Studies in electrophile-mediated heterocyclisation reactions

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Studies in Electrophile-Mediated Heterocyclisation Reactions

submitted by Robert W. Shaw

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To my parents

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Finally, I must thank the Directors of Shell Research Limited, Sittingbourne, for the opportunity given to me to conduct this research.

Summary

The Generation of 1,3-dipoles via Ag(I)-mediated heterocyclisation

Although our initial attempts to generate azomethine ylides via the Ag(I)-mediated heterocyclisation of allenic imines failed, we managed to overcome this problem by using the corresponding HCN adduct. The adducts were cyclised using Ag(I) and on heating readily lost HCN, to generate the corresponding azomethine ylides, which were successfully trapped.
We also used the tautomerisation method, to generate azomethine ylides for the synthesis of simple constrained amino esters via intramolecular cycloaddition of unactivated alkenes, allenes and alkynes.

We have been able to generate stable nitrones via the Ag(I)-mediated cyclisation of allenic ketoximes. Using the same Ag(I) procedure, an alkynic aldoxime was cyclised to generate a very reactive nitrone, which could be stabilised with either TMSCN, water or oximes.
The formation of the unstable seven-membered nitrone was shown to be an efficient cyclisation process and could be readily trapped with dipolarophiles.

Allene-based Electrophile-Mediated Heterocyclisations

The flexibility of the Ag(I)-activation of the allenic moiety towards intramolecular attack by nitrogen or oxygen nucleophiles, to form both five- and six-membered rings has been demonstrated. Other electrophiles ($Br^{\oplus}$, $PhSe^{\oplus}$ and $Pd^{2\oplus}$) have also been successfully employed to induce similar cyclisation to form five- and six-membered rings. However, the formation of the six-membered rings were limited to the oxygen nucleophile.

The formation of medium size rings via intramolecular nucleophilic attack onto an activated allenic moiety was successfully demonstrated using three different electrophiles ($Ag^{\oplus}$, $I^{\oplus}$ and $Pd^{2\oplus}$), but only with three specific nucleophiles.

The discovery of a two-step cyclisation of allenic sulphonamides was used to form 8-11 azacycles in reasonable yields. The addition of I_2 across the allenic moiety and then deprotonation of the sulphonamide under pseudo-high dilution conditions, resulted in exclusively or predominantly the formation of the larger of the two possible rings.

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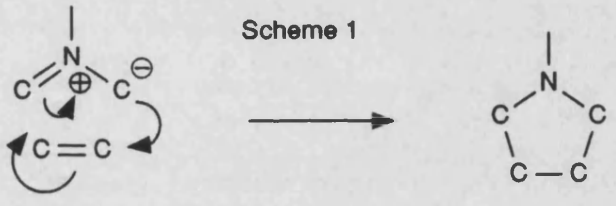
Azomethine Ylides

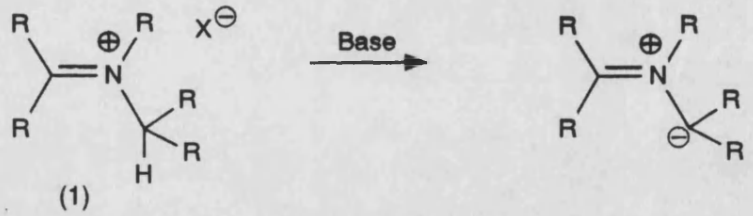
The cycloaddition of azomethine ylides provides a versatile and widely exploited route to nitrogen-containing five-membered heterocycles. Using this powerful methodology, the construction of two carbon-carbon bonds required to establish the ring structure is accomplished in a single step (Scheme 1).

Scheme 1



The mechanism of this and other 1,3-dipolar cycloadditions has been investigated extensively[1] by Huisgen, Houk and Firestone and these reactions are believed to proceed via a concerted mechanism. There are several methods available for the generation of an azomethine ylide, but the most direct way would appear to be the α-deprotonation of an iminium salt (1) (Scheme 2).

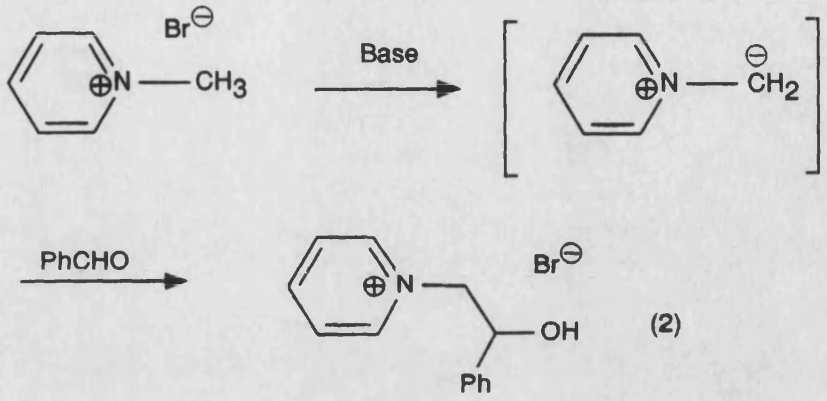
Scheme 2



(1)

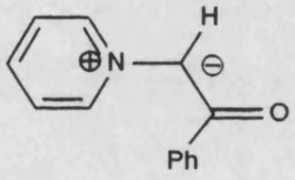
In practice, this route is complicated by dealkylation and dimerisation reactions, however, if the iminium salt is part of a heteroaromatic system, deprotonation is readily accomplished. In fact, this method was used to prepare one of the first azomethine ylides, by the depotonation of N-methylpyridinium bromide[2]. The resulting azomethine ylide was not isolated, but reacted with benzaldehyde to form adduct (2)(Scheme 3).

Scheme 3



(2)

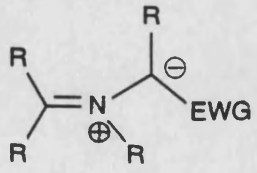
The first azomethine ylide stable enough to be to be isolated[3] was of the heteroaromatic type (3) and was also obtained by α-deprotonation of a pyridinium salt.



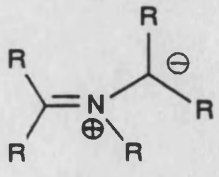
(3)

A complementary route to the α-deprotonation method was developed later by Vedejs[4] and was based on the α-elimination of "$^{\oplus}SiMe_3$". The scope of the "$^{\oplus}SiMe_3$" elimination procedure is not, however, limited to aromatic systems and this method has been applied to a broad range of substrates.

Azomethine ylides have been divided into two groups: stabilised and non-stabilised ylides (4) and (5) respectively.



Stabilised (4)



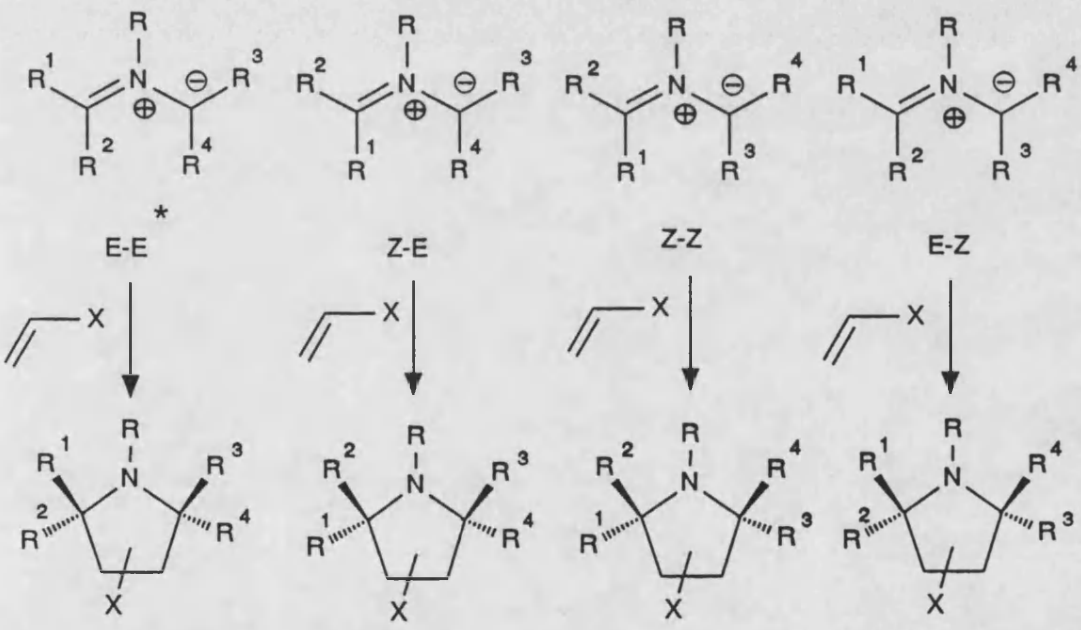
Non-stabilised (5)

EWG = Electron withdrawing group.

The division does not necessarily reflect the reactivity of these ylides towards dipolarophiles and many unstabilised ylides, for example, fail to react[5] in an intramolecular fashion with unactivated dipolarophiles, whilst stabilised ylides frequently react with such dipolarophiles in intramolecular reaction[6]. The only route developed to date for the formation of very reactive dipoles is the N-oxide methodology and this process will be discussed later (see p.31).

The reaction between an unsymmetrical azomethine ylide and an unsymmetrically substituted dipolarophile could, in theory, produce eight isomers and their mirror images from the four possible isomeric dipoles.

