as a white solid (0.83 g, 1.7 mmol, 91 %) mp 130-132 °C (ethanol); δ_H (250 MHz, $CDCl_3$) 1.82* (3 H, d, *J* 1.3, CH_3-C=), 2.26$^{\$}$ (3 H, s, CH_3-C=), 2.36$^{\$}$ (3 H, s, CH_3-Ar), 2.37* (3 H, s, CH_3-Ar), 6.13$^{\$}$ (1 H, d, *J* 15.9, olefinic H-3), 6.45* (1 H, dd, *J* 12.0, 1.3, olefinic H-3), 6.63* (1 H, d, *J* 12.0, olefinic H-4), 6.77-7.86 (22 H, m, Ar-H and (*Z*,*E*) isomer H-4), 8.15* (1 H, s, CH=N), 8.50$^{\$}$ (1 H, s, CH=N); δ_C (63 MHz, $CDCl_3$) 21.31 (CH_3), 21.41 (CH_3), 23.75 (CH_3-Ar), 125.90, 125.96, 126.12 (CH), 126.36 (2 x CH), 126.60, 127.01 (CH), 127.34, 127.36 , 127.68, 127.74, 128.05, 128.17, 128.44, 128.79, 128.92, 129.38, 129.47, 129.64, 129.87, 129.97, 130.28, 130.43, 131.32, 132.47 (CH), 132.85, 135.02, 135.16, 135.25, 135.97, 137.40, 137.64, 138.60, 139.02, 139.38, 143.86, 143.94*, 144.49 (quat)$^{\$}$, 146.46 (CH, CH=N)*, 146.69 (CH, CH=N)$^{\$}$. * Indicates major isomer signals, $^{\$}$ indicates minor isomer signals. Where signals from both isomers coincide or the signal cannot be conclusively assigned, no symbol is used.

ii. (*Z*,*E*)- and (*Z*,*Z*)-2-(1-Methyl-2-phenylpenta-1,3-dienyl)benzaldehyde Tosylhydrazone (546)

To a solution of (*Z*,*E*)- and (*Z*,*Z*)-2-(1-methyl-2-phenylpenta-1,3-dienyl)benzaldehyde **545** (0.24 g, 0.92 mmol) in methanol (10 cm^3) was added a

solution of *p*-tosylhydrazide (0.18 g, 0.95 mmol) in methanol (10 cm^3), along with a trace of conc. HCl solution. This solution was stirred at ca. 40 °C, in the dark and under nitrogen, for 3 hours. Removal of the solvent *in vacuo* gave a viscous yellow oil which upon flash column chromatography (silica, hexane then 7:3 hexane-ether) gave (*Z,E*)- and (*Z,Z*)-2-(1-methyl-2-phenylpenta-1,3-dienyl)benzaldehyde tosylhydrazone **546** as a white gum which would not crystallise (0.32 g, 0.74 mmol, 80 %); Found: M^+, 430.1715. $C_{26}H_{26}N_2O_2S$ requires M^+, 430.1715; δ_H (250 MHz, $CDCl_3$) 1.47* (3 H, dd, *J* 6.0, 1.8, C-4 CH_3), 1.78* (3 H, ddd, *J* 6.8, 1.6, 0.4, C-4 CH_3), 2.03* (3 H, d, *J* 0.9, C-1 CH_3), 2.12$ (3 H, s, C-1 CH_3), 2.41 (3 H, s, CH_3Ar), 5.28$ (1 H, dq, *J* 15.6, 6.8, olefinic H-4), 5.72 (1 H, dq, *J* 11.3, 7.0, olefinic H-4), 6.20 (1 H, dq, *J* 11.2, 0.5, olefinic H-3), 7.05-8.04 (14 H, m, aromatic, CH=N, and minor isomer olefinic H-3); δ_C (63 MHz, $CDCl_3$) 15.1* (CH_3), 18.6$ (CH_3), 21.1$ (CH_3), 21.5 (CH_3Ar), 23.3* (CH_3), 125.7, 125.8, 126.0, 126.3, 126.6, 127.4, 127.8, 127.8, 128.0, 129.1, 129.5, 129.7, 129.8, 129.9, 130.5, 131.1 (CH, aromatic and olefinic), 132.7, 135.3, 136.8, 138.7, 139.6, 140.6, 143.9, 144.2, 144.8 (quat), 146.8* (CH, CH=N), 146.9$ (CH, CH=N).

iii. (*Z*)-2-(1-Methyl-2-phenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (554)

To a solution of (*Z*)-2-(1-methyl-2-phenylbuta-1,3-dienyl)benzaldehyde (0.55 g, 2.2 mmol) in methanol (15 cm^3) was added a solution of *p*-tosylhydrazide (0.45 g, 2.4 mmol) in methanol. This solution was stirred in the dark and under nitrogen, with warming at *ca.* 35 °C, for 3 hours. The solvent was removed *in vacuo* and flash column chromatography of the residue (silica, 3:2 hexane-ether) gave (*Z*)-2-(1-methyl-2-phenylbuta-1,3-dienyl)benzaldehyde tosylhydrazone **554** (0.71 g, 1.7 mmol, 77 %), mp 95.0-96.5 °C (dec.) (hexane-ethanol); δ_H (250 MHz, $CDCl_3$) 1.75 (3 H, s, CH_3), 2.37 (3 H, s, CH_3), 4.51 (1 H, dd, *J* 17.2, 0.9, HC=CH_2 *cis*), 4.78 (1 H, dd, *J* 10.6, 0.9, HC=CH_2 *trans*), 6.12 (1 H, dd, *J* 17.1, 10.6, *H*C=CH_2), 7.16-7.39 (10 H, m, aromatic), 7.86-7.96 (4 H, m, aromatic and HC=N), 8.68 (1 H, s, NH); δ_C (63 MHz, $CDCl_3$) 21.44, 23.49 (CH_3), 116.88 (CH_2), 125.80, 126.74, 127.13 (CH), 127.77 (2 x CH, aromatic), 128.12 (2 x CH, aromatic), 128.78 (CH), 129.56 (2 x CH,

aromatic), 129.60 (2 x CH, aromatic), 130.19 (CH), 130.52, 134.36, 135.16 (quat), 136.39 (CH), 138.38, 139.69, 143.22, 144.02 (quat), 146.35 (CH, N=CH). This compound decomposed before it could be taken to the next stage.

iv. (*Z,E*)-2-[1-Methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl] benzaldehyde Tosylhydrazone (555)

To a solution of (*Z,E*)-2-[1-methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl]benzaldehyde (0.22 g, 0.53 mmol) in methanol (10 cm^3) was added a solution of *p*-tosylhydrazide (0.11 g, 0.59 mmol) in methanol (10 cm^3). The reaction mixture was stirred at *ca.* 40 °C in the dark and under nitrogen for 2 hours, after which the solvent was removed *in vacuo*. Flash column chromatography (silica, 3:2 hexane-ether) gave (*Z,E*)-2-[1-methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl]benzaldehyde tosylhydrazone **555** as a white crystalline solid (0.29 g, 0.50 mmol, 94 %), mp 124.5-125.5 °C (hexane-ethanol); Found: $[M+H]^+$, 583.1480. $C_{31}H_{23}F_5N_2O_2S$ requires $[M+H]^+$, 583.1479. δ_H (250 MHz, d_6-DMSO) 2.18 (3 H, s, CH_3), 2.34 (3 H, s, CH_3), 5.80 (1 H, d, *J* 16.3, olefinic H-3), 6.82 (2 H, dd, *J* 7.7, 1.5, aromatic), 6.92-7.19 (6 H, m, aromatic), 7.34-7.45 (3 H, m, aromatic), 7.67-7.73 (2 H, m, aromatic), 7.81 (1 H, d, *J* 16.3, olefinic H-4), 7.97 (1 H, s, CH=N), 11.45 (1 H, br. s, NH); δ_C (63 MHz, d_6-DMSO) 21.1 (CH_3), 21.4 (CH_3), 112.4 (quat, t, J_{CCF} 14.0, $C(CF)_5$), 115.1 (CH), 125.5 (CH), 126.8 (CH), 127.1 (CH), 127.3 (2 x CH, phenyl), 127.8 (2 x CH, phenyl), 129.4 (2 x CH, phenyl), 129.6 (quat), 129.8 (2 x CH, phenyl), 129.9 (2 x CH, phenyl), 136.1 (CH, olefinic C-4), 136.4 (quat), 137.7 (quat), 137.9 (quat), 140.0 (quat), 143.5 (2 x quat), 145.8 (CH, CH=N), 5 x quat C-F unobserved; δ_F (235 MHz, d_6-DMSO) –149.64 (2 x F, dd, *J* 23.3, 7.2, *ortho* F), -162.94 (1 x F, t, *J* 22.5, *para* F), -169.00 – -169.22 (2 x F, m, *meta* F).

XII. Synthesis of (*E,E*)-1,2,4-Trisubstituted Triene-Conjugated Tosylhydrazones

i. (*E,E*)- and (*E,Z*)-2-(1-Methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (443)

To a solution of (*E,Z*)- and (*E,E*)-2-(1-methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde **442** (0.60 g, 1.85 mmol) in methanol (15 cm^3) was added *p*-tosylhydrazide (0.35 g, 1.88 mmol) in methanol (15 cm^3). The solution was stirred in the dark under nitrogen at *ca.* 40 °C for 4 hours, after which the solvent was removed *in vacuo*. Flash column chromatography (silica, 35 % ether in hexane) yielded (*Z,E*) and (*Z,Z*)-2-(1-methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde tosylhydrazone **443** (87:13 (*E,E*):(*E,Z*) by ^1H NMR) as a white solid (0.83 g, 1.69 mmol, 91 %) mp 133-134 °C (ethanol), lit. [133] 134-136 °C; δ_H (250 MHz, $CDCl_3$) 1.79* (3 H, s, CH_3), 1.97$ (3 H, d, *J* 1.4, CH_3), 2.27* (3 H, s, Ar-Me), 2.33$ (3 H, s, Ar-Me), 5.78$ (1 H, dd, *J* 12.1, 1.4, olefinic), 5.88* (1 H, d, *J* 15.9, C*H*=CH *trans*), 5.98$ (1 H, d, *J* 12.2, olefinic), 6.61* (1 H, d, *J* 15.9, CH=C*H*Ph *trans*), 6.95-8.08 (19 H, m, Ar-H), 8.36$ (1 H, s, CH=N), 8.68* (1 H, s, CH=N); δ_C ($CDCl_3$, 63 MHz) 21.35 (CH_3), 23.78 (CH_3), 125.94 (CH), 126.21 (2 x CH), 126.87 (CH), 127.08 (CH), 127.24 (CH), 127.57 (2 x Ar CH), 128.21 (2 x Ar CH), 128.28 (2 x Ar CH), 128.83 (CH), 129.09 (CH), 129.54 (2 x Ar CH), 129.62 (2 x Ar CH), 130.28 (CH), 130.56 (quat), 131.56 (CH), 135.06 (quat), 135.17 (CH), 137.20 (quat), 138.80 (quat), 139.44 (quat), 143.33 (quat), 143.92 (CH), 146.41 (quat).

ii. (*E*)-2-(1-Methyl-2-phenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (457)

To a solution of (*E*)-2-(1-methyl-2-phenylbuta-1,3-dienyl)benzaldehyde (0.23 g, 0.9 mmol) in methanol (10 cm^3) was added a solution of *p*-tosylhydrazide (0.18 g, 0.97 mmol) in methanol (10 cm^3). This solution was stirred at *ca.* 40 °C for 2 hours, under nitrogen and in the dark. Removal of the solvent *in vacuo* followed by flash

column chromatography (silica, 2:3 hexane-ether) gave (*E*)-2-(1-methyl-2-phenylbuta-1,3-dienyl)benzaldehyde tosylhydrazone **457** as a white solid (0.30 g, 0.72 mmol, 77 %) mp 105-107 °C (ethanol-hexane); Found: M^+, 416.1552. $C_{25}H_{24}N_2O_2S$ requires M^+, 416.1552; δ_H (250 MHz, $CDCl_3$) 2.15 (3 H, s, CH_3), 2.39 (3 H, s, CH_3), 4.81 (1 H, dd, *J* 17.2, 1.8, olefinic H-4a), 5.23 (1 H, ddd, *J* 10.6, 1.7, 0.5, olefinic H-4b), 6.86-7.30 (10 H, m, 9 x aromatic H and 1 x olefinic H-3), 7.55-7.59 (1 H, m, aromatic), 7.81-7.87 (3 H, m, aromatic), 8.27 (1 H, s, HC=N), NH not observed; δ_C (63 MHz, $CDCl_3$) 21.1 (CH_3), 21.4 (CH_3), 118.0 (CH_2), 126.0 (CH), 126.1 (CH), 126.4 (CH), 127.2 (2 x CH, aromatic), 127.8 (2 x CH, aromatic), 129.4 (CH), 129.5 (CH), 129.5 (2 x CH, aromatic and 1 x quat), 130.0 (2 x CH, aromatic), 134.4 (quat), 134.8 (CH), 135.5 (quat), 138.6 (quat), 138.8 (quat), 143.9 (quat), 144.4 (quat), 146.7 (CH, H*C*=N); *m/z* 416 (M^+), 401 (M^+-CH_3) 232 (M-NHN*p*Ts).

iii. (*E,E*)-2-[1-Methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl] benzaldehyde Tosylhydrazone (467)

Solutions of (*E,E*)-2-[1-methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl]benzaldehyde (0.85 g, 1.9 mmol) in methanol (10 cm^3) and *p*-tosylhydrazide (0.34 g, 1.9 mmol) in methanol (10 cm^3) were mixed together and stirred, under nitrogen, in darkness and at *ca.* 40 °C for 2 hours. The solvent was removed *in vacuo* to give a viscous, pale-yellow oil, flash column chromatography (silica, 3:2 hexane-ether) of which yielded (*E,E*)-2-[1-methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl]benzaldehyde tosylhydrazone **467** (0.93 g, 1.6 mmol, 84 %) as a white solid, mp 154-155.5 °C (hexane-ethanol); Found: $[M+H]^+$, 583.1480. $C_{31}H_{24}F_5N_2O_2S$ requires $[M+H]^+$, 583.1479; δ_H (250 MHz, d_6-DMSO) 1.79 (3 H, s, CH_3), 2.23 (3 H, s, CH_3), 5.65 (1 H, d, *J* 16.4, olefinic H-3), 6.84 (1 H, d, *J* 16.4, olefinic H-4), 7.23-7.88 (13 H, m, aromatic), 8.06 (1 H, s, CH=N), 11.61 (1 H, br. s, NH); δ_C (63 MHz, d_6-DMSO) 20.9 (CH_3), 23.8 (CH_3), 112.1 (quat, t, J_{CCF} 10.8, *C*-CF), 114.2 (CH, olefinic C-3), 125.2 (CH), 127.1 (2 x CH, aromatic), 127.7 (CH), 127.9 (CH), 128.7 (2 x CH, aromatic), 128.8 (CH), 129.5 (2 x CH, aromatic), 129.7 (2 x CH, aromatic), 130.1 (CH), 131.1 (quat), 136.4 (quat), 137.4 (CH, olefinic C-4), 138.8 (CH), 140.0 (quat), 141.9 (quat), 143.2 (quat), 144.7 (CH, CH=N), 145.7 (quat, C-F), 4 x quat C-