Scheme 4

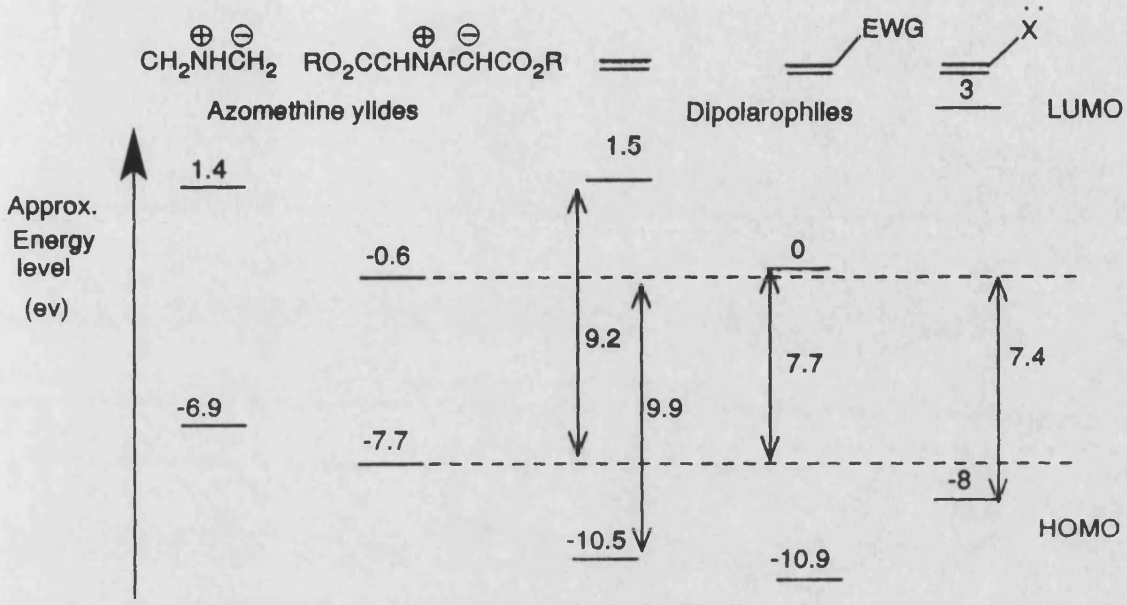


* assigment based on priority $R^1 > R^2$, $R^3 > R^4$.

Fortunately, many azomethine ylide cycloaddition reactions are both stereo- and regioselective which is, of course, important in terms of the synthetic utility of these dipolar cycloaddition reactions.

In accordance with frontier molecular orbital theory for concerted reactions, azomethine ylides generally react rapidly with electron-deficient alkenes or alkynes. The energy level of the LUMO of the dipolarophile is lowered by electron-withdrawing substituents, and hence narrows the gap between the

HOMO of the dipole and the LUMO of the dipolarophile.



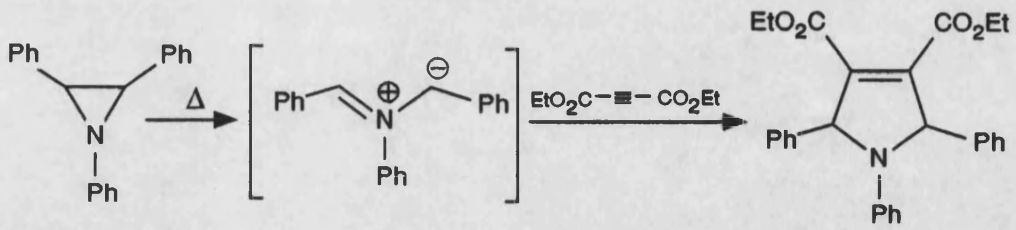
Most of the chemistry of azomethine ylides has been developed since 1978. Considerable progress in the techniques used to generate the 1,3-dipole has occurred, and stereo- as well as regioselective reactions have been developed and very recently, the first efficient asymmetric cycloaddition reaction was described [52]. Because of the vast range of azomethine ylide chemistry, this section will concentrate on the synthetic routes towards this type of dipole, together with a brief overview of their reactivity.

Synthetic Routes to Azomethine Ylides

Ring Cleavage of Aziridines

Electrocyclic ring cleavage of an aziridine provides an entry to azomethine ylides. The carbon-carbon bond cleavage of aziridine ring (6), to generate the azomethine ylide was first observed by Heine and Peavy[7] in 1965. The 1,3-dipole thermally generated was then trapped by either diethyl acetylene dicarboxylate to give cycloadduct (7) or maleic anhydride (Scheme 5).

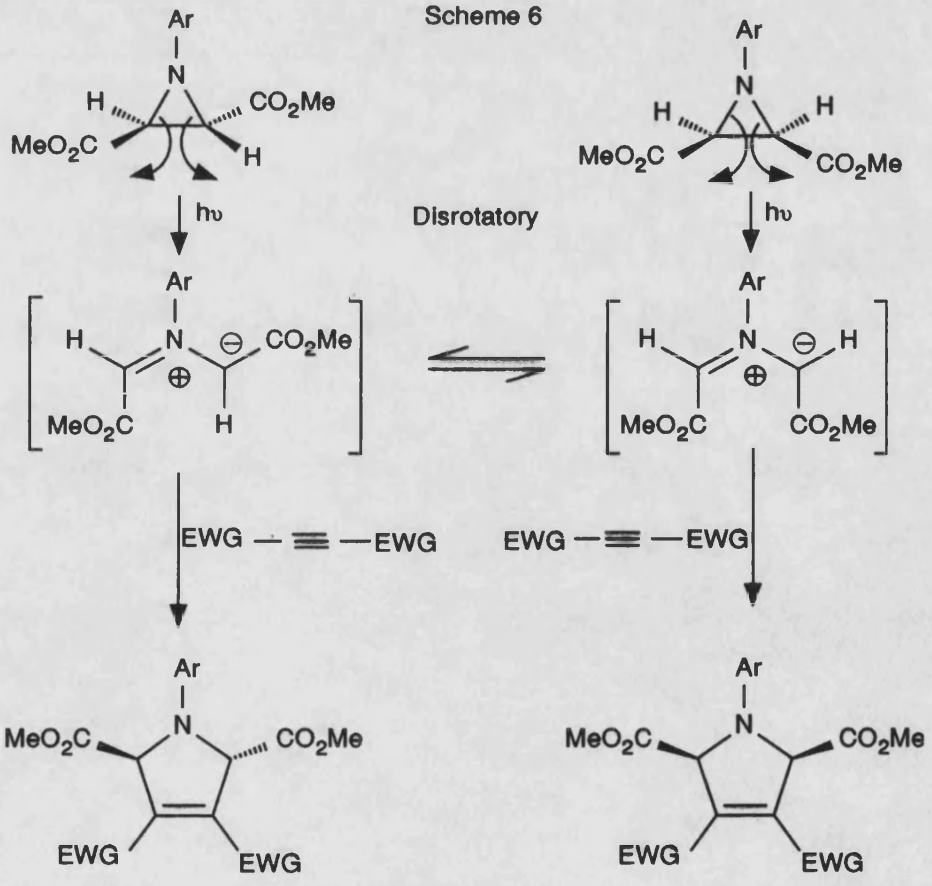
Scheme 5



(6) 98% (7)

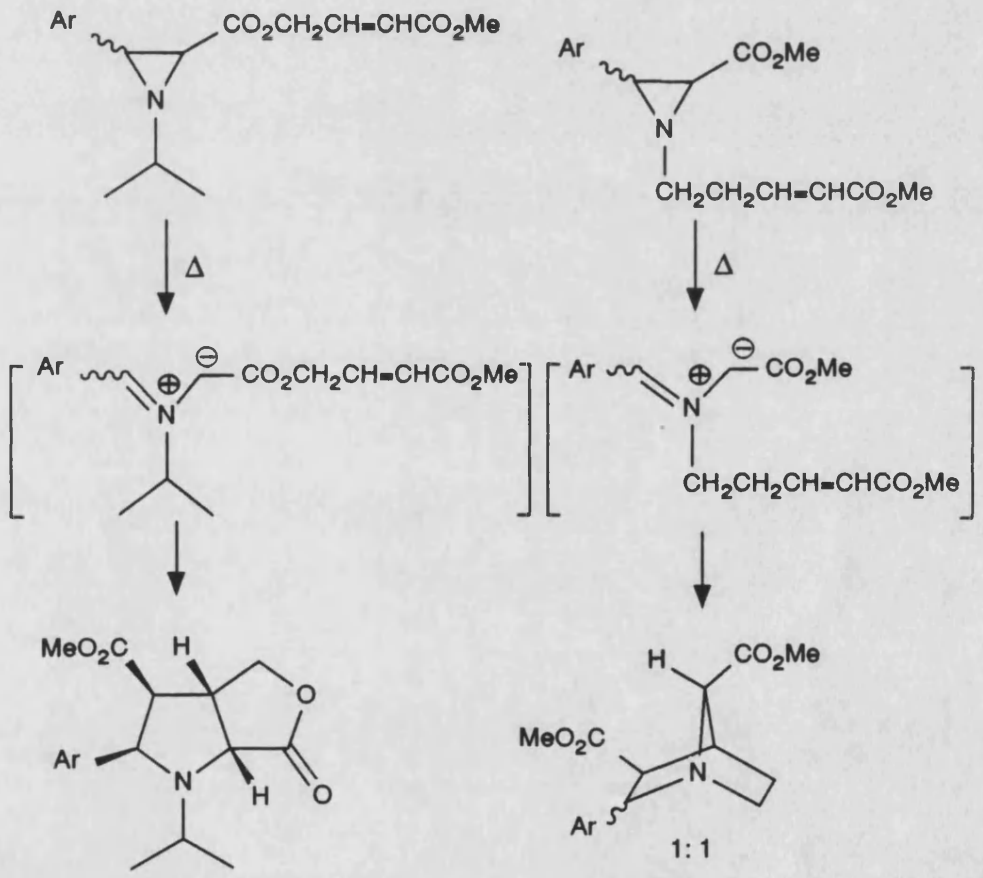
Invoking the rules of conservation of orbital symmetry (developed by Woodward and Hoffmann), Huisgen[8] accounted for the stereochemical outcome of the thermal ring opening of aziridines via a conrotatory process, whereas the photochemical ring opening could be explained by assuming a disrotatory cleavage process. The stereochemical consequences of the disrotatory process, in terms of ylide geometry are shown in Scheme 6.