F unobserved; δ_F (235 MHz, $CDCl_3$) -149.75 – -149.88 (2 F, m, *ortho* F), -163.44 (1 F, t, J_{FCCF} 21.8, *para* F), -169.16 – -169.38 (2 F, m, *meta* F); *m/z* (FAB, NOBA matrix) 583 (96 %, M+H), 427 (76 %, M-$SO_2C_6H_4CH_3$), 397 (base peak, M-$HNHNSO_2$-*p*-$C_6H_4CH_3$).

iv. (*E,E*)-2-(1-Methyl-2-phenyl-4-[*p*-methoxyphenyl]buta-1,3-dienyl) benzaldehyde Tosylhydrazone (475)

In the absence of daylight and under nitrogen a solution of *p*-tosylhydrazide (0.23 g, 1.3 mmol) in methanol (10 cm^3) was added to a warmed (*ca.* 40 °C) solution of (*E,E*)-2-(1-methyl-2-phenyl-4-[*p*-methoxyphenyl]buta-1,3-dienyl)benzaldehyde (0.40 g, 1.1 mmol) in methanol (20 cm^3). The solution was stirred for 2 hours, after which the solvent was removed to yield a pale yellow oil. Flash column chromatography (silica, 3:2 hexane-ether) gave (*E,E*)-2-(1-methyl-2-phenyl-4-[*p*-methoxyphenyl]buta-1,3-dienyl)benzaldehyde tosylhydrazone **475** as a white solid (0.30 g, 0.6 mmol, 53 %), mp 123.0-124.5 °C (ethanol); Found: $(M+H)^+$, 523.2056. $C_{32}H_{31}N_2O_3S$ requires $(M+H)^+$, 523.2055; δ_H (250 MHz, d_6-DMSO) 1.72 (3 H, s, CH_3-Ar), 2.24 (3 H, s, CH_3), 3.65 (3 H, s, CH_3O), 5.75 (1 H, d, *J* 15.9, olefinic), 6.38 (1 H, d, *J* 15.9, olefinic), 6.73 (2 H, d, *J* 8.7, aromatic), 6.86 (2 H, d, *J* 8.8, aromatic), 7.23-7.55 (10 H, m, aromatic), 7.71 (2 H, d, *J* 8.3, aromatic), 7.84 (1 H, dd, *J* 7.6, 1.3, aromatic), 8.09 (1 H, s, CH=N), 11.61 (1 H, br. s, NH); δ_C (63 MHz, d_6-DMSO) 21.0 (CH_3), 23.6 (CH_3), 55.1 (OCH_3), 114.3 (2 x CH), 125.0, 126.8 (CH), 127.1 (2 x CH), 127.3 (2 x CH), 127.3 (CH), 127.7 (CH), 128.6 (2 x CH), 129.3 (CH), 129.5 (quat, C-OMe), 129.8 (4 x CH), 130.3, 130.5 (CH), 131.2, 134.2, 136.4, 138.8, 138.9, 142.9, 143.4 (quat), 145.3 (CH, CH=N), 158.9 (quat, C-SO_2).

XIII. Generation and Reaction of the Nitrile Ylides Derived from (*E,E*) Triene-Conjugated Arylamides

i. Generation and Reaction of the Nitrile Ylide Derived from (*E,E*)-*N*-[2-(4-Phenylbuta-1,3-dienyl)benzyl]benzamide (262)

(*E,E*)-*N*-[2-(4-Phenylbuta-1,3-dienyl)benzyl]benzamide (**262**) (0.25 g, 0.74 mmol) and thionyl chloride (4.2 cm^3) were dissolved in dry ether (13 cm^3) and heated at reflux for 20 hours. The solvent and excess thionyl chloride were removed *in vacuo* and the residue was dried under high vacuum for 3 hours to yield the (*E,E*)-*N*-[4-phenylbuta-1,3-dienyl]benzimidoyl chloride (**263**) as a yellow gum; δ_H (200 MHz, $CDCl_3$) 5.04 (2 H, s, CH_2), 6.63 (1 H, d, *J* 15.4, olefinic H-4), 6.77-7.53 (13 H, m, aromatic and olefinic), 7.68 (2 H, d, *J* 7.3, aromatic), 8.01 (2 H, d, *J* 7.3, aromatic).

The crude imidoyl chloride was then dissolved in dry THF (15 cm^3) and cooled to 0 °C under dry nitrogen. Lithium bis(trimethylsilyl)amide (1 M in THF, 3 cm^3) was added dropwise and the solution was stirred for 1 hr at 0 °C, then allowed to warm to room temperature. Aqueous ammonium chloride (25 % w/v, 20 cm^3) was added and the mixture was stirred for 10 minutes. The layers were separated, the aqueous phase was extracted with DCM (2 x 20 cm^3) and the combined organics were washed with water and dried. Removal of the solvent *in vacuo* gave a brown oil, which upon dry-flash column chromatography gave (*E*)-1a-phenyl-1-*exo*-(2-phenylethenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (**265**) (0.18 g, 0.55 mmol, 74 %); Found: M^+, 321.1501. $C_{24}H_{19}N$ requires M^+, 321.1517; δ_H (200 MHz, $CDCl_3$) 1.29 (1 H, dd, *J* 5.5, 9.5, H-1), 3.02 (1 H, d, *J* 5.5, H-7), 5.50 (1 H, dd, *J* 15.8, 9.5, olefinic), 6.70 (1 H, d, *J* 16.1, olefinic), 7.05-7.51 (14 H, m, aromatic), 8.14 (1 H, s, CH=N); δ_C (63 MHz, $CDCl_3$) 32.5 (CH, C-1), 36.7 (CH, C-7), 123.5 (quat), 125.6 (2 x CH), 126.6 (CH), 126.9 (CH), 127.3 (CH), 127.4 (CH), 127.7 (CH), 128.3 (3 x CH), 128.3 (quat), 128.4 (2 x CH), 129.3 (CH), 129.4 (CH), 131.2 (CH), 131.7 (CH), 135.5 (quat), 137.1 (quat), 140.6 (quat), 154.1 (CH, CH=N).

ii. Generation and Reaction of the Nitrile Ylide Derived from (*E*)-*N*-[2-(Buta-1,3-dienyl)benzyl]benzamide (274)

Thionyl chloride (0.88 g, 7.5 mmol) was dissolved in dry DMF (9.5 cm^3) and the solution was stirred under dry nitrogen for 30 minutes. This solution (0.9 cm^3) was added dropwise to a solution of (*E*)-*N*-[2-(buta-1,3-dienyl)benzyl]benzamide (**274**) (0.14 g, 0.53 mmol) in dry THF (5 cm^3) and the mixture stirred under a dry nitrogen atmosphere for 30 minutes. This solution was cooled to 0 °C and lithium bis(trimethylsilyl)amide solution (1 M in THF, 2.7 cm^3) was added dropwise. The resulting solution was stirred at 0 °C for 30 minutes. Removal of the solvents *in vacuo* at room temperature yielded a brown oil, dry flash column chromatography of which (silica, 0-50 % hexane-ether) gave 1a-phenyl-1-*exo*-ethenyl-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (**277**) (0.06 g, 0.25 mmol, 47 %); Found: $(M+H)^+$, 246.1287. $C_{18}H_{16}N$ requires $(M+H)^+$, 246.1283. δ_H (250 MHz, $CDCl_3$) 1.19 (1 H, dd, *J* 8.4, 5.4, H-1), 3.02 (1 H, d, *J* 5.4, H-7b), 4.96 (1 H, m, olefinic), 5.03-5.34 (2 H, m, olefinic), 7.10-7.59 (9 H, m, aromatic), 8.19 (1 H, s, CH=N); δ_C (63 MHz, $CDCl_3$) 31.7 (CH, C-1), 36.8 (CH, C-7), 116.2 (CH_2), 123.6 (quat), 126.5 (CH), 127.3 (CH), 127.4 (CH), 128.0 (quat), 128.4 (2 x CH), 129.2 (3 x CH), 131.6 (CH), 135.5 (quat), 135.9 (CH), 140.7 (quat), 153.9 (CH, H*C*=N).

iii. Generation and Reaction of the Nitrile Ylide Derived from (*E,E*)-*N*-[2-(Penta-1,3-dienyl)benzyl]benzamide (289)

Distilled thionyl chloride (1.2 g, 10.1 mmol) was added to dry DMF (8.8 cm^3) under nitrogen and this solution was allowed to stir for 1 hour. A portion of this solution (5.0 cm^3) was added to a solution of (*E,E*)-*N*-[2-(penta-1,3-dienyl)benzyl]benzamide (**289**) (0.30 g, 1.10 mmol) in dry THF (10 cm^3). A fine precipitate formed and the suspension was stirred at room temperature for 1 hour then cooled in an ice-bath. Lithium bis(trimethylsilyl)amide solution (1.0 M in THF, 25 cm^3, 25 mmol) was added to this solution and the mixture was stirred for 30 minutes at 0 °C, then thirty minutes at room temperature. Ammonium chloride solution (25 % w/v, 40 cm^3) was added and the aqueous layer was extracted with DCM (3 x 40 cm^3). The combined

organic extracts were washed with water (40 cm^3), dried and the solvents were removed *in vacuo* without heating to give a dark brown oil. Dry-flash column chromatography (silica, hexane-ether, gradient elution) gave (*E*)-1a-phenyl-1-*exo*-(2-propenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (**291**) as a yellow oil (0.18 g, 0.70 mmol, 64 %); Found: M^+, 259.1361. $C_{19}H_{17}N$ requires M^+, 259.1361; δ_H (250 MHz, $CDCl_3$) 1.16 (1 H, dd, *J* 9.1, 5.6, H-1), 1.60 (3 H, dd, *J* 6.5, 1.6, CH_3), 2.93 (1 H, d, *J* 5.4, H-7b), 4.86 (1 H, ddq, *J* 15.2, 9.1, 1.6, C*H*=CHMe), 5.52 (1 H, ddq, *J* 15.2, 0.5, 6.6, C*H*CH_3), 7.25-7.56 (9 H, m, aromatic), 8.18 (1 H, s, HC=N); δ_C (63 MHz, $CDCl_3$) 18.12 (CH_3), 31.51 (CH), 36.02 (CH), 57.85 (quat), 123.43 (quat), 126.23 (CH), 127.01 (CH), 127.18 (CH), 127.29 (CH), 127.83 (CH), 128.19 (2 x CH), 129.01 (CH), 129.13 (2 x CH), 131,36 (CH), 135.71 (quat), 140.87 (quat), 153.53 (quat, HC=N).

iv. Generation and Reaction of the Nitrile Ylide Derived from (*E,E*)-*N*-[2-(Penta-1,3-dienyl)benzyl]-*o*-toluamide (299)

Distilled thionyl chloride (0.85 g, 7.1 mmol) was added to dry DMF (4.1 cm^3) under nitrogen and this solution was stirred for 1 hour. A portion of this solution (3.0 cm^3) was added to a solution of (*E,E*)-*N*-[2-(penta-1,3-dienyl)benzyl]-*o*-toluamide (**299**) (0.25 g, 0.86 mmol) in dry THF (15 cm^3) under nitrogen and this solution was stirred for 90 minutes, then cooled to 0 °C. Lithium bis(trimethylsilyl)amide solution (1.0 M, 20 cm^3, 20 mmol) was added dropwise and the resulting dark solution was stirred at 0 °C for 1 hour, then 30 minutes at room temperature. Ammonium chloride solution (25 % w/v, 40 cm^3) was added to this and the aqueous phase was extracted with DCM (3 x 30 cm^3). The combined extracts were washed with water (30 cm^3), dried and the solvents were removed *in vacuo*. Dry-flash column chromatography (silica, hexane-ether, gradient elution) of the dark residual oil gave (*E*)-1a-(*o*-tolyl)-1-*exo*-(2-propenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (**301**) as a yellow oil which resisted crystallisation (0.13 g, 0.48 mmol, 56 %); Found: M^+, 273.1522. $C_{20}H_{19}N$ requires M^+, 273.1518; δ_H (250 MHz, $CDCl_3$) 1.14 (1 H, dd, *J* 9.4, 5.3, H-1), 1.62 (3 H, dd, *J* 6.5, 1.6, C*H*$_3$CH=), 2.44 (3 H, s, CH_3-Ar), 2.71 (1 H, d, *J* 5.4, H-7), 4.89 (1 H, ddd, *J* 15.4, 9.5, 1.7, C*H*=CHMe), 5.54 (1 H, ddq, *J* 15.4, 1.0, 6.5,

=C*H*Me), 7.09-7.50 (8 H, m, aromatic), 8.18 (1 H, s, *H*C=N); δ_C (63 MHz, $CDCl_3$) 18.18 (CH_3), 19.30 (CH_3), 32.36 (CH), 35.67 (CH), 57.23 (quat), 123.45 (quat), 125.41, 126.22, 127.15, 127.27, 127.63, 128.28, 129.07, 129.88, 130.63, 131.41 (CH), 135.89 (quat), 138.81 (quat), 139.12 (quat), 153.82 (CH, H*C*=N).

v. Generation and Reaction of the Nitrile Ylide Derived from (*E,E*)-*N*-[2-(1-Methyl-4-phenylbuta-1,3-dienyl)benzyl]benzamide (326)

Method 1

(*E,E*)-*N*-[2-(1-Methyl-4-phenylbuta-1,3-dienyl)benzyl]benzamide (**326**) (0.07 g, 0.2 mmol) was dissolved in dry ether (7 cm^3) and heated at reflux with thionyl chloride (2 cm^3) for 20 hrs. The solvent and excess thionyl chloride were removed *in vacuo* and the residue was dried under high vacuum for 3 hrs, then dissolved in dry THF (10 cm^3) and cooled to 0 °C. Lithium bis(trimethylsilyl)amide (1 M in THF, 0.5 cm^3) was then added dropwise and the solution was stirred for 1 hr, then allowed to warm to room temperature. Aqueous ammonium chloride (25 % w/v, 10 cm^3) was added and the mixture was stirred for 10 minutes. The layers were separated, the aqueous phase was extracted with DCM (2 x 10 cm^3) and the combined organics were washed with water and dried. Removal of the solvent *in vacuo* gave a brown oil which could not be identified, with the ^1H NMR spectrum only showing a complex signal in the aromatic region.

Method 2

Thionyl chloride (0.675 g, 5.7 mmol) was dissolved in dry DMF (9.5 cm^3) and the solution was stirred under dry nitrogen for 30 minutes. This solution (0.8 cm^3) was added dropwise to a solution of (*E,E*)-*N*-[2-(1-methyl-4-phenylbuta-1,3-dienyl)benzyl]benzamide (**326**) (0.095 g, 0.27 mmol) in dry THF (5 cm^3) and the mixture stirred under a dry nitrogen atmosphere for 30 minutes to give the imidoyl chloride. This solution was cooled to 0 °C and lithium bis(trimethylsilyl)amide solution (1 M in THF, 1.4 cm^3) was added dropwise. The resulting solution was

stirred at 0 °C for 30 minutes. Removal of the solvents *in vacuo* at room temperature yielded only starting material and DMF.