Scheme 6



Unfortunately, syn-anti equilibration of the ylide is often rapid and the stereospecific nature of the aziridine ring-opening process is frequently lost. The synthetic value of this route is also limited to some extent by the nature of the substituents on the aziridine ring which are required in order to facilitate the ring-opening reaction. In an interesting extension of this method, the use of aziridine ring-opening to generate ylides capable of undergoing intramolecular 1,3-dipolar cycloadditions have been described by Padwa[9] et al (Scheme 7).

Scheme 7

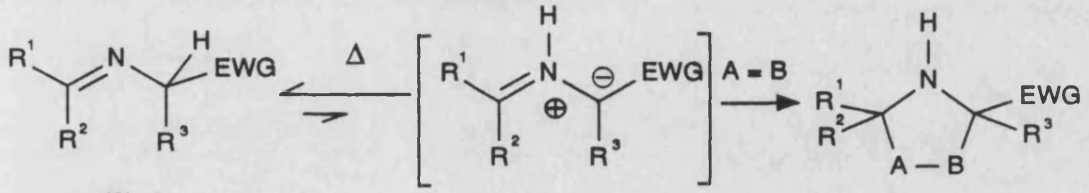


Once again a lack of stereospecificity was observed because equilibration of the dipoles occurred much faster than internal cycloaddition.

1,2-Prototropic Shift

This method, developed by Grigg et al[10] involves the 1,2-prototropic shift from C to N in imines (8) to generate an N-protonated, stabilised azomethine ylide (9) (Scheme 8). The 1,3-dipoles, which are only present in low concentrations via this equilibrium process, have been successfully trapped by a wide range of activated dipolarophiles.

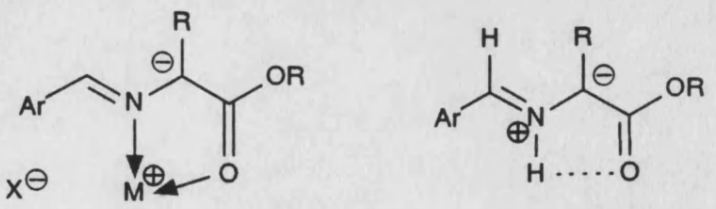
Scheme 8



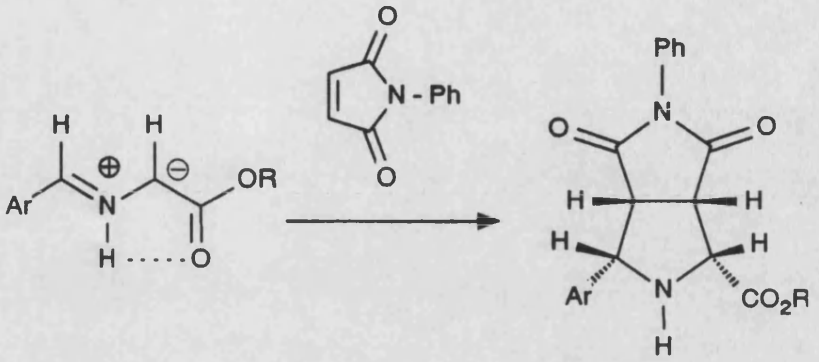
(8) (9)

When activated dipolarophiles (e.g. NPM) are used, the rate-limiting step for such cycloaddition reactions has been shown to be the formation of the azomethine ylide. Grigg[11] also demonstrated that the basicity of the imine nitrogen effects the rate of rearrangement and this tautomerisation has also been demonstrated to be catalysed by both Lewis and Brönsted acids. The Lewis-acid catalysed[12] reaction is believed to proceed either via a metallo-1,3-dipole or the azomethine ylide (Scheme 9) (metallo-1,3-dipoles will be discussed in more detail later) and the acid-catalysed rearrangement generates dipoles that react in both a regio- and stereoselective fashion (Scheme 10).

Scheme 9



Scheme 10

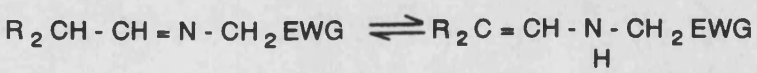


(10) (11)

The regio- and stereoselectivity of this reaction can explained by comparing the geometry of the four possible dipoles (see Scheme 4). From such an examination, it is clear that the dipole (10), the most stable due to hydrogen bonding and minimal steric interactions, then reacts with NPM in an endo sense to give a single product (11).

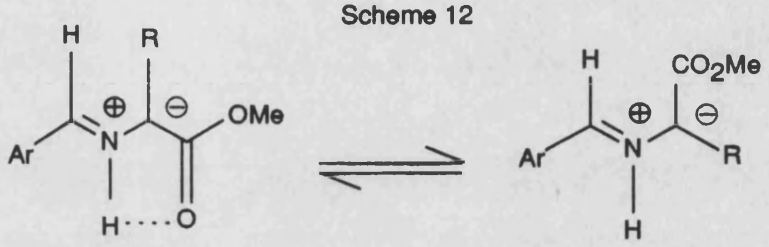
The example described above relates to aryl-substituted imines and the situation with alkyl-substituted derivatives is more complex. The extensive review by Tsuge[14] refers to the instability of aliphatic imines and the failure of aldehydes (propanal and cinnamaldehyde) to produce cycloadducts with methyl glycinate and the reactive trap, N-methylmaleimide. Aliphatic imines are therefore of limited use in this sense due to side reactions, which presumably involve imine-enamine tautomerism (Scheme 11).

Scheme 11



The stereochemistry of the cycloaddition products from a range of imines and dipolarophiles other than N-substituted maleimides has been investigated. With less reactive dipolarophiles, equilibration between the (E-E) dipole (10) and the (E-Z) ylide (12) can occur (Scheme 12).

Scheme 12



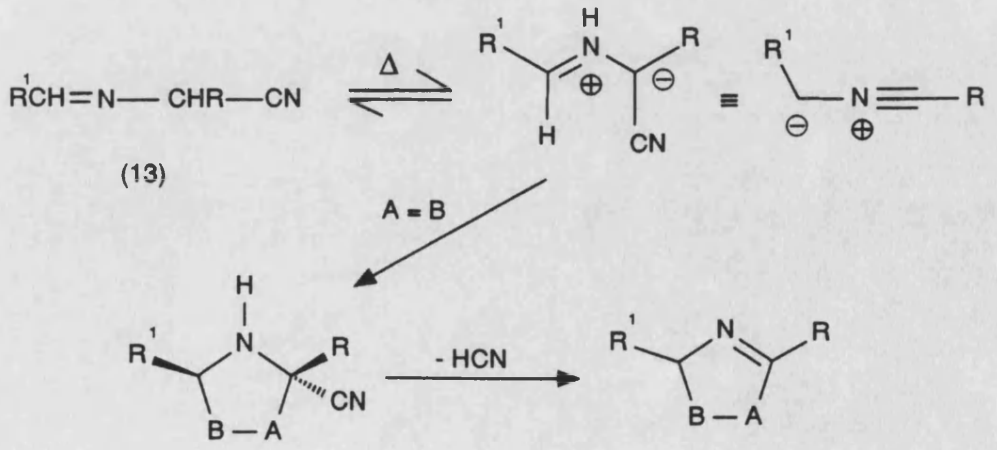
E-E ylide (10) E-Z ylide (12)

When R=Ph (α-phenyl substitution) a greater amount of the E-Z ylide (12) is trapped, presumably due to increased steric interactions.

Grigg et al[15] have used the cyclopropyl moiety adjacent to the imine to investigate the concerted nature of the 1,2-prototropic shift route to azomethine ylides. In all cases, no cleavage of the cyclopropane ring was observed and the intermediacy of a radical can be ruled out.