Method 3

(*E,E*)-*N*-[2-(1-Methyl-4-phenylbuta-1,3-dienyl)benzyl]benzamide (**326**) (0.60 g, 1.7 mmol) and thionyl chloride (4.0 cm^3) were stirred at room temperature under nitrogen for 30 minutes, after which the excess thionyl chloride and volatile side-products were removed *in vacuo*. The residue was dried under high vacuum over P_2O_5 for one hour to give a clear yellow gum consisting of (*E,E*)-[2-(1-methyl-4-phenylbuta-1,3-dienyl)benzyl]benzimidoyl chloride (**327**) along with starting amide (85 % conversion to imidoyl chloride by ^1H NMR); δ_H (200 MHz, $CDCl_3$) 2.17 (3 H, s, CH_3), 4.92 (2 H, s, CH_2-N=C), 6.11 (1 H, d, *J* 11.3, olefinic H-2), 6.46 (1 H, d, *J* 15.4, olefinic H-4), 7.00-7.70 (13 H, m, aromatic and olefinic H-3), 8.03-8.07 (2 H, m, aromatic).

The residual gum was dissolved in dry THF (25 cm^3) and cooled to 0 °C under dry nitrogen. Lithium bis(trimethylsilyl)amide (1 M in THF, 5.0 cm^3) was added dropwise and the solution was stirred at 0 °C for 30 minutes, then allowed to warm to room temperature. After 2 hours, ammonium chloride solution (25 cm^3, 25 % w/v) was added and the aqueous phase was extracted with DCM (2 x 25 cm^3). The combined extracts were washed with water (20 cm^3), dried, and the solvents removed *in vacuo* to leave a brown oil. Dry flash column chromatography (silica, 0-50 % hexane-ether) of this oil gave (*E*)-7b-methyl-1a-phenyl-1-*exo*-(2-phenylethenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (**329**) as a white solid (0.38 g, 1.1 mmol, 79 % based on converted amide), mp 138-138.5 °C (hexane); Found: M^+, 335.1680. $C_{25}H_{21}N$ requires M^+, 335.1674; δ_H (250 MHz, $CDCl_3$) 1.54 (1 H, d, *J* 10.1, H-1a), 1.55 (3 H, s, CH_3), 6.00 (1 H, dd, *J* 15.8, 10.1, olefinic), 6.51 (1 H, d, *J* 15.7, =C*H*Ph), 7.18-7.59 (14 H, m, aromatic), 8.16 (1 H, s, CH=N); δ_C (63 MHz, $CDCl_3$) 17.00 (CH_3), 33.9 (quat), 41.4 (CH), 61.9 (quat), 123.6 (quat), 124.6 (CH), 125.8 (2 x CH, aromatic), 125.9 (CH), 126.0 (CH), 127.0 (CH), 127.5 (CH), 128.4 (2

x CH, aromatic), 128.5 (2 x CH, aromatic), 129.5 (CH), 131.1 (2 x CH, aromatic), 131.6 (CH), 132.3 (CH), 137.4 (CH), 139.1 (CH), 140.8 (quat), 153.6 (CH, CH=N).

vi. Generation and Reaction of the Nitrile Ylide Derived from (*E,E*)-*N*-[2-(1-Methylpenta-1,3-dienyl)benzyl]benzamide (338)

Freshly distilled thionyl chloride (1.64 g, 1.0 cm^3, 13.8 mmol) was added to dry DMF (4.0 cm^3) and this solution was stirred for 1 hour at room temperature. An aliquot (3.0 cm^3) of this solution was added to a solution of (*E,E*)-*N*-[2-(1-methylpenta-1,3-dienyl)benzyl]benzamide (**338**) (0.22 g, 0.76 mmol) in dry THF (25 cm^3). A fine precipitate formed almost immediately and the solution was stirred at room temperature for 90 minutes before being cooled in an ice-bath. Lithium bis(trimethylsilyl)amide solution (1.0 M in THF, 20 cm^3, 20 mmol) was added dropwise with stirring. The solution turned deep red and was stirred at room temperature for 2 hours. After this time, ammonium chloride solution (25 %, 30 cm^3) was added and the aqueous phase was extracted with DCM (3 x 30 cm^3) and the combined organic extracts were washed with water and dried. On removal of the solvents *in vacuo* at room temperature a brown oil was obtained. Dry-flash column chromatography (silica, hexane-ether, gradient elution) gave (*E*)-1a-phenyl-7b-methyl-1-*exo*-(2-propenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (**339**) as a yellow foam which resisted crystallisation (0.14 g, 0.51 mmol, 67 %); Found: $[M+H]^+$, 274.1596. $C_{20}H_{20}N$ requires $[M+H]^+$, 274.1596; δ_H (250 MHz, $CDCl_3$) 1.24 (1 H, d, *J* 9.8, H-1), 1.37 (3 H, s, CH_3), 1.66 (3 H, dd, *J* 6.5, 1.6, CH_3CH=), 5.17 (1 H, ddq, *J* 15.2, 9.8, 1.6, H-9b), 5.50 (1 H, dq, *J* 15.2, 6.5, H-10b), 7.14-7.48 (9 H, m, aromatic), 8.05 (1 H, br. s, C*H*=N); δ_C (63 MHz, $CDCl_3$) 16.55 (CH_3), 18.32 (CH_3), 40.33 (CH, cyclopropyl C-1), 60.51 (quat, C-7), 123.24 (quat), 124.19 (CH), 125.46 (CH), 125.72 (CH), 127.00 (CH), 128.05 (2 x CH), 128.19 (CH), 129.10 (CH), 130.86 (2 x CH), 131.20 (CH), 139.05 (quat), 140.71 (quat), 152.93 (CH, CH=N), 157.31 (quat).

vii. Generation and Reaction of the Nitrile Ylide Derived from (*E*)-*N*-[2-(1-Methylbuta-1,3-dienyl)benzyl]benzamide (343)

Distilled thionyl chloride (0.66 g, 5.6 mmol) was added to dry DMF (4.6 cm^3, 4.32 g, 59.2 mmol) under a nitrogen atmosphere and the resulting solution was stirred for 1 hour at room temperature. An aliquot of this solution (2.50 cm^3) was added to a solution of (*E*)-*N*-[2-(1-methylbuta-1,3-dienyl)benzyl]benzamide (**343**) (0.13 g, 0.47 mmol) in dry THF (15 cm^3) under a nitrogen atmosphere and the resulting suspension was stirred for 2 hours at room temperature, then cooled in an ice bath. Lithium bis(trimethylsilyl)amide (1.0 M in THF, 4.7 cm^3, 4.7 mmol) was added dropwise and the solution was stirred for 30 minutes with cooling, then 30 minutes at room temperature. Ammonium chloride solution (25 % w/v, 20 cm^3) was added and the aqueous phase was extracted with DCM (3 x 40 cm^3). The combined organic extracts were washed with water (40 cm^3), dried and the solvents were removed *in vacuo* to leave a dark solid residue. Dry-flash column chromatography (silica, hexane-ether, gradient elution) gave only 1a-phenyl-7b-methyl-1-*exo*-ethenyl-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (**344**) as a clear yellow gum which did not solidify (0.10 g, 0.39 mmol, 82 %); Found: M^+, 259.1363. $C_{19}H_{17}N$ requires M^+, 259.1361; δ_H (250 MHz, $CDCl_3$) 1.35 (1 H, d, *J* 10.0, H-1), 1.49 (3 H, s, CH_3), 5.16 (1 H, dd, *J* 10.2, 1.9, *E* CH=C*H*$_2$), 5.19 (1 H, dd, *J* 16.9, 1.9, *Z* CH=C*H*$_2$), 5.62 (1 H, ddd, *J* 17.0, 10.1, 10.1, C*H*=CH_2) 7.25-7.59 (9 H, m, aromatic), 8.16 (1 H, br. s, HC=N); δ_C (63 MHz, $CDCl_3$) 16.8 (CH_3), 41.4 (CH, C-1), 61.3 (quat *C*-CH_3) 117.4 (CH_2), 124.53 (CH), 125.88 (CH), 127.4 (CH), 127.4 (quat), 128.4 (3 x CH), 129.41 (CH), 131.02 (CH), 131.5 (CH), 131.5 (quat), 134.02 (CH), 139.07 (quat), 140.75 (quat), 153.44 (CH=N).

viii. Generation and Reaction of the Nitrile Ylide Derived from (*E,E*)-*N*-[2-(2-Methyl-4-phenylbuta-1,3-dienyl)benzyl]benzamide (372)

Thionyl chloride (0.94 g, 7.9 mmol) was added to dry DMF (8.8 cm^3) and the solution was stirred at room temperature under nitrogen for 30 minutes. This solution (5 cm^3) was added to a solution of (*E,E*)-*N*-[2-(2-methyl-4-phenylbuta-1,3-

dienyl)benzyl]benzamide (**372**) (0.20 g, 0.57 mmol) in dry THF (10 cm^3) and the mixture was stirred for 30 minutes at room temperature, again under nitrogen. The solution was cooled in an ice-bath and lithium bis(trimethylsilyl)amide solution (10 cm^3, 1 M in THF, 10 mmol) was added. The solution was stirred for 1 hour then allowed to warm to room temperature, when ammonium chloride solution (25 % w/v, 20 cm^3) was added. The aqueous layer was extracted with DCM (2 x 25 cm^3) and the combined extracts were washed with water (2 x 25 cm^3) and dried. Removal of the solvents *in vacuo* gave a black gum, which upon dry flash column chromatography (silica, hexane-ether gradient elution) gave 8-methyl-11,13-diphenyl-12-azatetracyclo[7.3.1.$0^{2,7}$.$0^{8,10}$]trideca-2(7),3,5,11-tetraene (**378**) (0.12 g, 0.36 mmol, 63 %); Found: M^+, 335.1674. $C_{25}H_{21}N$ requires M^+, 335.1674. δ_H (250 MHz, $CDCl_3$) 2.03 (3 H, dd, *J* 1.8, 1.8, CH_3), 3.75 (1 H, dq, 3.9, 1.8, H-9), 4.56 (1 H, d, *J* 1.2, H-1), 4.98 (1 H, ddt *J* 3.8, 2.8, 1.5, H-10), 5.51 (1 H, dd, *J* 2.7, 1.6, H-13), 7.15-7.65 (12 H, m, aromatic), 7.92-7.98 (2 H, m, aromatic); δ_C (90 MHz, $CDCl_3$) 26.1 (CH_3), 48.2 (CH), 48.4 (CH), 68.1 (CH), 124.0 (CH), 124.4 (CH), 125.6 (CH), 127.1 (CH), 127.3 (CH), 127.3 (CH), 127.5 (2 x CH, aromatic), 128.8 (2 x CH, aromatic), 128.9 (2 x CH, aromatic), 129.0 (2 x CH, aromatic), 130.8 (CH), 135.9 (quat), 137.6 (quat), 139.3 (quat), 140.2 (quat), 141.9 (quat), 174.5 (quat, C=N).

^1H-^{13}C Correlation NMR data;

δ_H(ppm)	2.03 (3 H)	3.75	4.56	4.98	5.51	7.91-7.98 (2 H)
δ_C(ppm)	26.1 (CH_3)	48.2	48.4	124.4	68.1	127.5 (2 x CH)
Position	8	9	1	10	13	2 x *o*-H, Ph-C-11

COSY ^1H-^1H Correlation NMR data;

δ_H(ppm)	Couples with signal at (ppm);
2.03 (3 H, CH_3)	3.75 (H-9), 4.98 (H-10)
3.75 (1 H, H-9)	2.03 (CH_3), 4.98 (H-10), 5.51 (H-13)
4.56 (1 H, H-1)	-
4.98 (1 H, H-10)	2.03 (CH_3), 3.75 (H-9)
5.51 (1 H, H-13)	3.75 (H-9)

Signals are from a single proton or CH carbon unless otherwise stated.

ix. Generation and Reaction of the Nitrile Ylide Derived from (*E,E*)-*N*-Benzoyl-2-aminomethyl-3-(4-phenylbuta-1,3-dienyl)thiophene (395)

Method 1

(*E,E*)-*N*-Benzoyl-2-aminomethyl-3-(4-phenylbuta-1,3-dienyl)thiophene (**395**) (0.10 g, 0.29 mmol) and thionyl chloride (5 cm^3) were stirred at room temperature under nitrogen for one hour, after which the volatile residues were removed *in vacuo*. The remaining dark-red oil was stored under high vacuum for one hour and then dissolved in dry THF (30 cm^3), transferred to a three-necked flask and cooled to 0 °C under nitrogen. Lithium bis(trimethylsilyl)amide (3.0 cm^3, 1 M in THF, 3.0 mmol) was added and the solution was stirred for an hour, then allowed to warm to room temperature. After one hour ammonium chloride solution (40 cm^3) was added and the aqueous phase was extracted with DCM (2 x 40 cm^3), washed with water (40 cm^3), dried, and the solvents were removed *in vacuo* to leave a yellow oil. Dry-flash column chromatography gave no identifiable products.

Method 2

A solution of thionyl chloride (0.49 g, 4.13 mmol) in dry DMF (1.2 cm^3) was added dropwise to a solution of (*E,E*)-*N*-benzoyl-2-aminomethyl-3-(4-phenylbuta-1,3-dienyl)thiophene (**395**) (0.10 g, 0.29 mmol) in dry THF (20 cm^3) and this mixture was stirred for 45 minutes at room temperature. The solution was then cooled to –78 °C and lithium bis(trimethylsilyl)amide solution (1 M in THF, 15.0 cm^3, 15.0 mmol) was added dropwise with vigorous stirring. The reaction was stirred at –78 °C for 30 minutes then allowed to warm to room temperature, when saturated ammonium chloride solution (20 cm^3) was added. The organic layer was extracted with ether (2 x 25 cm^3) and the combined extracts were washed with water (25 cm^3), dried, and the solvents were removed *in vacuo*. Dry-flash column chromatography (silica, hexane-ether, gradient elution) gave, in order of elution; a) 10,12-diphenyl-3-thia-11-azatricyclo[6.3.2.$0^{2,7}$]dideca-2(6),4,8,11-tetraene (**396**) (0.06 g, 0.17 mmol, 59 %);

Found: M^+, 327.1081. $C_{22}H_{17}NS$ requires M^+, 327.1082; δ_H (250 MHz, $CDCl_3$) 3.79 (1 H, dd, *J* 5.8, 2.4, H-10), 4.88 (1 H, d, *J* 8.1, H-7), 5.34 (1 H, dd, *J* 10.6, 1.5, H-9), 5.65 (1 H, dd, *J* 2.0, 2.0, H-1), 6.36 (1 H, ddd, *J* 10.6, 8.1, 2.5, H-8), 6.99 (1 H, d, *J* 4.9, thienyl), 7.19 (1 H, d, *J* 5.0, thienyl), 7.25-7.50 (8 H, m, aromatic), 7.88-7.92 (2 H, m, aromatic, N=C-Ph, *ortho* H); δ_C (63 MHz, $CDCl_3$) 40.0 (CH, C-10), 46.8 (CH, C-7), 63.1 (CH, C-1), 123.4 (CH), 123.5 (CH), 127.0 (CH), 127.0 (2 x CH, aromatic), 127.7 (CH), 128.29 (2 x CH, aromatic), 128.34 (2 x CH, aromatic), 128.4 (2 x CH, aromatic), 130.3 (CH), 131.4 (CH), 136.9 (quat), 137.3 (quat), 140.2 (quat), 144.1 (quat), 175.8 (quat, C-12);

and b) 3-phenyl-4-(*E*)-(2-phenylethenyl)[7,6h]thieno-1*H*-2-azepine (**400**) (0.03 g, 0.08 mmol, 28 %); Found: M^+, 327.1083. $C_{22}H_{17}NS$ requires M^+, 327.1082; δ_H (250 MHz, $CDCl_3$/DMSO) 6.23 (1 H, d, *J* 16.4, olefinic), 6.85 (1 H, d, *J* 16.4, =C*H*Ph) 7.08-7.54 (13 H, m, aromatic and H-4); methylene protons unobserved at 298 K; δ_C (63 MHz, $CDCl_3$); 39.9 (CH_2), 122.8 (CH), 125.4 (2 x CH, aromatic), 126.1 (CH), 127.0 (CH), 127.3 (2 x CH, aromatic), 127.8 (2 x CH, aromatic), 128.1 (CH), 128.3 (2 x CH, aromatic), 128.6 (CH), 130.3 (CH), 132.3 (CH), 136.0 (quat), 136.6 (quat), 137.5 (quat), 137.5 (quat), 139.2 (quat), 166.0 (quat, C=N).

x. Attempted Generation and Reaction of the Nitrile Ylide Derived from (E,E)-N-Benzoyl-2-aminomethyl-3-(penta-1,3-dienyl)thiophene (404)

Method 1

To a solution of (*E,E*)-*N*-benzoyl-2-aminomethyl-3-(penta-1,3-dienyl)thiophene (**404**) (0.05 g, 0.18 mmol) in dry THF (10 cm^3) was added DMF-$SOCl_2$ (1.0 cm^3, prepared by adding $SOCl_2$ (0.50 g) to dry DMF (5.0 cm^3) and stirring for 30 minutes at room temperature). This mixture was stirred for 1 hour, then cooled to 0 °C and lithium bis(trimethylsilyl)amide solution (5.0 cm^3, 1.0 M in THF) was added. After 3 hours of stirring at 0 °C, TLC analysis of the reaction showed consumption of starting material but formation of no new products. Workup of the reaction gave no identifiable products.

Method 2

This experiment was carried out as detailed for the previous reaction, but the imidoyl chloride solution was cooled in a cardice-acetone bath prior to the addition of the base. The outcome was similar to the previous reaction.

XIV. Thermally Promoted Rearrangements of 1-Alkenyl *exo*-Cyclopropa[*c*]isoquinolines

i. Thermal Rearrangement of (*E*)-1a-Phenyl-1-*exo*-(2-phenylethenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (265)

The reactant **265** (0.06g, 0.19 mmol) was dissolved in deuteriochloroform and heated in refluxing ethyl formate (bp 54-55 °C) in an NMR tube for 30 minute periods, with a spectrum being obtained after each period. After the tenth period (*ie.* 5 hours) no further changes in the spectrum occurred. Evaporation of the solvent gave 11,13-diphenyl-12-azatricyclo[6.3.2.$0^{2,7}$]trideca-2(7),3,5,9,12-pentaene (**268**) in quantitative yield; Found: $(M+H)^+$, 322.1596. $C_{24}H_{20}N$ requires $(M+H)^+$, 322.1598; δ_H (250 MHz, $CDCl_3$) 3.76 (1 H, ddd, *J* 3.5, 2.6, 2.6, H-11), 4.67 (1 H, d, *J* 8.3, H-8), 5.27 (1 H, dddd, *J* 10.5, 3.5, 1.7, 0.9, H-10), 5.45 (1 H, dd, *J* 2.6, 1.7, H-1), 6.32 (1 H, ddd, *J* 10.5, 8.3, 2.6, H-9), 7.21- 7.64 (12 H, m, aromatic), 7.85 (2 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 42.7 (CH), 47.0 (CH), 67.9 (CH), 123.8 (CH), 125.1 (CH), 126.3 (CH), 126.6 (CH), 126.7 (CH), 127.5 (CH), 128.2 (CH), 128.3 (CH), 130.2 (CH), 130.4 (CH), 136.7 (CH), 136.9 (quat), 138.7 (quat), 140.5 (quat), 140.6 (quat), 175.9 (CH).

ii. Thermal Rearrangement of 1a-Phenyl-1-*exo*-ethenyl-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (277)

The reactant **277** (0.07 g, 0.29 mmol) was dissolved in deuteriochloroform and heated in refluxing ethyl formate (bp 54-55 °C) in an NMR tube for measured periods of time, with an NMR spectrum being obtained after each period. After 17

hrs of heating no further changes between the spectra occurred, with a mixture of two compounds now present. Dry-flash column chromatography (silica, hexane-ether, gradient elution) of this mixture gave, in order of elution; a) 3-phenyl-4-ethenyl-1*H*-2-benzazepine (**279**); (0.04 g, 0.17 mmol, 60 %); Found: M^+, 245.1208. $C_{18}H_{15}N$ requires M^+, 245.1205; δ_H (250 MHz, $CDCl_3$) 3.93 (1 H, br. d, *J* 9.4, methylene), 5.00 (br. d, *J* 9.4, methylene), 5.05 (1 H, d, *J* 17.5, olefinic), 5.17 (1 H, d, *J* 11.0, olefinic), 6.54 (1 H, ddd, *J* 17.6, 11.0, 0.8, C*H*=CH_2), 7.25-7.56 (10 H, m, aromatic and H-4); δ_C (63 MHz, $CDCl_3$) 56.1 (CH_2), 118.8 (=CH_2), 127.2 (CH), 127.9 (3 x CH), 128.7 (CH), 128.8 (2 x CH), 129.2 (2 x CH), 135.6 (quat), 136.5 (CH), 136.6 (CH), 137.7 (quat), 138.0 (quat), 139.3 (quat), 165.4 (quat, C=N);

and b) 13-phenyl-12-azatricyclo[6.3.2.$0^{2,7}$]trideca-2(7),3,5,9,12-pentaene (**281**) (0.03 g, 0.12 mmol, 40 %); Found: M^+, 245.1205. $C_{18}H_{15}N$ requires M^+, 245.1205; δ_H (360 MHz, $CDCl_3$) 2.51 (1 H, dddd, *J* 18.9, 5.3, 3.2, 1.5, H-11a), 2.78 (1 H, ddd, *J* 18.9, 6.0, 3.5, H-11b), 4.60 (1 H, d, *J* 8.3, H-8), 5.12-5.23 (2 H, m, H-1 and H-10), 6.14 (1 H, dddd, *J* 10.7, 8.2, 2.2, 2.2, H-9), 7.08-7.42 (7 H, m, aromatic), 7.78-7.83 (2 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 29.6 (CH_2), 42.9 (CH, C-8), 61.5 (CH, C-1), 123.7 (CH), 125.2 (CH), 126.4 (CH), 126.6 (CH), 126.8 (3 x CH), 127.3 (CH), 128.5 (2 x CH, aromatic), 130.4 (CH), 138.3 (quat), 141.3 (quat), 159.8 (quat), 175.6 (quat, C=N).

iii. Thermal Rearrangement of (*E*)-1a-Phenyl-1-*exo*-(2-propenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (291)

(*E*)-1a-Phenyl-1-*exo*-(2-propenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (**291**) (0.04 g, 0.15 mmol) was dissolved in $CDCl_3$ in an NMR tube. This tube was heated at 64 °C and after each 30-minute period of heating a ^1H NMR spectrum was obtained. After 16 hours of heating the starting material was found to have completely rearranged. Dry-flash column chromatography (silica, hexane-ether gradient elution) gave a pale-yellow oil in quantitative yield, which was found by ^1H NMR and mass spectrometry [Found: M^+, 259.1361. $C_{19}H_{17}N$ requires M^+, 259.1361] to be a 1:3 mixture of; a) 11-methyl-13-phenyl-12-

azatricyclo[6.3.2.$0^{2,7}$]trideca-2(7),3,5,9,12-pentaene (**293**); δ_H (360 MHz, $CDCl_3$) 1.37 (3 H, d, *J* 7.4, CH_3), 2.63-2.68 (1 H, m, H-11, C*H*Me), 4.56 (1 H, d, *J* 8.3, H-8), 5.10-5.14 (1 H, m, H-10), 5.32 (1 H, dd, *J* 2.0, 2.1, H-1), 6.25 (1 H, ddd, *J* 10.5, 8.6, 2.0, H-9), 7.00-7.56 (7 H, m, aromatic), 7.88-8.22 (2 H, m, aromatic);

and b) 4-*E*-(2-propenyl)-3-phenyl-1*H*-2-benzazepine (**292**); δ_H (360 MHz, $CDCl_3$) 1.73 (3 H, dq, *J* 6.7, 1.6, CH_3), 3.97 (1 H, br. d, *J* 9.9, methylene), 5.04 (1 H, br. d, *J* 9.9, methylene), 5.60 (1 H, dq, *J* 15.6, 6.7, =C*H*Me), 6.32 (1 H, dq, *J* 15.6, 1.6, C*H*=CHMe), 7.20-7.56 (8 H, m, aromatic and H-4), 7.56-7.64 (2 H, m, aromatic). Mixture; δ_C (90 MHz, $CDCl_3$) 19.0$^{\$}$ (CH_3), 19.2* (CH_3), 36.8$^{\$}$ (CH, C-11), 43.2$^{\$}$ (CH, C-7), 56.8* (CH_2), 67.9$^{\$}$ (CH, C-1), 124.3 (CH), 125.8 (CH), 126.6 (CH), 126.8 (CH), 127.0 (CH), 127.3 (CH), 127.6 (CH), 128.4 (CH), 128.4* (2 x CH, aromatic), 128.9 (CH), 129.0 (CH), 129.2 (CH), 129.3* (2 x CH, aromatic), 129.6 (CH), 130.6 (CH), 131.7* (CH, C*H*=CHMe), 131.8* (CH, C*H*Me), 134.0$^{\$}$ (CH, C-10), 134.7* (CH), 136.6$^{\$}$ (CH), 138.1$^{\$}$ (quat), 138.1* (quat), 138.8* (quat), 139.9$^{\$}$ (quat), 140.3* (quat), 141.2$^{\$}$ (quat), 166.1* (quat, C=N), 176.7$^{\$}$ (quat, C=N). * Denotes signals from the azepine. $^{\$}$ Denotes signals from the bridged isoquinoline.

These compounds proved inseparable by further chromatography and were indistinguishable under all TLC eluent systems used. A ^1H-^{13}C correlation experiment allowed assignment of some carbon signals.

^1H-^{13}C Correlation NMR Data for Bridged Isoquinoline **293**

δ_H (ppm)	1.37 (3 H)	4.56	5.14	5.32	6.25	7.88-8.22 (2 H)
δ_C (ppm)	19.0 (CH_3)	43.2	134.0	67.9	126.6	127.3 (2 x CH)

^1H-^{13}C Correlation NMR Data for 1*H*-2-Benzazepine **292**

δ_H (ppm)	1.73 (3 H)	3.97	5.04	5.60	6.32	7.56-7.64 (2 H)
δ_C (ppm)	19.2 (CH_3)	56.8 (CH_2)		131.8	131.7	129.3 (2 x CH)

Signals are from a single proton or CH carbon atom unless otherwise stated.

iv. Thermal Rearrangement of (*E*)-1a-(*o*-Tolyl)-1-*exo*-(2-propenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (301)

A solution of (*E*)-1a-(*o*-tolyl)-1-*exo*-(2-propenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (**301**) (0.05 g, 0.18 mmol) in $CDCl_3$ (0.7 cm^3) was heated at 64 °C in an NMR tube until ^1H NMR spectroscopy showed absence of starting material (after 21 hours). Two new products were observed, which were found to be inseparable by all techniques applied. Mass spectrometry of the mixture gave the following data; Found: M^+, 273.1525. $C_{20}H_{19}N$ requires M^+, 273.1518. The ^1H NMR spectrum of the mixture allowed identification of the components as; a) 11-methyl-13-(*o*-tolyl)-12-azatricyclo[6.3.2.$0^{2,7}$]trideca-2(7),3,5,9,12-pentaene (**302**); δ_H (250 MHz, $CDCl_3$) 1.38 (3 H, d, *J* 7.4, CH_3), 2.30 (3 H, s, CH_3-Ar), 2.52-2.68 (1 H, m, H-11), 4.14 (1 H, d, *J* 8.2, H-8), 5.08 (1 H, ddd, *J* 10.7, 3.6, 1.0, H-10), 5.22-5.24 (1 H, m, H-1), 5.98 (1 H, ddd, *J* 10.5, 8.5, 2.1, H-9), 7.06-7.46 (8 H, m, aromatic); and b) (*E*)-4-(2-propenyl)-3-(*o*-tolyl)-1*H*-2-benzazepine (**303**); δ_H (250 MHz, $CDCl_3$) 1.65 (3 H, dd, *J* 6.7, 1.7, CH_3), 2.16 (3 H, s, CH_3-Ar), 5.70 (1 H, dq, *J* 15.6, 6.6, =C*H*CH_3), 6.05 (1 H, dq, *J* 15.6, 1.6, C*H*=$CHCH_3$), 7.06-7.46 (9 H, m, aromatic and H-4), methylene H unobserved at 298 K; δ_C (63 MHz, $CDCl_3$) (for mixture) 18.3$^\$$ (CH_3), 18.7* (CH_3), 19.7* (CH_3), 20.3$^\$$ (CH_3), 36.0 (CH), 46.3 (CH), 56.0* (CH_2), 67.6 (CH), 123.4 (CH), 125.3 (CH), 125.5 (CH), 125.6 (CH), 126.2 (CH), 126.4 (CH), 127.1 (CH), 127.7 (2 x CH), 128.0 (CH), 128.2 (2 x CH), 128.7 (CH), 128.9 (CH), 129.3 (CH), 129.6 (CH), 130.3 (2 x CH), 130.5 (CH), 133.0 (CH), 133.5 (CH), 134.9$^\$$ (quat), 135.6* (quat), 135.9* (quat), 137.0* (quat), 139.1* (quat), 139.5$^\$$ (quat), 139.7* (quat), 140.7$^\$$ (quat), 147.4$^\$$ (quat), 166.9* (quat, C=N), 179.7$^\$$ (quat, C=N). * Denotes signals due to the alkenyl benzazepine, $^\$$ denotes signals due to the bridged isoquinoline. Where unambiguous assignment was not possible no symbol is used. The ratio of azepine to bridged isoquinoline was determined as 3:1 from the integral traces on the ^1H NMR spectrum.

v. Thermal Rearrangement of (*E*)-7b-Methyl-1a-phenyl-1-*exo*-(2-phenylethenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (329)