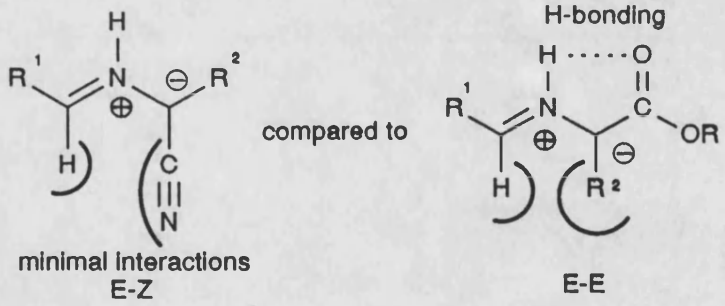
Other electron-withdrawing groups apart from the ester moiety, have been used to stabilise the dipole[16] and for example, the imines of α-amino alkyl nitriles (13) undergo thermal tautomerisation to ylides which can be trapped by dipolarophiles (Scheme 13).

Scheme 13



The subsequent loss of HCN[16c] from the resulting cycloadducts has been demonstrated, making these nitrile-substituted ylides synthetically equivalent to the corresponding nitrile ylides.

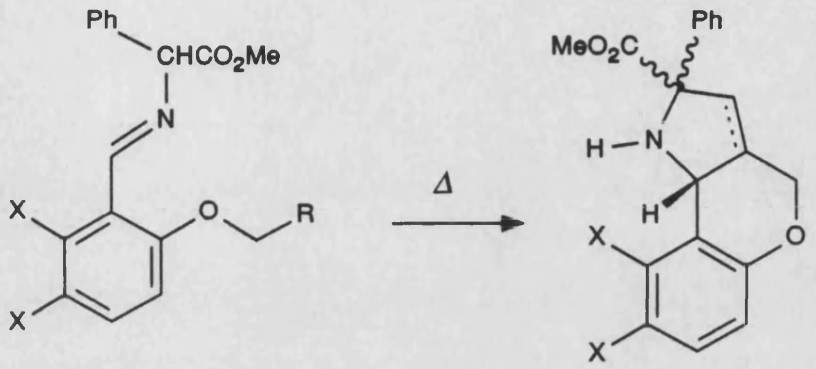
The geometry of nitrile-stabilised azomethine ylides is different from the related ester-stabilised series. Steric requirements determine the most stable ylide geometry in the nitrile case, whereas hydrogen bonding dictates the geometry of the ester-stabilised dipoles. The nitrile and ester groups thus complement each other in this respect.



Other functional groups which have been used to stabilise the 1,3-dipole include thioesters and amides.

The use of 1,2-prototropic shift to generate azomethine ylides capable of undergoing intramolecular cycloaddition to unactivated dipolarophiles has also been examined[17](Scheme 14).

Scheme 14

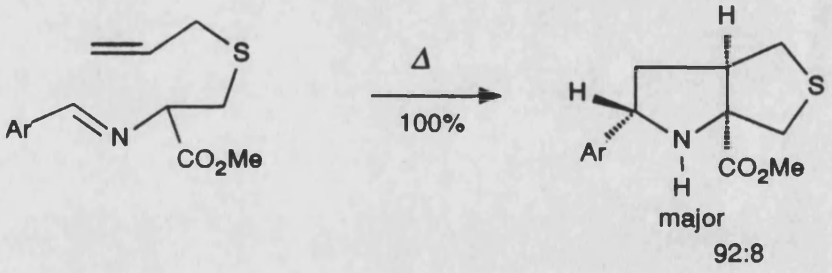


R = C≡C-H

X = Ar 93% 3:1 140°C 24h
X = H 75% 4:1 140°C 24h
X = H 39% 1:0 140°C 3h

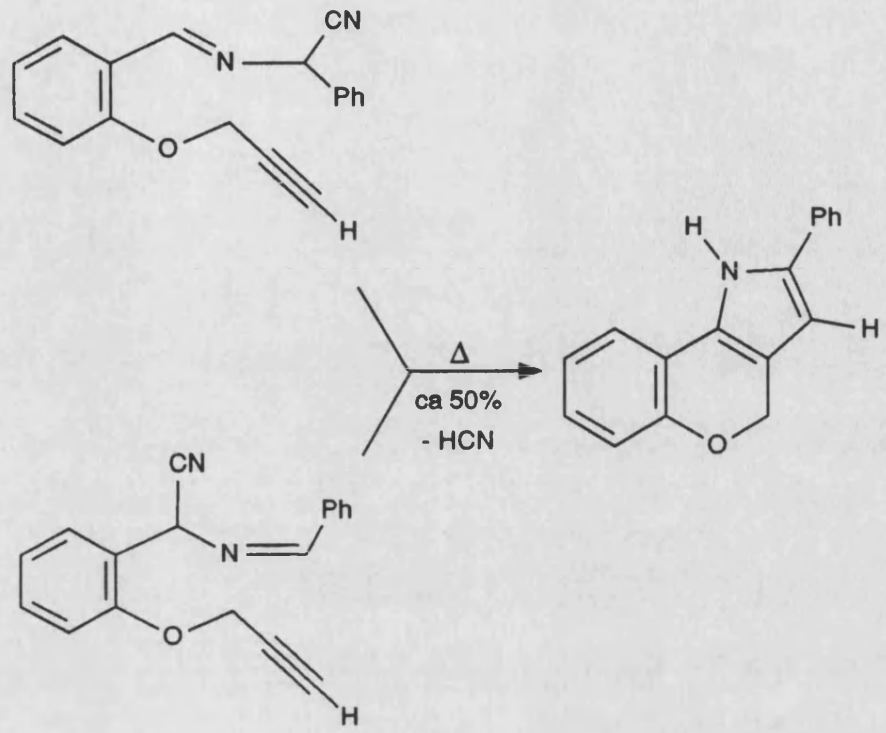
R = CH = CH_2

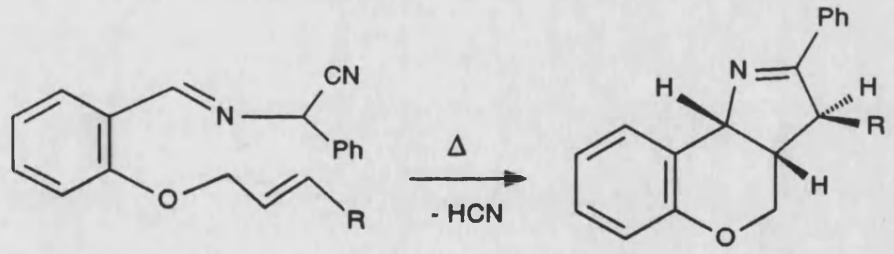
X = Ar 71% 47:53 140°C 3days

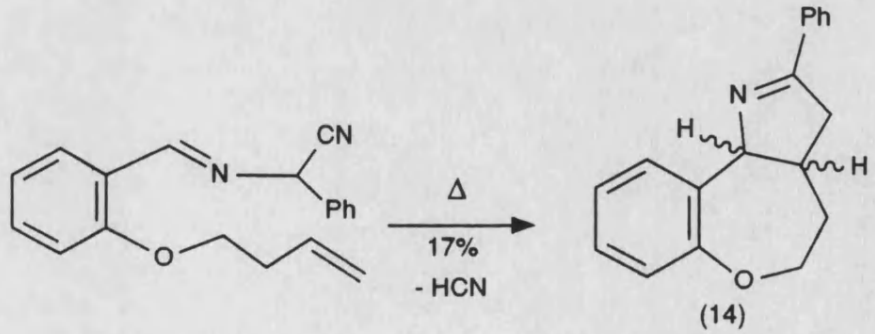


Examples involving nitrile-stabilised ylides are shown in Scheme 15 and, as with the intermolecular cases, elimination of HCN from the initially-formed cycloadduct is observed.

Scheme 15


CN
N
Ph
O
H
Δ
ca 50%
- HCN
H
Ph
N
H
O
CN
Ph
N
O
H


CN
N
Ph
O
R
Δ
- HCN
Ph
N
H
H
R
H
O

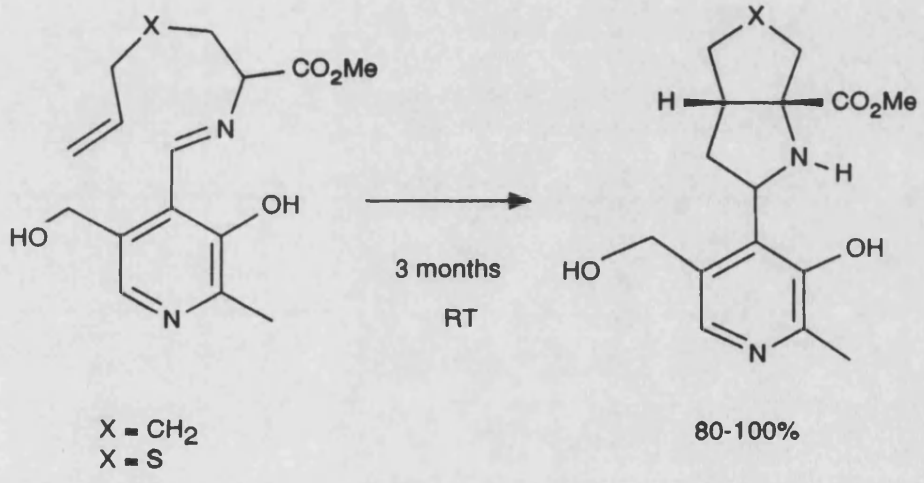

CN
N
Ph
O
Δ
17%
- HCN
Ph
N
H
H
O

(14)

The formation of the seven-membered ring[17e] (14) is of particular interest to us and we shall describe our investigations relating to cyclisations leading to medium rings later (see p.93).