A solution of (*E*)-7b-methyl-1a-phenyl-1-*exo*-(2-phenylethenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (**329**) was placed in an NMR tube and the tube was immersed in refluxing ethyl formate (bp 54 °C). ^{1}H NMR spectra were obtained at regular intervals and after a total of 8 hours of heating all starting material was observed to have rearranged. The only observed product was (*E*)-5-methyl-4-(2-phenylethenyl)-3-phenyl-1*H*-2-benzazepine (**331**), which was obtained in quantitative yield; Found: $(M+H)^+$, 336.1749. $C_{25}H_{22}N$ requires $(M+H)^+$, 336.1752. δ_H (200 MHz, $CDCl_3$) 2.54 (3 H, d, *J* 1.1, CH_3), 3.95 (1 H, d, *J* 9.9, CH_2), 4.80 (1 H, d, *J* 9.6, CH_2), 6.14 (1 H, d, *J* 16.1, olefinic), 7.12-7.52 (15 H, m, aromatic and olefinic); δ_C (63 MHz, $CDCl_3$) 20.1 (CH_3), 56.0 (CH_2), 124.9 (CH), 126.2 (2 x CH, aromatic), 127.1 (CH), 127.1 (CH), 127.4 (CH), 127.7 (CH), 127.9 (2 x CH, aromatic), 128.2 (CH), 128.4 (4 x CH, aromatic), 128.8 (CH), 133.9 (quat), 136.2 (CH), 137.1 (quat), 139.8 (quat), 140.0 (quat), 140.3 (quat), 141.5 (quat), 166.0 (quat, C=N).

vi. Thermal Rearrangement of (*E*)-1a-Phenyl-7b-methyl-1-*exo*-(2-propenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (339)

(*E*)-1a-Phenyl-7b-methyl-1-*exo*-(2-propenyl)-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (**339**) (0.06 g, 0.22 mmol) was dissolved in $CDCl_3$ in an NMR tube, which was immersed in refluxing ethyl formate (bp 54 °C). The progress of the rearrangement was checked by ^{1}H NMR after every 30 minutes of heating and the starting material was found to have completely disappeared after 4 hours. The only product of the rearrangement was (*E*)-5-methyl-4-(2-propenyl)-3-phenyl-1*H*-2-benzazepine (**340**), in quantitative yield; Found $[M+H]^+$, 274.1597. $C_{20}H_{20}N$ requires $[M+H]^+$, 274.1596; δ_H (250 MHz, $CDCl_3$) 1.59 (3 H, dd, *J* 6.6, 1.5, =CHC*H*$_3$), 2.43 (3 H, s, CH_3), 3.89 (1 H, d, *J* 9.8, methylene), 4.76 (1 H, d, *J* 9.8, methylene), 5.30 (1 H, dq, *J* 15.8, 6.7, =C*H*CH$_3$), 6.55 (1 H, dq, *J* 15.8, 1.8, CH$_3$CH=C*H*), 7.14-7.49 (9 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 18.73 (CH_3), 19.58

(CH_3), 55.66 (CH_2), 126.70 (CH), 126.74 (CH), 126.91 (CH), 127.19 (CH), 127.46 (2 x CH), 127.56 (CH), 128.20 (2 x CH), 128.31 (CH), 133.71 (CH), 139.05 (quat), 139.51 (quat), 139.61 (quat), 140.23 (quat), 157.34 (quat, C-4), 166.19 (quat, C=N).

vii. Thermal Rearrangement of 1a-Phenyl-7b-methyl-1-*exo*-ethenyl-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (344)

1a-Phenyl-7b-methyl-1-*exo*-ethenyl-1a,7b-dihydro-1*H*-cyclopropa[*c*]isoquinoline (**344**) (0.09 g, 0.35 mmol) was dissolved in $CDCl_3$ (0.5 cm^3) in an NMR tube and this was immersed in refluxing ethyl formate. After each 30 minutes of heating in this manner a ^1H NMR spectrum was recorded. After 4 hours of heating the starting material had converted exclusively to 5-methyl-4-ethenyl-3-phenyl-1*H*-2-benzazepine (**346**) in quantitative yield; Found: $[M+H]^+$, 260.1434. $C_{19}H_{18}N$ requires $[M+H]^+$, 260.1439; δ_H (250 MHz, $CDCl_3$) 2.52 (3 H, s, CH_3), 3.97 (1 H, d, *J* 9.8, methylene), 4.85 (1 H, d, *J* 9.6, methylene), 4.90 (1 H, dd, *J* 17.4, 1.1, =CH, *Z*), 5.27 (1 H, dd, *J* 11.1, 1.0, =CH, *E*), 6.96 (1 H, dd, *J* 17.6, 11.1, *H*C=CH_2), 7.22-7.58 (9 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 20.56 (CH_3), 55.91 (CH_2-N), 121.54 (CH_2, vinylic), 126.98 (2 x CH), 127.29 (CH), 127.77 (2 x CH), 128.19 (CH), 128.44 (2 x CH), 128.72 (CH), 132.97 (CH), 134.06 (quat), 139.60 (quat), 139.84 (quat), 140.31 (quat), 141.58 (quat), 166.16 (quat, N=*C*-Ph).

XV. Generation and Thermal Decomposition of the Diazoalkanes Derived from (*E,E*) Triene-Conjugated Tosylhydrazones

i. Generation and Thermal Decomposition of the Sodium Salt of (*E,E*)-2-(4-Phenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (496)

To a solution of (*E,E*)-2-(4-phenylbuta-1,3-dienyl)benzaldehyde tosylhydrazone **496** (0.20 g, 0.50 mmol) in dry ethanol (10 cm^3) was added sodium ethoxide solution (1.0 cm^3, 0.48 M in ethanol). The solution was stirred at room temperature, in the dark and under nitrogen, for 1 hour, when the solvent was removed *in vacuo*. The solid red residue was dried at high vacuum over P_2O_5 overnight, then dissolved in dry

DME (20 cm^3). This solution was heated at reflux, under nitrogen and in the dark, for 3 hours, after which TLC analysis showed absence of starting material and one major new product spot. The solvent was removed *in vacuo* and dry-flash column chromatography (silica, hexane-ether) of the red oily residue gave (*E*)-4-phenylethenyl-1*H*-2,3-benzodiazepine **499** as a bright yellow oil (0.10 g, 0.4 mmol, 80 %); Found: M^+, 246.1157. $C_{17}H_{14}N_2$ requires M^+, 246.1154; δ_H (250 MHz, $CDCl_3$) 3.09 (1 H, br. d, *J* 9.3, methylene), 6.38 (1 H, br. d, *J* 9.3, methylene), 6.75 (1 H, s, H-4), 7.08 (1 H, dd, *J* 16.2, 0.5, olefinic), 7.19-7.59 (10 H, m, aromatic and olefinic); δ_C (63 MHz, $CDCl_3$) 69.20 (CH_2), 117.09, 125.71 (CH), 126.16 (quat), 126.71 (2 x CH, aromatic), 127.88, 127.98, 128.11, 128.42 (CH), 128.65 (2 x CH, aromatic), 130.68, 131.70 (CH), 133.96, 136.53 (quat); T_c (methylene) 343 K.

ii. Generation and Thermal Decomposition of the Sodium Salt of (*E*)-2-(Buta-1,3-dienyl)benzaldehyde Tosylhydrazone (506)

In the dark and under nitrogen, freshly prepared sodium methoxide solution (1.9 M, 1.0 cm^3) was added to a solution of (*E*)-2-(buta-1,3-dienyl)benzaldehyde tosylhydrazone **506** (0.66 g, 2.02 mmol) in dry methanol (10 cm^3) and this solution was stirred for 1 hour. The solvent was removed *in vacuo* and the residual orange salt was dried overnight in a high vacuum, over fresh P_2O_5. The salt was dissolved in dry DME (25 cm^3) and the solution was heated at reflux, under nitrogen and in the dark, for 2 hours. Filtration of the resultant suspension and removal of the solvent *in vacuo*, followed by dry-flash column chromatography (silica, hexane-ether, gradient elution) gave 4-ethenyl-1*H*-2,3-benzodiazepine **510** (0.27 g, 1.6 mmol, 79 %); Found: M^+, 170.0844. $C_{11}H_{10}N_2$ requires M^+, 170.0844; δ_H (250 MHz, $CDCl_3$) 3.00 (1 H, d, *J* 9.4, H-1 ax), 5.45 (1 H, ddd, *J* 10.9, 1.1, 0.6, $=CH_2$, *E*), 5.88 (1 H, ddd, *J* 17.7, 1.1, 0.4, $=CH_2$, *Z*), 6.36 (1 H, d, *J* 9.3, H-1 eq), 6.65 (1 H, s, H-5), 6.74 (1 H, ddd, *J* 17.3, 10.8, 0.5, C*H*=CH_2), 7.15-7.58 (4 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 69.1 (CH_2), 117.0 (CH), 117.3 (CH_2, $=CH_2$), 126.1 (quat), 127.8 (CH), 128.0 (CH), 128.3 (CH), 130.8 (CH), 133.6 (quat), 134.2 (CH), 150.4 (quat).

iii. Generation and Thermal Decomposition of the Sodium Salt of (*E,E*)-2-(Penta-1,3-dienyl)benzaldehyde Tosylhydrazone (505)

In the dark and under nitrogen, sodium methoxide solution (1.0 cm^3, 1.39 M, 1.39 mmol) was added to a solution of (*E,E*)-2-(penta-1,3-dienyl)benzaldehyde tosylhydrazone **505** (0.50 g, 1.47 mmol) in dry methanol (10 cm^3) and the mixture was stirred for 1 hour at room temperature. The solvent was removed and the residue was dried under high vacuum over P_2O_5 overnight. The salt was dissolved in dry DME (20 cm^3) and the solution was heated to reflux under nitrogen and in the dark for 2 hours, after which TLC analysis showed absence of starting material. The mixture was cooled, filtered through a celite pad and the solvents were removed *in vacuo*. Dry-flash column chromatography (silica, hexane-ether, 0-25 %) gave (*E*)-4-(2-propenyl)-1*H*-2,3-benzodiazepine **509** as a bright yellow oil (0.234 g, 1.27 mmol, 91 %); Found: M^+, 184.1000. $C_{12}H_{12}N_2$ requires M^+, 184.1001; δ_H (250 MHz, $CDCl_3$) 1.93 (3 H, d, *J* 5.1, CH_3), 2.99 (1 H, d, *J* 9.2, CH_2), 6.30 (1 H, d, *J* 9.2, CH_2), 6.31-6.46 (2 H, m, olefinic), 6.51 (1 H, s, H-5), 7.32-7.53 (4 H, m, Ar-H); δ_C (63 MHz, $CDCl_3$) 18.5 (CH_3), 68.9 (CH_2), 115.0 (CH, =*C*HCH_3), 125.9 (quat), 127.6 (CH), 127.7 (CH), 128.2 (CH), 128.5 (CH), 129.8 (CH), 130.2 (CH), 133.9 (quat), 150.7 (quat).

iv. Generation and Thermal Decomposition of the Sodium Salt of (*E,E*)-2-(1-Methylpenta-1,3-dienyl)benzaldehyde Tosylhydrazone (512)

To a solution of (*E,E*)-2-(1-methylpenta-1,3-dienyl)benzaldehyde tosylhydrazone **512** (0.35 g, 0.99 mmol) in dry methanol (15 cm^3) was added a solution of sodium methoxide in methanol (1 cm^3, 0.96 M). This solution was stirred at room temperature, in the dark and under nitrogen, for 1 hour, after which the solvent was removed *in vacuo*. After drying the residue overnight, in a high vacuum, over P_2O_5 and in the dark, it was dissolved in dry DME (20 cm^3). This solution was heated at reflux in the dark, under dry nitrogen, for 3 hours. The precipitated sodium *p*-toluenesulfinate was removed by filtration through a celite pad and the solvent was removed from the filtrate *in vacuo*. Dry-flash column chromatography (silica,

hexane-ether) of the bright-yellow residue gave (*E*)-5-methyl-4-(2-propenyl)-1*H*-2,3-benzodiazepine **514** as a yellow oil (0.15 g, 0.75 mmol, 76 %); Found: M^+, 198.1156; $C_{13}H_{14}N_2$ requires M^+, 198.1156; δ_H (250 MHz, $CDCl_3$) 1.95 (3 H, dd, *J* 6.8, 1.6, C*H*$_3$-CH), 2.40 (3 H, s, CH_3), 3.16 (1 H, d, *J* 9.9, methylene), 6.09 (1 H, d, *J* 9.9, methylene), 6.33 (1 H, dq, *J* 15.4, 6.8, =C*H*CH_3), 6.67 (1 H, dq, *J* 15.4, 1.6, C*H*=$CHCH_3$), 7.25-7.59 (4 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 17.67 (CH_3), 18.96 (CH_3), 68.35 (CH_2), 120.70 (quat), 124.85 (CH), 125.83 (CH), 127.59 (CH), 127.89 (CH), 128.72 (quat), 129.25 (CH), 130.90 (CH), 136.34 (quat), 148.18 (quat).

v. Preparation and Thermal Decomposition of the Sodium Salt of (*E,E*)-2-(2-Methyl-4-phenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (518)

Sodium methoxide solution (1.0 cm^3, 0.87 M in methanol) was added to a solution of (*E,E*)-2-(2-methyl-4-phenylbuta-1,3-dienyl)benzaldehyde tosylhydrazone **518** (0.38 g, 0.91 mmol). This solution was stirred in the dark and under a dry nitrogen atmosphere for 1 hour, after which the solvent was removed *in vacuo*. The residual salt was dried at high vacuum, over P_2O_5 and in the dark, overnight, then dissolved in dry DME (25 cm^3). This solution was heated at reflux for 3 hours, after which the precipitated salt was filtered off and the filtrate was evaporated to leave a viscous yellow oil. Dry flash column chromatography (silica, hexane) gave 2,2'-di-[(*E,E*)-2-methyl-4-phenylbuta-1,3-dienyl]-*E*-stilbene **521** (0.16 g, 0.36 mmol, 78 %) as fine white needles, mp 168-169.5 °C (hexane); Found: M^+, 464.2493. $C_{36}H_{32}$ requires M^+, 464.2504; δ_H (250 MHz, $CDCl_3$) 1.90 (6 H, d, *J* 1.0, 2 x CH_3), 6.63 (2 H, d, *J* 16.1, olefinic H-3 and H-3'), 6.77 (2 H, s, olefinic H-1 and H-1'), 7.04 (2 H, d, *J* 16.4, olefinic H-4 and H-4'), 7.14-7.59 (20 H, m, 18 x aromatic H and Ar-C*H*=C*H*-Ar); δ_C (63 MHz, $CDCl_3$) 14.0 (2 x CH_3), 125.6 (2 x CH), 126.3 (4 x CH, aromatic), 127.0 (2 x CH), 127.1 (2 x CH), 127.2 (2 x CH), 128.0 (2 x CH), 128.4 (2 x CH), 128.5 (4 x CH, aromatic), 130.0 (2 x CH), 130.8 (2 x CH), 133.4 (2 x CH), 136.4 (2 x quat), 136.4 (2 x quat), 136.8 (2 x quat), 137.4 (2 x quat).

vi. Generation and Thermal Decomposition of the Sodium Salt of (*E,E*)- and (*Z,E*)-2-Formyl-3-(Penta-1,3-dienyl)thiophene Tosylhydrazone (526) at 80 °C

To a solution of (*E,E*)- and (*Z,E*)-2-formyl-3-(penta-1,3-dienyl)thiophene tosylhydrazone **526** (0.43 g, 1.24 mmol) in dry methanol (10 cm^3) was added a solution of sodium methoxide (1.13 M in methanol, 1 cm^3, 1.13 mmol). The reaction mixture was stirred, in the dark and under dry nitrogen, for 1 hour, after which the solvent was removed *in vacuo* and the residue was dried at high vacuum over P_2O_5 for 18 hours. The dry salt was dissolved in freshly distilled DME (15 cm^3) and this solution was heated at reflux, in darkness and under nitrogen, for 2 hours. Filtration of the solution through a celite pad and removal of the solvent *in vacuo* gave a bright yellow oil, dry-flash column chromatography (silica, hexane) of which afforded 1-methyl-1a,6b-dihydro-1*H*-6-thia-cyclopropa[*e*]indene **531** as a yellow oil (0.11 g, 0.7 mmol, 56 %) Found: M^+, 162.0502. $C_{10}H_{10}S$ requires M^+, 162.0503; δ_H (360 MHz, $CDCl_3$) 0.65 (1 H, m), 1.07 (3 H, d, *J* 5.4, CH_3), 1.96 (1 H, dd, *J* 13.3, 5.7), 2.49 (1 H, dd, *J* 7.7, 5.9), 6.07 (1 H, dd, *J* 9.6, 5.2), 6.42 (1 H, d, *J* 9.6), 6.90 (1 H, d, *J* 5.1), 7.03 (1 H, d, *J* 5.1); δ_C (63 MHz, $CDCl_3$) 0.91 (CH), 18.4 (CH_3), 24.7 (CH), 26.9 (CH), 85.6 (quat), 119.6 (CH), 120.8 (CH), 123.3 (CH), 125.5 (CH), 131.4 (quat); *m/z* 162 (M^+, 72 %), 161 (M^+-H, 98 %), 148 (base peak).

vii. Generation and Thermal Decomposition of the Sodium Salt of (*E,E*)- and (*Z,E*)-2-Formyl-3-(penta-1,3-dienyl)thiophene Tosylhydrazone (526) at Room Temperature

A solution of sodium methoxide (0.39 M in methanol, 1.1 cm^3, 0.43 mmol) was added to a solution of (*E,E*)- and (*Z,E*)-2-formyl-3-(penta-1,3-dienyl)thiophene tosylhydrazone **526** (0.157 g, 0.45 mmol) in dry methanol (10 cm^3). This solution was stirred at room temperature, in the dark and under nitrogen, for 1 hour, then the solvent was removed *in vacuo*. The residue was dried over P_2O_5 at high vacuum for 3 hours, dissolved in dry DME (15 cm^3) and stirred at room temperature, in the dark, for 96 hours. Filtration of the resultant suspension through a celite pad followed by

removal of the solvent *in vacuo* yielded a dark yellow oil, which upon dry-flash column chromatography (silica, hexane-ether gradient elution) gave (*E*)-4-(2-propenyl)thieno[6,7-d]-1*H*-2,3-diazepine **533** as a yellow oil (0.06 g, 0.32 mmol, 74 %); Found: $[M+H]^+$, 191.0649. $C_{10}H_{11}N_2$ requires $[M+H]^+$, 191.0643; δ_H (250 MHz, $CDCl_3$) 1.94 (3 H, dd, *J* 6.5, 1.4, CH_3), 2.83 (1 H, br. d, *J* 10.1, methylene H), 6.26 (1 H, dq, *J* 15.6, 6.5, C*H*CH_3), 6.44 (1 H, dq, *J* 15.6, 1.4, C*H*=$CHCH_3$), 6.52 (1 H, s, H-4), 7.13 (1 H, d, *J* 5.2, thienyl H), 7.29 (1 H, d, *J* 5.3, thienyl H); δ_C (63 MHz, $CDCl_3$) 18.5 (CH_3), 63.5 (CH_2), 109.3 (CH), 124.8 (quat), 125.3 (CH), 125.6 (CH), 128.5 (CH), 129.0 (CH), 137.0 (quat), 151.9 (quat); The compound decomposed before T_c was reached. The second (axial) methylene proton was located beneath the signals at δ 6.50 in a 2D ^1H-^1H COSY NMR experiment.

XVI. Generation and Reaction of the Diazoalkanes Derived from 1,2,4-Trisubstituted (*Z,E*) Triene-Conjugated Tosylhydrazones

i. Generation and Thermal Decomposition of the Sodium Salt of (*Z,E*)- and (*Z,Z*)-2-(1-Methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (540)

Freshly prepared sodium methoxide (0.48 M in methanol, 2.0 cm^3, 0.96 mmol) was added to a solution of (*Z,E*) and (*Z,Z*)-2-(1-methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde tosylhydrazone **540** (0.50 g, 1.02 mmol) in dry methanol (10 cm^3) and the resulting mixture was stirred in the dark and under nitrogen for 1 hour, before removal of the solvent *in vacuo*. The residue was dried overnight, dissolved in dry DME (15 cm^3) and the solution was heated at reflux, in the dark and under nitrogen, for 3 hours. Filtration of the resulting suspension and evaporation of the filtrate *in vacuo* gave a yellow oil, the ^1H NMR spectrum of which showed signals characteristic of the phthalazine **417** and none of the signals expected of the cyclopropa[*a*]naphthalene **424**. Dry-flash column chromatography (silica, hexane-ether, gradient elution) afforded only 10b-methyl-1,3-diphenyl-1,10b-dihydropyrrolo[2,1a]phthalazine **417** (0.24 g, 0.72 mmol, 75 %) identical with that

obtained by Wilson[133]; δ_H (200 MHz, $CDCl_3$) 1.62 (3 H, s, CH_3), 3.82 (1 H, d, *J* 3.3, CH), 5.22 (1 H, d, *J* 3.3, CH), 6.82-7.43 (14 H, m, aromatic).

ii. Preparation and Thermal Decomposition of the Sodium Salt of (*Z,E*)- and (*Z,Z*)-2-(1-Methyl-2-phenylpenta-1,3-dienyl)benzaldehyde Tosylhydrazone (546)

To a solution of (*Z,E*)- and (*Z,Z*)-2-(1-methyl-2-phenylpenta-1,3-dienyl)benzaldehyde tosylhydrazone **546** (0.25 g, 0.58 mmol) in methanol (10 cm^3) was added freshly prepared sodium methoxide solution (0.5 cm^3, 1.13 M in methanol, 0.57 mmol). This mixture was stirred, in the dark and under nitrogen, for 1 hour at room temperature, after which the solvent was removed *in vacuo*. The residue was dried overnight in a high vacuum over P_2O_5, then dissolved in dry DME (20 cm^3) and this solution was heated at reflux under dry nitrogen for 3 hours with regular monitoring by TLC. When the reaction was judged to have gone to completion the cooled solution was filtered free of the precipitated sodium *p*-toluenesulfinate through celite, with the pad being flushed with ether to collect all of the product. The solvents were removed *in vacuo* and dry-flash column chromatography (silica, hexane) of the residue gave a product identified as (*Z,E*)- and (*Z,Z*)-2,2'-di-(1-methyl-2-phenylpenta-1,3-dienyl)benzaldehyde azine **549** (0.11 g, 0.22 mmol, 77 %) as a pale yellow gum; Found: $(M+H)^+$, 521.2957. $C_{38}H_{37}N_2$ requires $(M+H)^+$, 521.2957; δ_H (250 MHz, $CDCl_3$) 1.54 (6 H, m, C-4 and C-4' CH_3), 1.80 (6 H, d, *J* 6.6, C-4 and C-4' CH_3), 5.31 (2 H, dq, *J* 15.4, 6.8, olefinic H-4 and H-4', *Z,E*), 5.75 (2 H, dq, *J* 11.2, 6.9, olefinic H-4 and H-4', *Z,Z*), 6.29 (2 H, dq, *J* 11.3, 1.0, olefinic H-3 and H-3', *Z,Z*), 6.80 (2 H, dd, *J* 15.4, 1.6, olefinic H-3 and H-3', *Z,E*), 6.85-7.46 (16 H, m, aromatic), 7.90-8.00 (2 H, m, aromatic), 8.65-8.79 (2 H, m, 2 x CH=N); δ_C (63 MHz, $CDCl_3$) 15.0 (CH_3), 18.6 (CH_3), 21.4 (CH_3), 23.5 (CH_3), 125.9 (CH), 126.1, 126.3, 126.5, 126.6, 127.2 (2 x CH), 127.3 (2 x CH), 127.9, 128.1, 129.5 (2 x CH), 129.7 (CH), 130.0 (CH), 130.2 (2 x CH), 130.4 (CH), 130.9 (CH), 131.4 (CH), 133.3, 133.5, 137.0, 138.9, 139.8, 140.9, 145.8, 146.4 (quat), 160.7 (CH, CH=N), 160.8 (CH, CH=N).

iii. Preparation and Thermal Decomposition of the Sodium Salt of (*Z*,*E*)-2-[1-Methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl]benzaldehyde Tosylhydrazone (555)

To a solution of (*Z*,*E*)-2-(1-methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl)benzaldehyde tosylhydrazone **555** (0.18 g, 0.32 mmol) in dry methanol (10 cm^3) was added sodium methoxide solution (0.5 cm^3, 0.59 M). This solution was stirred, in the dark and under nitrogen, for 1 hour, after which the solvent was removed *in vacuo*. The residue was dried over P_2O_5 overnight before being dissolved in freshly distilled DME (20 cm^3). This solution was heated at reflux, in the dark and under nitrogen, for 3 hours, after which the solid was filtered off and the filtrate was evaporated to dryness *in vacuo*. The ^1H NMR spectrum of the crude product showed that only phthalazine **558** had been formed. Dry-flash column chromatography (silica, hexane-ether gradient elution) gave 10b-methyl-3-phenyl-1-(pentafluorophenyl)-1,10b-dihydropyrrolo[2,1-*a*]phthalazine **558** as a pale-yellow solid (0.094 g, 0.22 mmol, 73 %); Found: M^+, 426.1155. $C_{24}H_{15}F_5N_2$ requires M^+, 426.1155. δ_H (250 MHz, $CDCl_3$); 1.70 (3 H, s, CH_3), 4.48 (1 H, d, *J* 3.5, H-2), 4.93 (1 H, d, *J* 3.5, H-1), 6.65 (1 H, d, *J* 7.5, benzo H), 7.06-7.19 (4 H, m, phenyl), 7.35-7.47 (3 H, m, aromatic), 7.66-7.71 (2 H, m, phenyl); δ_C (63 MHz, $CDCl_3$) 31.9 (CH_3), 48.3 (CH), 64.3 (quat), 96.5 (CH), 114.2 (quat, $C(CF)_5$), 123.7 (quat), 124.7 (CH), 124.8 (CH), 127.5 (CH), 128.0 (2 x CH, phenyl), 128.2 (2 x CH, phenyl), 128.9 (CH), 129.4 (CH), 131.1 (quat), 132.0 (CH), 132.1 (quat), 148.8 (quat), 5 x quat C-F unobserved; δ_F (235 MHz, $CDCl_3$) -163.07 – -162.17 (2 F, m, *meta* F), -156.27 (1 F, t, *J* 21.0, *para* F), -145.00 – -137.49 (2 F, m, *ortho* F).

COSY Data

δ_H (ppm)	Couples with signal (δ_H)
4.48 (H-1)	4.93 (H-2)
4.93 (H-2)	4.48 (H-1)
6.65	7.06-7.19 (aromatic)
7.35-7.47	7.66-7.71 (aromatic)
7.66-7.71	7.35-7.47 (aromatic)

NOESY Data

δ_H (ppm)	Correlates with signals (δ_H)
1.70 (CH_3)	4.48 (H-1), 6.65
4.48 (H-1)	1.70 (CH_3), 4.93 (H-2), 6.65
4.93 (H-2)	4.48 (H-1), 7.66-7.71
6.65	1.70 (CH_3), 4.48 (H-1), 7.35-7.47
7.35-7.47	6.65
7.66-7.71	4.93 (H-2)

HSQC (Carbon-Proton correlation) Data

δ_H (ppm)	Correlates with signal (δ_C)
1.70 (3 H)	31.9 (CH_3)
4.48 (1 H, H-1)	48.3 (CH, C-1)
4.93 (1 H, H-2)	96.5 (CH, C-2)
6.65 (1 H)	124.7 (CH)
7.66-7.71 (2 x H)	128.1 (2 x CH, aromatic)

HMBC (Carbon-Proton correlation) Data

δ_H (ppm)	Correlates with (δ_C)
1.70 (CH_3)	48.3 (CH, C-1), 64.4 (quat, C-10), 132.0 (CH)
4.48 (1 H, H-1)	31.9 (CH_3), 96.5 (CH, C-3), 114.2 (quat, C-10).
4.93 (1 H, H-2)	48.3 (CH, C-1), 64.4 (quat, C-10)
6.65 (1 H)	64.4 (quat, C-10), 124.7 (CH), 127.5 (CH)

XVII. Generation and Reaction of the Diazoalkanes Derived from (*E,E*) Triene-Conjugated Tosylhydrazones

i. Generation and Thermal Decomposition of the Sodium Salt of (*E,E*) and (*E,Z*)-2-(1-Methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (443)

To a solution of (*E,E*)- and (*E,Z*)-2-(1-methyl-2,4-diphenylbuta-1,3-dienyl)benzaldehyde tosylhydrazone **443** (0.40 g, 0.81 mmol) in dry methanol (10 cm^3) was added sodium methoxide solution (0.78 M in methanol, 1.0 cm^3, 0.78 mmol). This mixture was stirred in the dark and under nitrogen for 1 hour, then the solvent was removed *in vacuo* and the residue was dried overnight in a high vacuum dessicator over P_2O_5. The dry residue was dissolved in dry DME and the solution was heated at reflux, in the dark and under dry nitrogen, for 3 hours. The pale yellow suspension was filtered through a celite pad and the solvent was removed *in vacuo*. The ^1H NMR spectrum of the crude product showed that the *cis*- and *trans*-1*H*-1a,7b-dihydro-3-methyl-1,2-diphenylcyclopropa[*a*]naphthalenes **424** had formed. These were isolated as a mixture by dry-flash column chromatography (silica, hexane) as a colourless oil (0.14 g, 0.41 mmol, 53 %); δ_H (200 MHz, $CDCl_3$) 1.50* (1 H, dd, *J* 4.3, 4.3, H-1), 1.91$ (3 H, s, CH_3), 2.19* (3 H, s, CH_3), 2.55* (1 H, dd, *J* 8.4, 4.0), 2.40$ (1 H, dd, *J* 8.2, 4.0), 2.69$ (1 H, dd, *J* 8.4, 8.4), 2.78* (1 H, dd, *J* 8.2, 4.3), 3.11$ (1 H, dd, *J* 8.4, 8.4), 6.75-7.45 (14 H, m, aromatic). The product mixture was also found to contain 10b-methyl-1,3-diphenyl-1,10b-dihydropyrrolo[2,1*a*]phthalazine **417** (0.07 g, 0.2 mmol, 25 %); δ_H (200 MHz, $CDCl_3$) 1.76 (3 H, s, CH_3), 3.95 (1 H, d, *J* 3.5, H-1), 5.35 (1 H, d, *J* 3.5, H-2), 6.69-7.75 (15 H, m, aromatic). The ratio of these two products was determined from the crude ^1H NMR of the mixture as 3:2 in favour of the cyclopropa[*a*]naphthalene.

ii. Preparation and Thermal Decomposition of the Sodium Salt of (*E*)-2-(1-Methyl-2-phenylbuta-1,3-dienyl)benzaldehyde Tosylhydrazone (457)