A recent example of the intramolecular reaction as a model for the possible inhibition of the pyridoxal enzyme (Scheme 16) has been investigated[17a].

Scheme 16



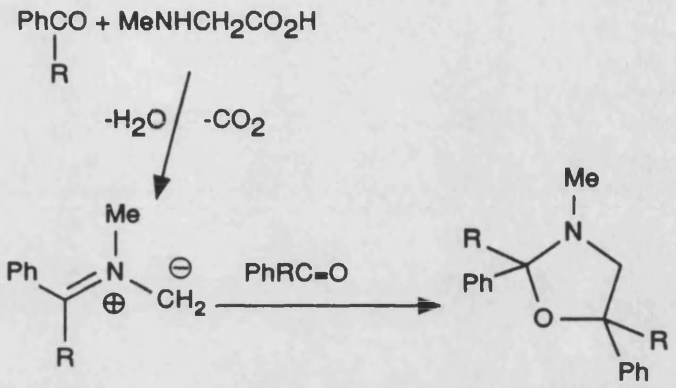
X = CH_2
X = S

80-100%

Decarboxylation of Amino Acid Derivatives

This route to azomethine ylides is based on the Strecker degradation of α-amino acids, via imine formation. During an investigation of carbonyl-assisted decarboxylation of N-alkyl α-amino acids, Rizzi[18] observed the formation of (16a) and (16b). Rizzi suggested that the reactive species involved was the azomethine ylide (15) and that this was produced as a result of decarboxylation of the initially-formed iminium ion. The azomethine ylide was trapped, with the carbonyl component acting as a 1,3-dipolarophile (Scheme 17).

Scheme 17

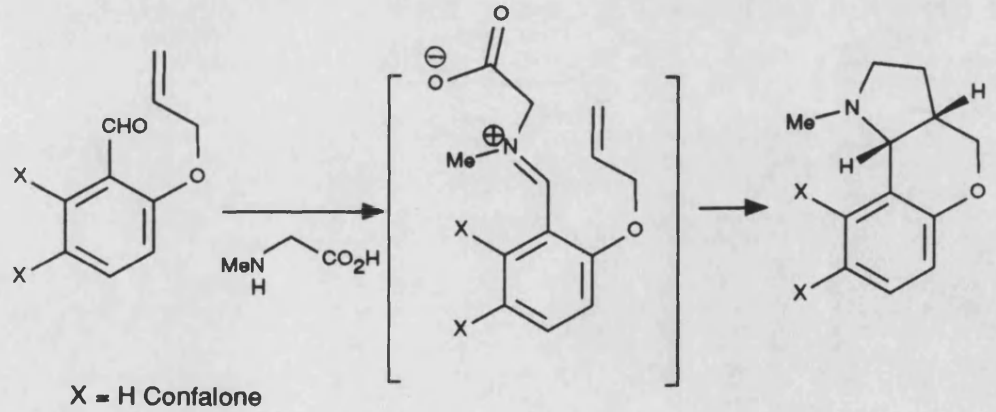


(15)

R = Ph (16a) 1.3%
R = H (16b) 27%

This area of chemistry remained essentially dormant for fourteen years, when the value of this route to unstabilised azomethine ylides was fully recognised as a powerful tool for synthetic chemists. Two groups, Confalone et al[19a,b] and Grigg et al[19c,d], both demonstrated the intramolecular cycloaddition of an azomethine ylide generated by the loss of CO_2 from an iminium ion intermediate (Scheme 18).

Scheme 18

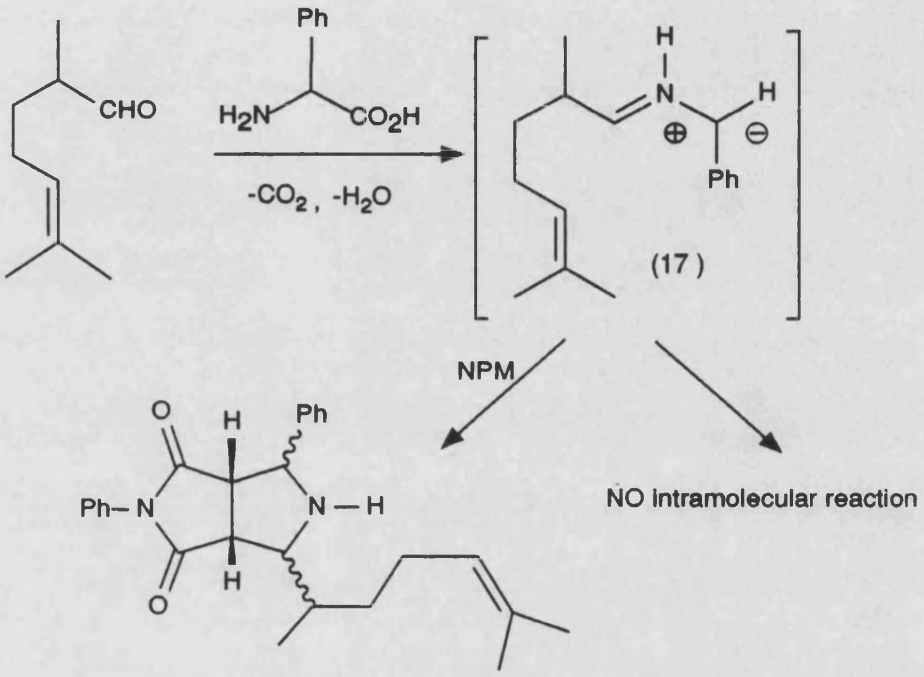


X = H Confalone
X - X = C_4H_4 Grigg

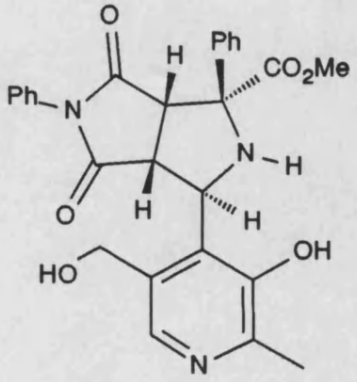
Intramolecular reactions are not always facile and Grigg found that the ylide (17), derived from phenylglycine and 2,6-dimethylhept-5-enal, failed to undergo

intramolecular cycloaddition. The presence of the ylide (17) was, however, confirmed by intermolecular trapping with NPM (Scheme 19).

Scheme 19



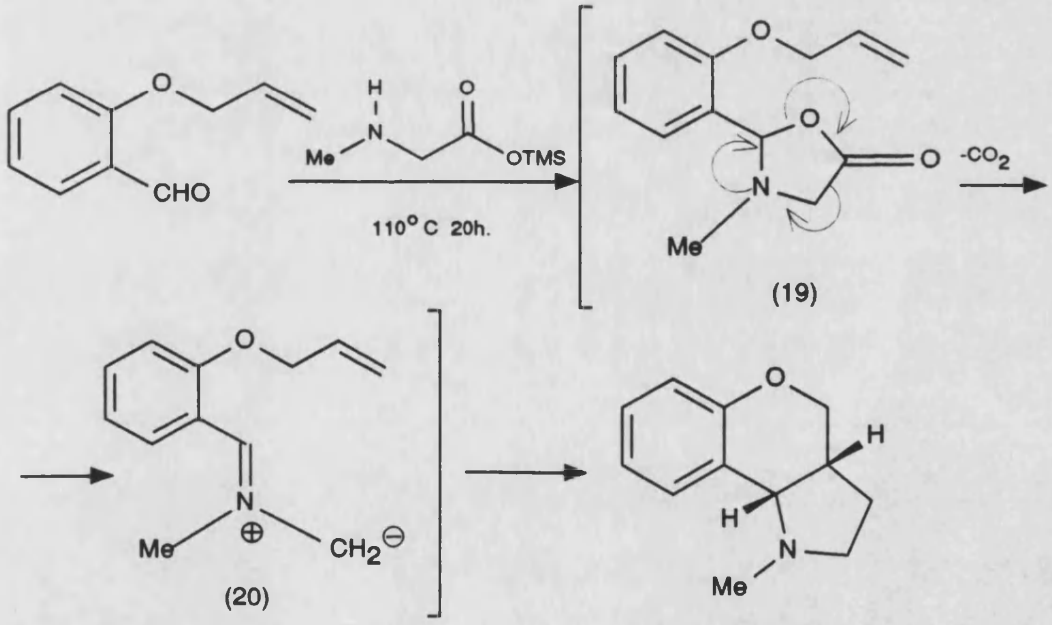
Grigg also suggested that the biological decarboxylative transamination of amino acids, which is a fundamentally important process in amino acid metabolism, could proceed via an unstabilised azomethine ylide. Pyridoxal, employed in most decarboxylases as the prosthetic group, reacted with phenyl glycinate and NPM to give (18) in 50% yield.