To a solution of (*E*)-2-(1-methyl-2-phenylbuta-1,3-dienyl)benzaldehyde tosylhydrazone **457** (0.35 g, 0.84 mmol) in dry methanol (10 cm^3) was added sodium methoxide in methanol (1.0 cm^3, 0.79 M). This solution was stirred in the dark, under nitrogen, for 1 hour. The solvent was removed *in vacuo* and the residue was dried overnight at high vacuum over P_2O_5, then dissolved in dry DME (20 cm^3). This solution was heated at reflux for 3 hours, when TLC analysis showed complete consumption of starting material. The precipitated sodium *p*-toluenesulfinate was removed by filtration through a celite pad and the filtrate was evaporated to dryness *in vacuo*. Dry-flash column chromatography (silica, hexane) of the crude oily residue gave 1*H*,1a,7b-dihydro-3-methyl-2-phenylcyclopropa[*a*]naphthalene **460** (0.11 g, 0.50 mmol, 63 %) as a colourless oil; Found: M^+, 232.1250. $C_{18}H_{16}$ requires M^+, 232.1252; δ_H (250 MHz, $CDCl_3$) -0.01 (1 H, dt, *J* 3.4, 8.3), 1.64 (1 H, ddd, *J* 8.8, 8.8, 3.4, CH), 2.07 (3 H, s, CH_3), 2.09 (1 H, m), 2.53 (1 H, m, H-7), 7.23-7.81 (9 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 10.3 (CH_2), 16.3 (CH_3), 20.6, 21.4 (CH), 122.6 (quat), 124.5, 125.6, 126.5, 126.7 (CH), 127.8 (2 x CH, aromatic), 128.0 (CH), 128.8 (2 x CH, aromatic), 132.4, 135.2, 136.8, 142.4 (quat); *m/z* (EI+) 232 (M^+, 90 %), 217 (M^+-CH_3, base peak).

iii. Preparation and Thermal Decomposition of the Sodium Salt of (*E,E*)-2-(1-Methyl-2-phenyl-4-[*p*-methoxyphenyl]buta-1,3-dienyl)benzaldehyde Tosylhydrazone (475)

To a solution of (*E,E*)-2-(1-methyl-2-phenyl-4-[*p*-methoxyphenyl]buta-1,3-dienyl)benzaldehyde tosylhydrazone **475** (0.23 g, 0.44 mmol) in dry methanol (10 cm^3) was added sodium methoxide in methanol (0.50 cm^3, 0.84 M, 0.42 mmol). This solution was stirred in the dark, under nitrogen, for 1 hour and the solvent was removed *in vacuo*, with the residual orange solid then being dried overnight, in a high vacuum over P_2O_5. The dried salt was dissolved in dry DME (15 cm^3) and this solution was heated at reflux, under nitrogen and in the dark, for 3 hours. The

precipitated sodium *p*-toluenesulfinate was removed by filtration and the filtrate was evaporated *in vacuo* to give a viscous red oil. Dry-flash column chromatography (silica, hexane-ether gradient elution) afforded, in order of elution; a) a 1:1.3 mixture of *cis*- and *trans*-1*H*-1a,7b-dihydro-3-methyl-2-phenyl-1-(*p*-anisyl)cyclopropa[*a*]naphthalene **477** as a colourless oil which solidified on trituration with hexane (0.10 g, 0.30 mmol, 71 %), mp 107-108 °C (hexane); Found 88.67 % C, 6.61 % H, M^+, 338.1670. $C_{25}H_{22}O$ requires 88.72 % C, 6.55 % H, M^+, 338.1671; Major isomer; δ_H (250 MHz, $CDCl_3$) 1.47-1.49 (1 H, m, H-1), 2.18 (3 H, s, CH_3), 2.44-2.47 (1 H, dd, *J* 8.3, 4.1), 2.84 (1 H, dd, *J* 8.3, 4.5), 3.84 (3 H, s, O-CH_3), 6.92 (2 H, d, *J* 8.9, anisyl), 7.06 (2 H, d, *J* 8.9, anisyl), 7.18-7.57 (9 H, m, phenyl); Minor isomer; δ_H (250 MHz, $CDCl_3$) 1.92 (3 H, s, CH_3), 2.64 (1 H, dd, *J* 8.4, 8.4), 2.76 (1 H, dd, *J* 9.1, 8.9), 3.10 (1 H, dd, *J* 9.1, 8.2), 3.80 (3 H, s, OCH_3), 6.55 (2 H, d, *J* 8.8, anisyl), 6.83 (2 H, dd, *J* 8.8, 0.8, anisyl), 7.18-7.57 (9 H, m, phenyl); δ_C (63 MHz, $CDCl_3$) 16.2$^{\$}$ (CH_3), 16.4* (CH_3), 17.0$^{\$}$ (CH), 26.6$^{\$}$ (CH), 27.5* (CH), 28.0$^{\$}$ (CH), 32.3* (CH), 32.4* (CH), 54.8$^{\$}$ (CH_3, OCH_3), 55.2* (CH_3, OCH_3), 112.5$^{\$}$ (2 x CH, anisyl), 113.9* (2 x CH, anisyl), 123.3 (quat), 123.8 (CH), 124.6 (CH), 125.4* (quat), 125.6 (CH), 126.0 (CH), 126.1 (2 x CH, aromatic), 126.3$^{\$}$ (quat), 126.4 (CH), 126.6 (CH), 126.7 (CH), 126.8 (CH), 127.1 (quat), 127.9 (2 x CH, aromatic), 128.1 (CH), 128.7 (CH), 129.0 (2 x CH), 129.4 (CH), 131.4$^{\$}$ (quat), 132.2 (CH), 132.5$^{\$}$ (quat), 134.1* (quat), 134.2* (quat), 134.6$^{\$}$ (quat), 136.0* (quat), 136.0* (quat), 142.1* (quat), 142.9$^{\$}$ (quat), 157.2$^{\$}$ (quat), 157.7* (quat);

and b) 10b-methyl-1-(*p*-anisyl)-3-phenyl-1,10b-dihydropyrrolo[2,1*a*]phthalazine **480** (0.03 g, 0.08 mmol, 18 %); Found: $[M+H]^+$, 367.1809. $C_{25}H_{23}N_2O$ requires $[M+H]^+$, 367.1809; δ_H (200 MHz, $CDCl_3$) 1.61 (3 H, s, CH_3), 3.61 (3 H, s, OCH_3), 3.81 (1 H, d, *J* 3.3, H-1), 5.20 (1 H, d, *J* 3.7, H-2), 6.55 (2 H, d, *J* 6.6, anisyl), 6.64-6.68 (1 H, m, aromatic), 6.84-7.03 (5 H, m, aromatic), 7.20-7.41 (4 H, m, aromatic), 7.64-7.69 (2 H, m, aromatic); δ_C (63 MHz, $CDCl_3$) 31.1 (CH_3), 55.0 (CH_3, OCH_3), 59.2 (CH), 66.0 (quat), 105.7 (CH), 113.4 (2 x CH, anisyl), 124.2 (2 x CH, anisyl), 126.5 (CH), 127.9 (2 x CH, phenyl), 128.2 (2 x CH, phenyl), 128.3 (CH), 128.4 (CH), 129.3 (CH), 129.5 (CH), 130.0 (CH), 132.8 (quat), 133.5 (quat), 140.0 (quat), 145.9 (quat), 150.4 (quat), 158.2 (quat). * Indicates major isomer signal; $^{\$}$ indicates minor

isomer. Where no symbol is used, signals from both isomers coincide or assignment was not possible.

iv. Generation and Thermal Decomposition of the Sodium Salt of (*E,E*)-2-[1-Methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl]benzaldehyde Tosylhydrazone (467)

In the dark and under nitrogen, freshly prepared sodium methoxide solution (1.0 cm^3, 0.65 M in methanol) was added to a solution of (*E,E*)-2-[1-methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl]benzaldehyde tosylhydrazone **467** (0.40 g, 0.69 mmol). This solution was stirred for 1 hour, then the solvent was removed *in vacuo* and the residue was dried in a high vacuum, over P_2O_5, overnight. The dry salt was then dissolved in dry DME (25 cm^3) and the solution was heated at reflux for 3 hours, when TLC analysis of the crude reaction mixture showed complete consumption of starting material. The precipitated solid was filtered off and the filtrate was evaporated to give an orange oil, dry-flash column chromatography of which yielded, in order of elution; a) 1*H*-1a,7b-dihydro-3-methyl-2-phenyl-1-(pentafluorophenyl)cyclopropa[*a*]naphthalene **473** (0.12 g, 0.3 mmol, 46 %); Found: M^+, 398.1092. $C_{24}H_{15}F_5$ requires M^+, 398.1094; δ_H (250 MHz, $CDCl_3$) 1.56 (1 H, dd, *J* 4.5, 4.5), 2.11 (3 H, s, CH_3), 2.81 (1 H, dd, *J* 8.6, 4.4), 3.25 (1 H, dd, *J* 8.6, 4.8), 7.10-7.46 (9 H aromatic); δ_C (63 MHz, $CDCl_3$) 16.3 (CH_3), 19.5 (CH, C-1), 28.8 (CH), 29.7 (CH), 114.9 (quat, *C*-CF), 124.8 (CH), 126.7 (CH), 127.0 (CH), 127.1 (CH), 128.1 (2 x CH, aromatic), 128.3 (CH), 128.5 (quat), 128.7 (2 x CH, aromatic), 132.4 (quat), 132.8 (quat), 135.0 (quat), 142.0 (quat), 5 x quat C-F not observed; δ_F (235 MHz, $CDCl_3$) -163.35 – -163.11 (2 F, m, *meta* F), -158.20 (1 F, t, *J* 21.0, *para* F), -144.98 – -144.84 (2 F, m, *ortho* F); *m/z* (EI+) 398 (29 %, M^+), 383 (17 %, M-CH_3);

and b) 10b-methyl-3-phenyl-1-(pentafluorophenyl)-1,10b-dihydropyrrolo[2,1-*a*]phthalazine **471** (0.06 g, 0.15 mmol, 23 %); Found: M^+, 426.1155. $C_{24}H_{15}F_5N_2$ requires M^+, 426.1155; δ_H (250 MHz, $CDCl_3$) 1.70 (3 H, s, CH_3), 4.47 (1 H, d, *J* 3.5), 4.93 (1 H, d, *J* 3.5), 6.64 (1 H, d, *J* 8.4), 7.05-7.70 (9 H, m, aromatic and CH=N); δ_C (63 MHz, $CDCl_3$) 32.0 (CH_3), 48.3 (CH), 64.4 (quat), 96.5 (CH), 114.2 (quat, *C*-CF),

123.7 (quat, C-10), 124.7 (CH), 124.8 (CH), 127.6 (CH), 128.1 (2 x CH, aromatic), 128.2 (2 x CH, aromatic), 128.9 (CH), 129.4 (CH), 131.1 (quat), 132.0 (CH), 132.1 (quat), 148.9 (quat), 5 x quat C-F unobserved; *m/z* 426 (base peak, M^+), 411 (40 %, $M-CH_3$).

The ^1H NMR spectrum of the crude product mixture showed that the products had been formed in a ratio of 1.5:1 in favour of the cyclopropa[*a*]naphthalene.

v. Generation and Thermal Decomposition of the Sodium Salt of (*E,E*)-2-[1-Methyl-2-phenyl-4-(pentafluorophenyl)buta-1,3-dienyl]benzaldehyde Tosylhydrazone (467) at Room Temperature

A solution of the tosylhydrazone **467** (0.20 g, 0.34 mmol) in dry methanol (5 cm^3) was treated with sodium methoxide solution (1.0 cm^3, 0.33 mmol, 0.33 M in methanol) and this was stirred for 1 hour at room temperature, in the dark and under nitrogen. The solvent was removed *in vacuo* and the residue was dried overnight over P_2O_5. The dried salt was dissolved in dry DME (10 cm^3) and this solution was stirred at room temperature, in the dark and under nitrogen, for 5 days. Over this period a white solid was observed to form and TLC analysis showed disappearance of starting material and development of two new, higher-running spots. Filtration of the mixture through a celite pad and evaporation of the solvent *in vacuo* gave a yellow-brown oil. The ^1H NMR spectrum of this mixture showed that it consisted of the phthalazine **471** and the cyclopropa[*a*]naphthalene **473** obtained in the previous experiment, in a ratio of 1:1.5.

[1] R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565.

[2] P. Caramella and K. N. Houk, *J. Am. Chem. Soc.*, 1976, **98**, 6397.

[3] R. Huisgen, W. Mack and E. Anneser, *Angew. Chem.*, 1961, **73**, 656.

[4] G. Just and K. Dahl, *Tetrahedron*, 1968, **24**, 5251.

[5] T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, 1960, **82**, 5339.

[6] W. A. F. Gladstone, *Chem. Commun.*, 1969, 179.

[7] R. Huisgen, M. Seidel, J. Sauer, J. W. McFarland and G. Wallbillich, *J. Org. Chem.*, 1959, **24**, 892.

[8] H. S. Clovis, A. Eckell, R. Huisgen and R. Sustmann, *Chem. Ber.*, 1967, **60**, 100.

[9] H. Reimlinger, J. J. Vandewalle, G. S. D. King, W. R. F. Lingier and R. Merenyi, *Chem. Ber.*, 1970, **103**, 1918.

[10] M. Marky, H. Meier, A. Wunderli, H. Heimgartner, H. Schmidt and H. J. Hansen, *Helv. Chim. Acta.*, 1978, **61**, 1477.

[11] A. Padwa (Ed.), *1,3-Dipolar Cycloaddition Chemistry*, vols. 1 and 2, Wiley Interscience, 1984, New York.

[12] G. Bianchi, C. DeMichaeli and R. Gandolfini in *The Chemistry of Double-Bonded Functional Groups* (ed. S. Patai), Interscience, 1977, London.

[13] E. C. Taylor and I. J. Turchi, *Chem. Rev.*, 1979, **79**, 181.

[14] G. Zecchi, *Synthesis*, 1991, 181.

[15] E. P. Janulis, S. R. Wilson and A. J. Arduengo, *Tetrahedron Lett.*, 1984, **25**, 405.

[16] K. N. Houk, L. J. Luskus, J. Sims and C. R. Watts, *J. Am. Chem. Soc.*, 1973, **95,** 7301.

[17] R. E. Duke, J. K. George, K. N. Houk, J. Sims and R. W. Strozier, *J. Am. Chem. Soc.*, 1973, **95**, 7287.

[18] R. Huisgen, *Angew. Chem. Int. Ed. Engl.*, 1963, **2**, 633.

[19] R. Sustmann, *Pure Appl. Chem.*, 1974, **40**, 569.

[20] R. Sustmann, *Tetrahedron Lett.*, 1971, 2717.

[21] J. Sauer and R. Sustmann, *Angew. Chem. Int. Ed. Engl.*, 1980, **19**, 779.

[22] P. Gilgen, H. Heimgartner, H. Schmidt and H. J. Hansen, *Heterocycles*, 1977, **6**, 143.

[23] R. Huisgen, H. Stangl, H. J. Sturm, R. Raab and K. Bunge, *Chem. Ber.*, 1972, **105**, 1258.

[24] B. C. Challis and J. A. Challis, in S. Patai, (Ed), *The Chemistry of Functional Groups*; J. Zablicky, (Ed), *The Chemistry of Amides*, Interscience, 1970, London.

[25] R. Huisgen, R. Grashey and J. Sauer, in S. Patai, (Ed), *The Chemistry of Alkenes*, Interscience, London, 1964, 739.

[26] A. Padwa, P. H. J. Carlsen and A. Ku, *J. Am. Chem. Soc.*, 1977, **99**, 2798.

[27] A. Padwa, P. H. J. Carlsen and A. Ku, *J. Am. Chem. Soc.*, 1978, **100**, 3494.

[28] K. Burger, R. Ottlinger, H. Goth and J. Firl, *Chem. Ber.*, 1980, **113**, 2699.

[29] G. Höfle and W. Steglich, *Chem. Ber.*, 1971, **104**, 1408.

[30] W. Steglich, P. Gruber, H.-U. Heininger and F. Kneidl, *Chem. Ber.*, 1971, **104**, 3816.

[31] P. Gruber, L. Muller and W. Steglich, *Chem. Ber.*, 1973, **106**, 2863.

[32] M. R. Johnson and L. R. Sousa, *J. Org. Chem.*, 1977, **42**, 2493.

[33] K. Burger, J. Albanbauer and F. Manz, *Chem. Ber.*, 1974, **107**, 1823.

[34] K. Burger, W. Thenn and E. Müller, *Angew. Chem. Int. Ed. Engl.*, 1973, **12**, 149.

[35] A. Padwa and P. H. J Carlsen, in *Reactive Intermediates*, vol 2, R. A. Abranovitch (Ed), Plenum Press, London, 1982.

[36] W. Stegmann, P. Vebelhart, H. Heimgartner and H. Schmidt, *Tetrahedron Lett.*, 1978, 3091.

[37] D. Griller, L. Hadel, A. S. Nazram, M. S. Platz, P. C. Wong, T. G. Savino and J. C. Scaiano, *J. Am. Chem. Soc.*, 1984, **106**, 2227.

[38] P. B. Grasse, B.-E. Brauer, J. J. Zupanic, K. J. Kaufman and G. B. Schuster, *J. Am. Chem. Soc.*, 1983, **105**, 6833.

[39] A. S. Kende, P. Hebeisen, P. J. Sanfilippo and B. H. Toder, *J. Am. Chem. Soc.*, 1982, **104**, 4244.

[40] N. J. Turro, D. A. Hrovat, I. R. Gould, A. Padwa, W. Dent and R. J. Rosenthal, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 625.

[41] R. L. Barcus, B. B. Wright, M. S. Platz and J. C. Scaiano, *Tetrahedron Lett.*, 1983, **24**, 3955.

[42] L. M. Hadel, M. S. Platz and J. C. Scaiano, *Chem. Phys. Lett.*, 1983, **97**, 466.

[43] K. Burger and J. Fehn, *Angew. Chem. Int. Ed. Engl.*, 1972, **11**, 47.

[44] K. Bunge, R. Huisgen, R. Raab and H. Stangl, *Chem. Ber.*, 1972, **105**, 1279.

[45] K. Burger, J. Albanbauer and F. Manz, *Chem. Ber.*, 1974, **107**, 1823.

[46] A. Padwa, J. Smolanoff and S. I. Wetmore, *J. Org. Chem.*, 1973, **38**, 1333.

[47] R. Huisgen, *J. Org. Chem.*, 1968, **33**, 2291.

[48] R. Huisgen, *J. Org. Chem.*, 1976, **41**, 403.

[49] W. Sieber, P. Gilgen, S. Chaloupka, H.-J. Hansen and H. Schmidt, *Helv. Chim. Acta*, 1973, **56**, 1679.

[50] A. S. Orahovats, H. Heimgartner, H. Schmidt and W. Heinzelmann, *Helv. Chim. Acta.*, 1975, **58**, 2662.

[51] A. Padwa, M. Dharan, J. Smolanoff and S. I. Wetmore, *J. Am. Chem. Soc.*, 1973, **95**, 1954.

[52] J. P. Strachan, PhD Thesis, University of Edinburgh, 1996.

[53] R. N. Butler, J. P. Duffy, D. Cunningham, P. McArdle and L. A. Burke, *J. Chem. Soc., Chem. Commun.*, 1990, 882.

[54] P. W. Groundwater, I. Garnet, A. J. Morton, T. Sharif, S. J. Coles, M. B. Hursthouse, M. Nyerges, R. J. Anderson, D. Bendell, A. McKillop and W. Zhang, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2781.

[55] W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 10.

[56] A. Padwa, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 123.

[57] A. Padwa and P. H. J. Carlsen, *J. Am. Chem. Soc.*, 1977, **99**, 1514.

[58] P. D. Cox, I. R. Gould, N. P. Hacker, R. A. Moss and N. J. Turro, *Tetrahedron Lett.*, 1983, **24**, 5313.

[59] J. Fischer and W. Steglich, *Angew. Chem. Int. Ed. Engl.*, 1979, **18**, 167.

[60] N. Engel, J. Fischer and W. Steglich, *J. Chem. Res. (S)*, 1977, 162.

[61] P. W. Groundwater, C. Struthers-Semple and J. T. Sharp, *J. Chem. Soc. Chem. Commun.*, 1987, 2064.

[62] K. R. Motion, I. R. Robertson and J. T. Sharp, *J. Chem. Soc., Chem. Commun.*, 1984, 1531.

[63] A. P. Cox, L. F. Thomas and J. Sheridan, *Nature*, 1958, **181**, 1000.

[64] C. B. Moore and G. C. Pimentel, *J. Chem. Phys.*, 1964, **40**,1529.

[65] W. R. Bamford and T. S. Stevens, *J. Chem. Soc.* 1952, 4735.

[66] M. O. Forster, *J. Chem. Soc.*, 1915, 260.

[67] T. Severin, H. Krämer and P. Adhikary, *Chem. Ber.*, 1971, **104**, 972.

[68] M. S. Newman and A. Arkell, *J. Org. Chem.*, 1959, **24**, 385.

[69] T. Curtius, *Chem. Ber.*, 1889, **22**, 2162.

[70] M. A. Garcia-Garibay, S. S. Shin, C. N. Sanrame, *Tetrahedron*, 2000, **36**, 6729.

[71] Werner, *J. Chem. Soc.*, 1919, 1101.

[72] R. A. Moss and Y. Ma, *Tetrahedron Lett.*, 2001, **42**, 6045.

[73] T. Curtius, *J. Prakt. Chem.*, 1888, 401.

[74] R. A. Aitken, J. M. Armstrong, M. J. Drysdale, F. C. Ross, B. M. Ryan, *J. Chem. Soc. Perkin Trans. 1*, 1999, 593.

[75] J. C. Martin, D. R. Bloch, *J. Am. Chem. Soc.* 1971, **93**, 451.

[76] M. Regitz, *Synthesis*, 1971, 351.

[77] A. J. Trevor and W. L. Way, in *Basic and Clinical Pharmacology*, 8th edn, ed. B. G. Katzung, McGraw-Hill, New York, 2001, p 364-382.

[78] S. D. Andrews, A. C. Day and A. N. McDonald, *J. Chem. Soc. (C)*, 1969, 789.

[79] W. Kirmse and H. Dietrich, *Chem. Ber.*, 1967, **100**, 2710.

[80] A. Padwa and A. Rodriguez, *Tetrahedron Lett.*, 1981, **22**, 187.

[81] A. Padwa and A. Ku, *Tetrahedron Lett.*, 1980, **21**, 1009.

[82] Y. Nishizawa, T. Miyashi and T. Mukai, *J. Am. Chem. Soc.*, 1980, **102**, 1176.

[83] T. Miyashi, Y. Fujii, Y. Nishizawa and T. Mukai, *J. Am. Chem. Soc.*, 1981, **103**, 725.

[84] T. Miyashi, Y. Nishizawa, Y. Fujii, K. Yamakawa, M. Kamata, *et al.*, *J. Am. Chem. Soc.*, 1986, **108**, 1617.

[85] R. M. Wilson and J. W. Rekers, *J. Am. Chem. Soc.*, 1979, **101**, 4005.

[86] A. Padwa and H. Ku, *J. Org. Chem.*, 1980, **45**, 3756.

[87] A. A. Reid, J. T. Sharp, H. R. Sood and P. B. Thorogood, *J. Chem. Soc. Perkin Trans. 1*, 1973, 2543.

[88] D. P. Munro and J. T. Sharp, *J. Chem. Soc. Perkin Trans. 1*, 1984, 849.

[89] I. R. Robertson and J. T. Sharp, *J. Chem. Soc. Chem. Commun.*, 1983, 1003.

[90] M. Bohill, Ph. D. Thesis, University of Edinburgh, 1996.

[91] M. Dorra, K. Gomann, M. Guth and W. Kirmse, *J. Phys. Org. Chem.*, 1996, **9**, 598.

[92] E. C. Palik and M. S. Platz, *J. Org. Chem.*, 1983, **48**, 963.

[93] J. T. Sharp, R. H. Findlay and P. B. Thorogood, *J. Chem. Soc. Perkin Trans. 1*, 1975, 102.

[94] J. P. Strachan, J. T. Sharp and M. Crawshaw, *J. Chem. Soc. Perkin Trans. 1*, 1999, 443.

[95] J. P. Strachan, J. T. Sharp and S. Parsons, *J. Chem. Soc. Chem. Commun.*, 1996, 2739.

[96] A. Padwa and S. Nahm, *J. Org. Chem.*, 1981, **46**, 1402.

[97] A. Alemagna, L. Garanti, E. Licandro and G. Zecchi, *Tetrahedron*, 1984, **11**, 2165.

[98] L. Garanti and G. Zecchi, *J. Chem. Soc. Perkin Trans. 1*, 1977, 2092.

[99] K. R. Motion, I. R. Robertson, J. T. Sharp and M. D. Walkinshaw, *J. Chem. Soc. Perkin Trans. 1*, 1992, 1709.

[100] J. M. Brown, B. T. Golding and J. J. Stofko, *J. Chem. Soc., Chem. Commun*, 1973, 319.

[101] F. Vogtle and E. Goldschmitt, *Chem. Ber.*, 1976, **109**, 1.

[102] D. Brombach, *Synthesis*, 1977, 800.

[103] L. E. Overman, L. J. Mendelson and E. J. Jacobsen, *J. Am. Chem. Soc.*, 1983, **105**, 6629.

[104] P. J. Battye, D. W. Jones, *J. Chem. Soc. Perkin Trans. 1*, 1986, 1479.

[105] S. R. Wilson, in *Organic Reactions*, ed L. A. Paquette *et al*, Wiley, New York, 1993, vol 43.

[106] I. Fleming, "*Frontier Orbitals and Organic Chemical Reactions*", Wiley Interscience, New York, 1976, p. 98.

[107] T. L. Gilchrist and C. W. Rees, *Carbenes, Nitrenes and Arynes*, Pitman Press, Bath, 1969, p 10-23.

[108] K. Burger, S. Tremmel, W.-D. Roth and H. Goth, *J. Heterocycl. Chem*, 1981, **18**, 247.

[109] D. P. Munro and J. T. Sharp, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1718.

[110] T. K. Miller and J. T. Sharp, *J. Chem. Soc., Perkin Trans. 1*, 1984, 223.

[111] D. P. Munro, PhD Thesis, University of Edinburgh, 1981.

[112] *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees (Eds.), Oxford Pergamon Press, London, 1978.

[113] A. Maercker, in *Organic Reactions*, ed. A. C. Cope *et al*, Wiley, New York, vol 14, 1965.

[114] T. Minami, T. Okauchi, R. Kouno, *Synthesis*, 2001, 349.

[115] W. J. Stec, *Acc. Chem. Res.*, 1983, 41.

[116] W. S. Wadsworth, in *Organic Reactions*, ed W. G. Dauben *et al*, Wiley, New York, 1977, vol 25.

[117] R. Engel, in *Organic Reactions*, ed A. S. Kende *et al*, Wiley, New York, 1988, vol 36, p 191.

[118] K. Ando, *J. Synth. Org. Chem. Japan*, 2000, **9**, 869.

[119] T. Minami and J. Motoyisha, *Synthesis*, 1992, 333.

[120] Y. C. Shen, *Acc. Chem. Res*, 1998, **9**, 584.

[121] N. Miyaura, A. Suzuki, *Chem. Rev.* 1995, **95**, 2457.

[122] A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147.

[123] A. Suzuki, in: *Metal-Catalyzed Cross-coupling Reactions*, ed. F. Diederich, P.J. Stang, VCH, Weinheim, 1998, pp. 49-97.

[124] S. Gronowitz, V. Bobosik and K. Lawitz, *Chemica Scripta*, 1984, 120.

[125] L. Carrillo, D. Badia, E. Dominguez, J. L. Vicario and I. Tellitu, *J. Org. Chem.*, 1997, **62**, 6716.

[126] A. Padwa, Y. S. Kulkarni and L. W. Terry, *J. Org. Chem.*, 1990, **55**, 2478.

[127] H. Ikeda, Y. Naruse and S. Inagaki, *Chem. Lett*, 1999, 363.

[128] A. J. Blake, M. Harding and J. T. Sharp, *J. Chem. Soc. Perkin Trans. 1*, 1994, 3149.

[129] P. Seneci, I. Leger, M. Souchet and G. Nadler, *Tetrahedron*, 1997, **50**, 17097.

[130] K. Cullen and J. T. Sharp, *J. Chem. Soc. Perkin Trans. 1*, 1993, 2961.

[131] D. W. Knight and A. P. Nott, *Tetrahedron Lett.*, 1980, **21**, 5051.

[132] P. Wilson, PhD Thesis, University of Edinburgh, 2001.

[133] J. T. Sharp, P. Wilson, S. Parsons and R. O. Gould, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1139.

[134] T. Hudlicky, J. O. Frazier, G. Seone, M. Tiedje, A. Seone, L. D. Kwart and C. Beat, *J. Am. Chem. Soc.*, 1986, **108**, 3755.

[135] D. P. Munro and J. T. Sharp, *Tetrahedron Lett.*, 1980, **21**, 4109.

[136] Z. Arnold, A. Holy, *Collect. Czech. Chem. Commun.*, 1961, **26**, 3059.

[137] I. R. Robertson and J. T. Sharp, *Tetrahedron*, 1984, **40**, 3095.

[138] A. Suzuki, N. Miyaura and T. Yanagi, *Synth. Comm.*, 1981, **11**, 513.

[139] A. Padwa and H. Ku, *Tetrahedron Lett.*, 1979, **20**, 4425.

[140] L. M. Harwood, *Aldrichimica Acta*, 1978, **18**, 25.

[141] W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

[142] A. I. Vogel, *Handbook of Practical Organic Chemistry*, 4th edition, 1978, Longmans, London.

[143] H. Finch, D. H. Reece and J. T. Sharp, *J. Chem. Soc. Perkin Trans. 1*, 1994, 1193.

[144] J. A. Blanchette and E. V. Brown, *J. Am. Chem. Soc.*, 1951, **73**, 2779.

[145] W. J. Archer, R. Cook and R. Taylor, *J. Chem. Soc. Perkin Trans. 2*, 1983, 813.