(18)

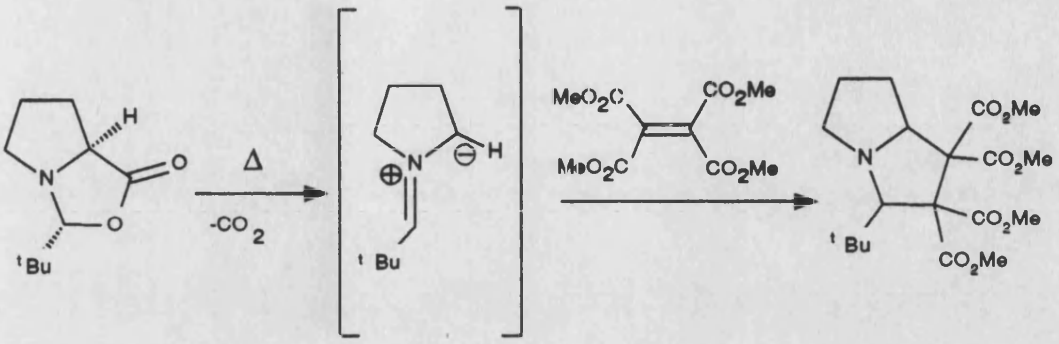
Confalone's work in this area concentrated mainly on the synthesis of sceletium alkaloid A_4 and (+)-α-lycorane. The latter alkaloid was prepared stereospecifically in five steps via the decarboxylative route to azomethine ylides. A cyclic intermediate (19) was postulated as the precursor to the key unstabilised ylide (20)(Scheme 20).

Scheme 20



In support of this mechanism, the oxazolidinone (21) is known[20] to thermally eliminate CO_2, to generate the 1,3-dipole (22) which can be trapped (Scheme 21).

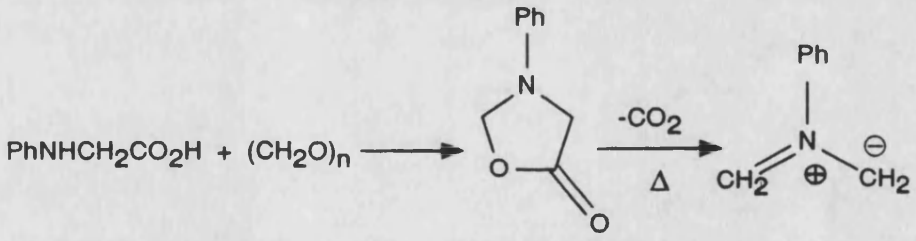
Scheme 21



(21) (22) (23)

In 1987 Tsuge et al[14] isolated the dihydrooxazoline (24) from the reaction between paraformaldehyde and N-phenylglycine, which readily eliminated CO_2 to generate an ylide which was subsequently trapped (Scheme 22).

Scheme 22

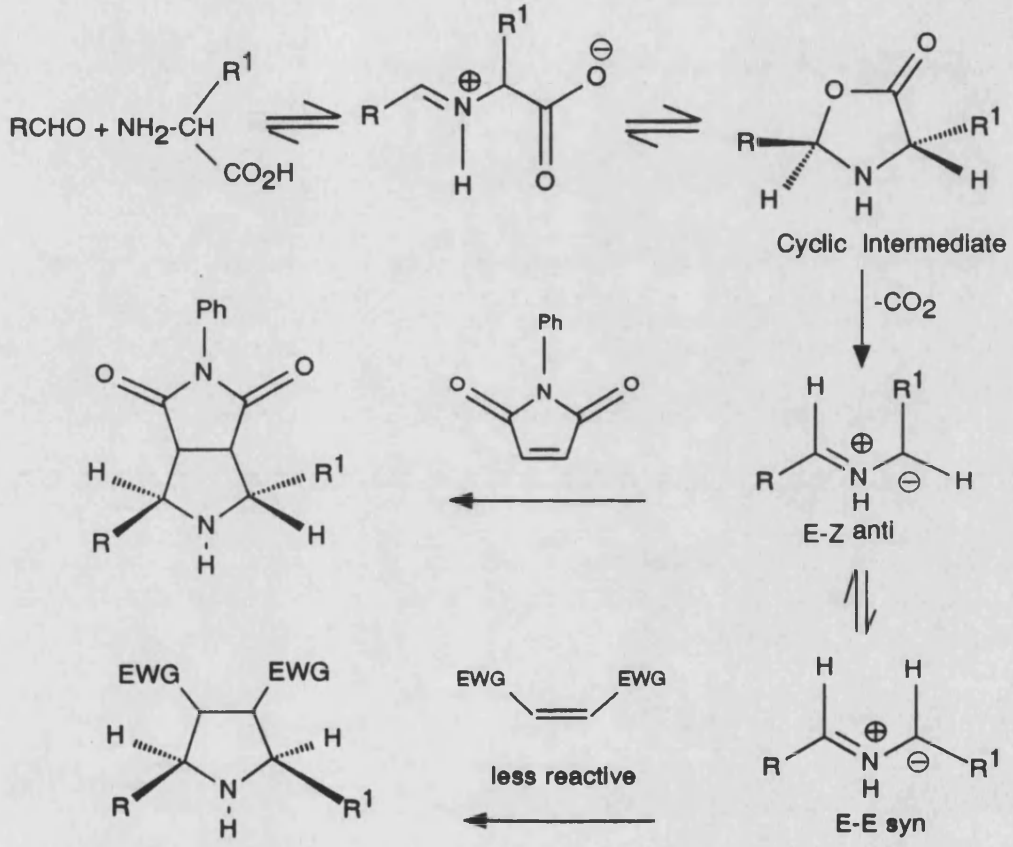


(24) Isolated

The generation of ylides by this decarboxylative route is a stereoselective process and this has been demonstrated by Grigg and his co-workers who have trapped the anti-(E-Z) dipole with the reactive dipolarophile (NPM) for a vast range of azomethine ylides. When NPM is used, stereomutation of the dipole to the thermodynamically more stable (E-E) dipole does not normally occur, because cycloaddition is faster than this rotation. However, the dipole stereochemistry is sensitive to the structure of the amino acid, the aldehyde, and reaction temperature, and mixtures of exo- and endo- products are often

isolated. All of the above observations strongly support a mechanism involving a cyclic intermediate (Scheme 23).

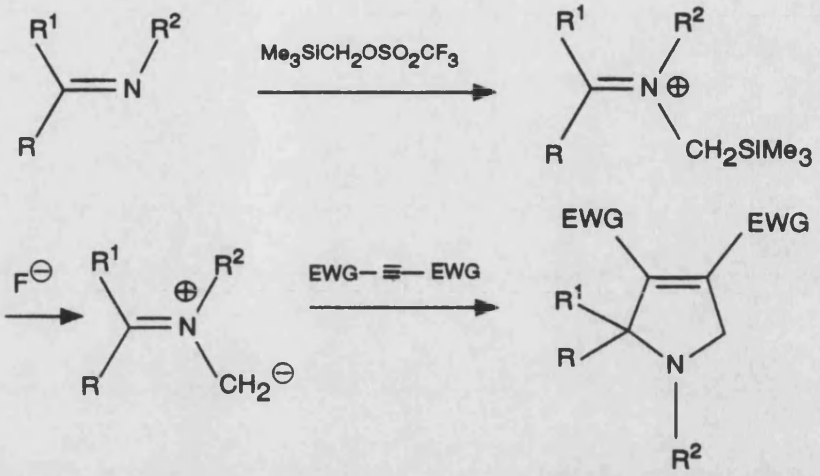
Scheme 23



Cleavage of α-(Trimethylsilyl)amines as a Route to Azomethine Ylides

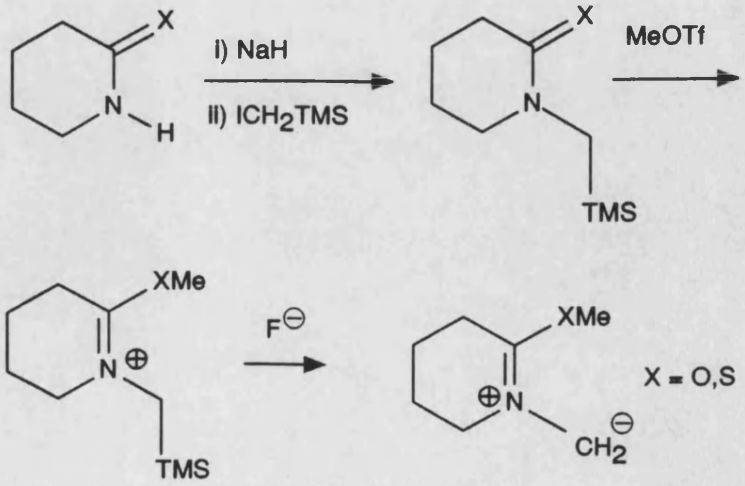
This route to unstabilised azomethine ylides was first developed by Vedejs and Martinez[4]. Initial alkylation of the imine was accomplished with trimethylsilylmethyl triflate and the resulting iminium ion was then desilyated by CsF (under anhydrous conditions) to generate the unstabilised ylide which was trapped with suitable dipolarophiles (Scheme 24).

Scheme 24



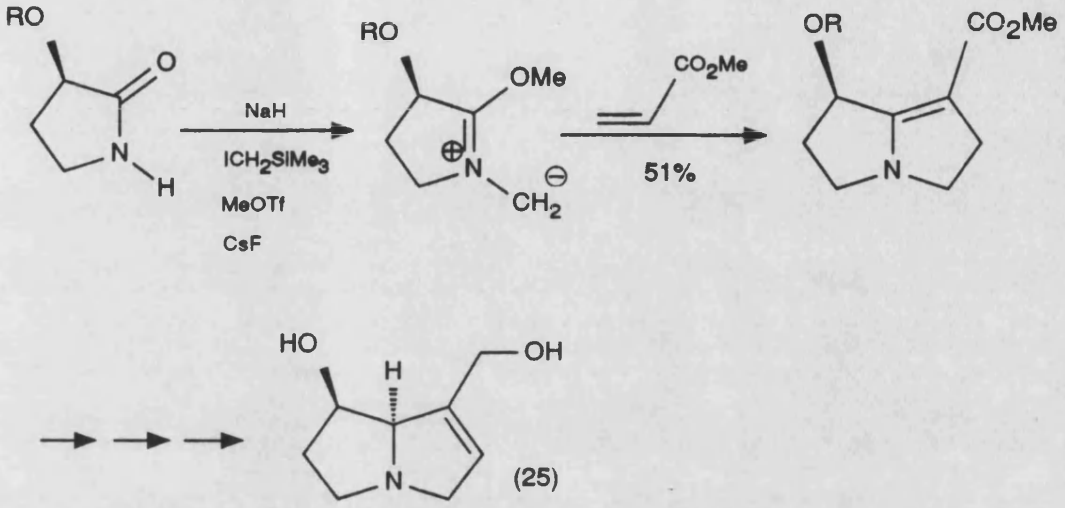
The driving force for the desilylation was the strength of the Si-F bond and although this process takes place under very mild conditions, there are certain disadvantages associated with this methodology. The preparation of silicon-containing iminium salts is not a trivial process, and other methods have been developed for the generation of unstabilised azomethine ylides by this general route. The sodium salts of amides and thioamides (which are usually available in better overall yield[21]) can be readily alkylated with Me_3SiCH_2I[21] (less esoteric than Me_3SiCH_2OTf) and the iminium salts can be prepared by selective O-alkylation (Scheme 25).

Scheme 25



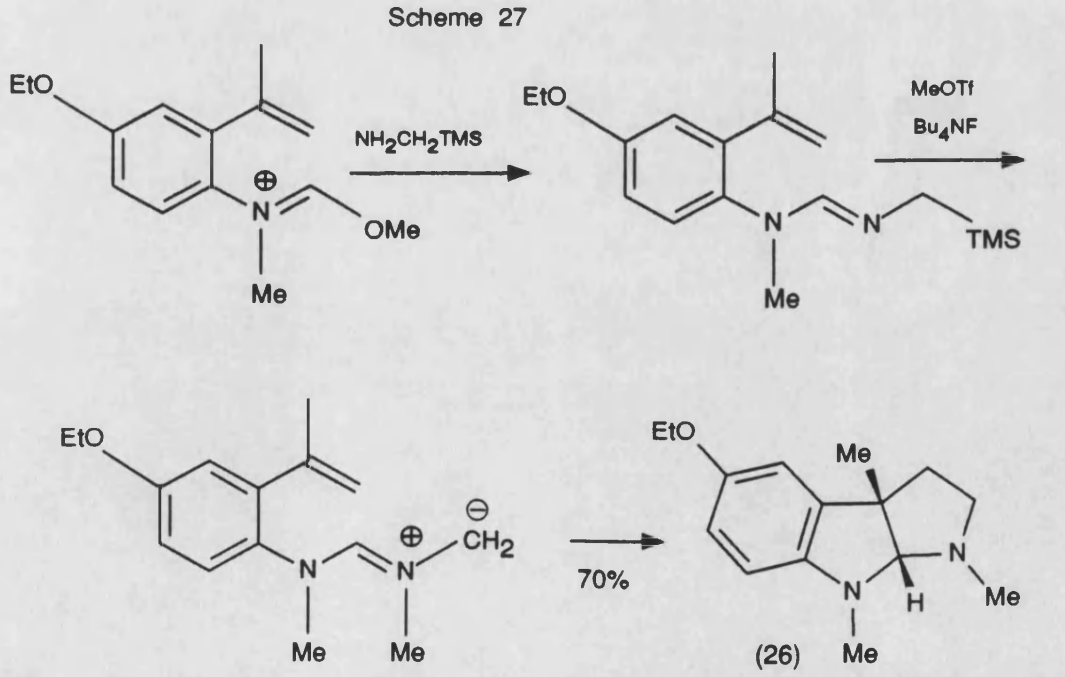
Vedejs[5c] has applied this silicon-based methodology to the stereospecific synthesis of enantiomerically pure retronecine (25) as illustrated in Scheme 26.

Scheme 26



Livinghouse[22] has further developed the scope of this chemistry by using an amidine-derived azomethine ylide in the synthesis of eserethiole (26).

Scheme 27

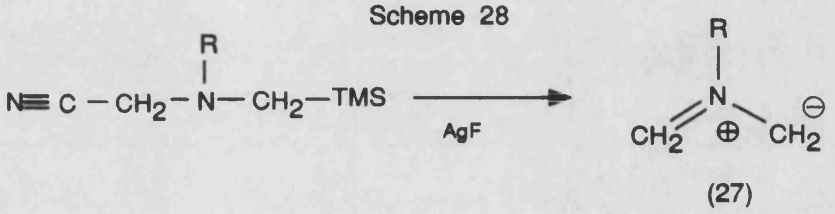


This latter process is of interest as it is the only example of an unactivated dipolarophile reacting with an azomethine ylide generated by desilylation. The

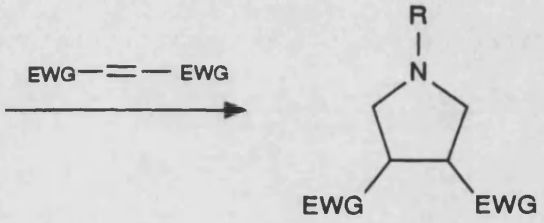
use of an unactivated alkyne in an analogous reaction failed to achieve an intramolecular cycloaddition reaction[23].

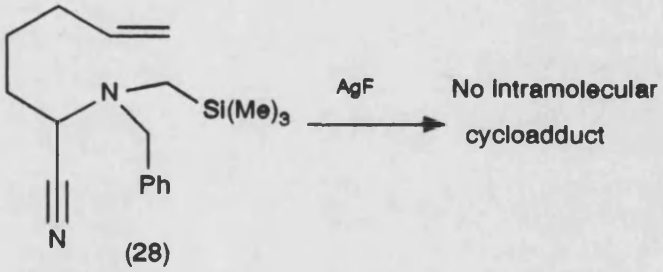
Another variation of the desilylation theme has been developed by Padwa[5b] which involved the generation of dipole (27) by decyanation and desilylation of an N-cyanomethyl-N-(trimethylsilyl)methylamine with AgF (Scheme 28).

Scheme 28

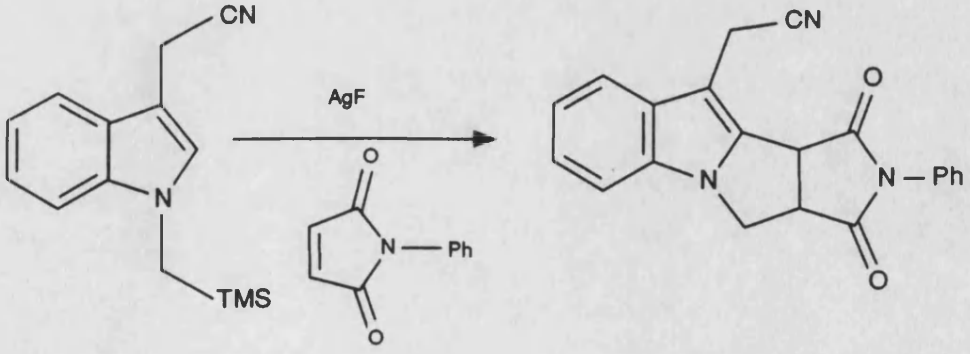


(27)





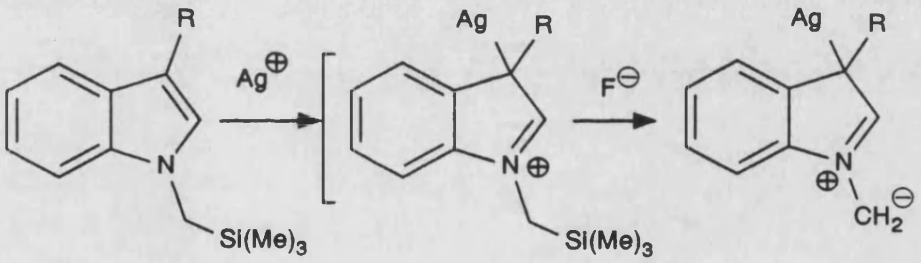
(28)



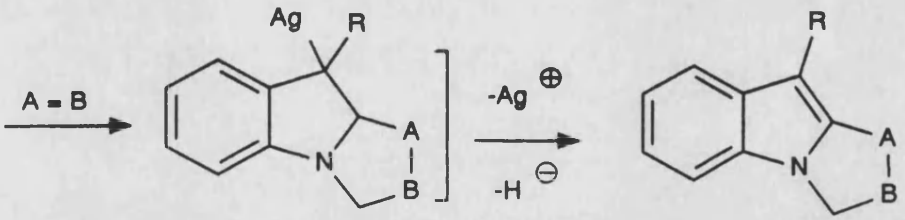
Padwa also observed problems with the intramolecular process involving the unactivated olefin (28), which failed to undergo cycloaddition.

A more extensive study of this reaction carried out by Padwa[24] gave rise to some interesting observations which indicate that the nitrile actually plays little or no role in the formation of the azomethine ylide (Scheme 29). A range of groups were used in place of the nitrile substituent and all underwent cycloaddition reactions in the presence of AgF. Other Lewis acids and F^- sources all failed to generate an azomethine ylide and Padwa has postulated that this reaction proceeds via the mechanism shown in Scheme 29.

Scheme 29

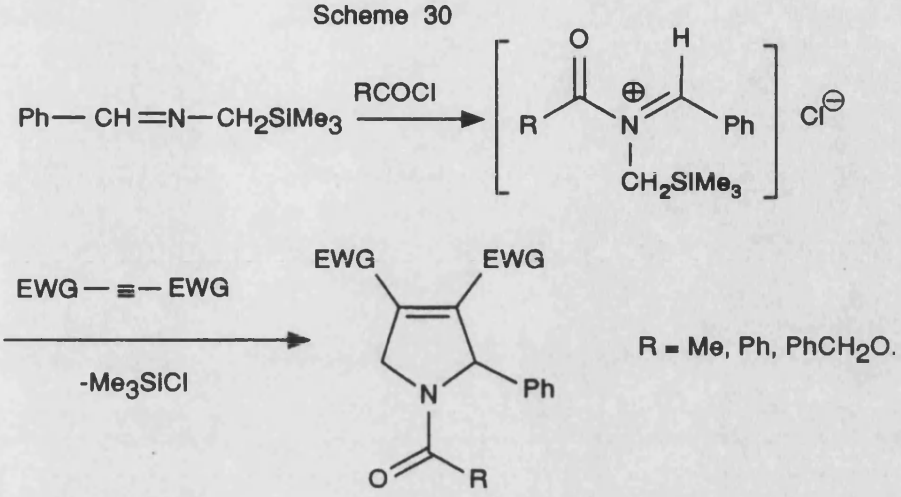


R = H, Me, CHO.



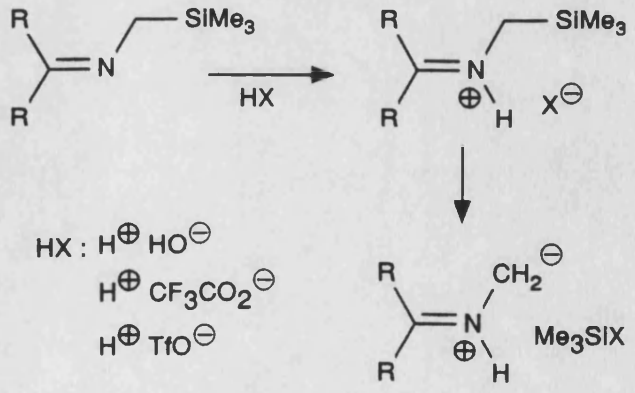
An alternative approach to unstabilised azomethine ylides uses the N-acylation[25] of trimethylsilyl imines (Scheme 30).

Scheme 30



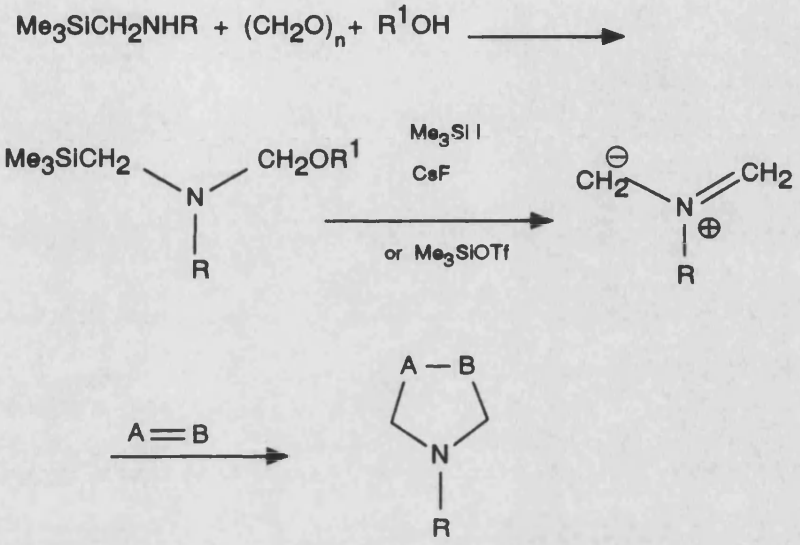
A related route has been described that is based on N-protonation of the N-(trimethylsilyl)methyl moiety[26](Scheme 31) which are readily prepared by condensation of the corresponding carbonyl compound with silylmethyl amine, or silylmethyl azide/ triphenylphosphine[27].

Scheme 31



Another silicon-based procedure was explored by Sakurai[28] which allowed access to the simplest azomethine ylide (Scheme 32).

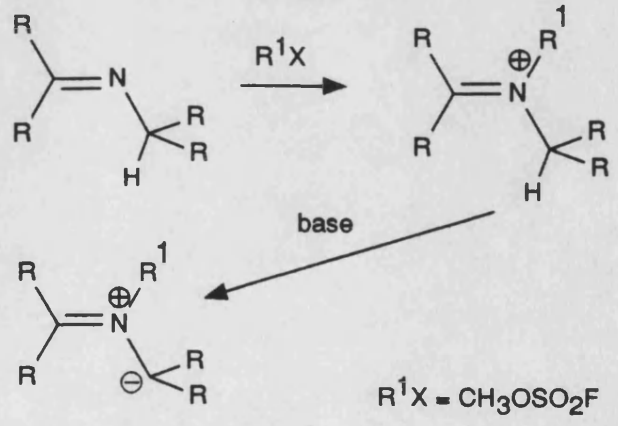
Scheme 32



Deprotonation of Iminium ions as a Route to Azomethine Ylides

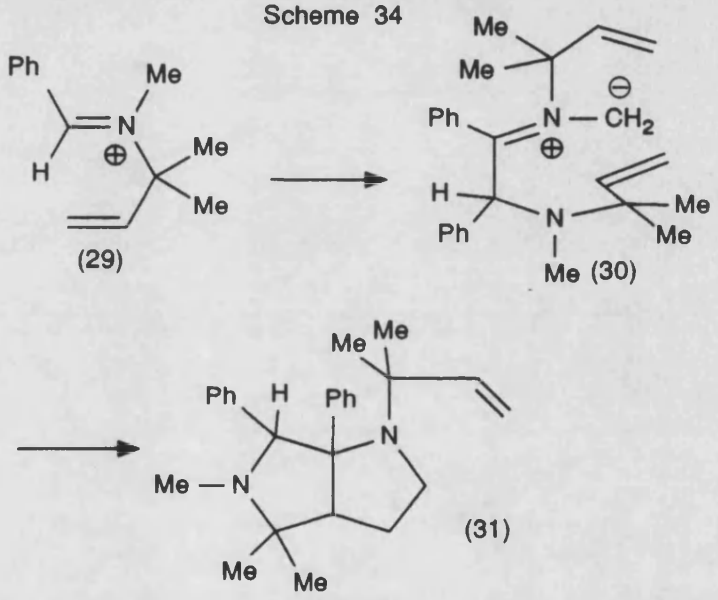
The deprotonation of pyridinium ions was one of the earlier synthetic entries into azomethine ylide chemistry (Scheme 3). Even so, it was not until 1975[29] that deprotonation chemistry was extended to non-aromatic systems. This involved the N-alkylation of an imine and subsequent deprotonation using a base such as sodium bis(trimethylsilyl)amide[29], the objective being to minimise competitive dealkylation (Scheme 33).

Scheme 33



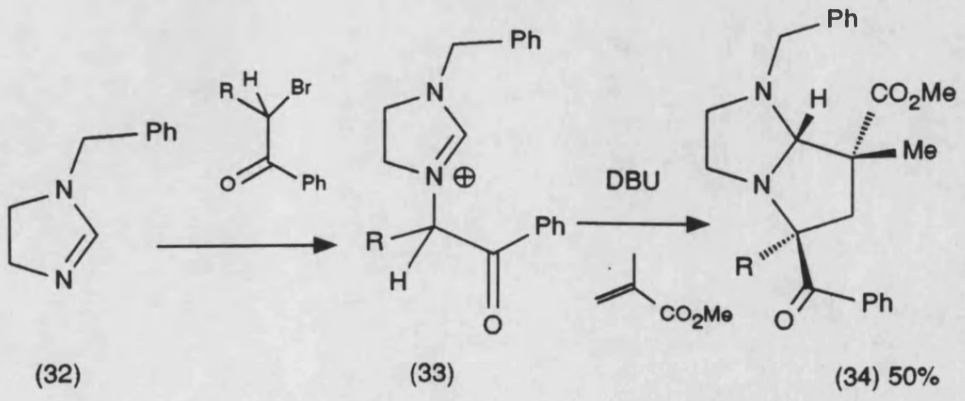
In early studies, the only products isolated were aziridines and all attempts to trap the intermediate dipoles were unsuccessful; the use of the standard dipolarophiles was precluded due to the strongly basic conditions. This route did however lead later to the first intramolecular cycloaddition of an azomethine ylide. In 1977 Deyrup et al[30] effected the deprotonation of (29) to form the dipole (30) which subsequently underwent dimerisation followed by intramolecular cycloaddition to give (31) (Scheme 34).

Scheme 34



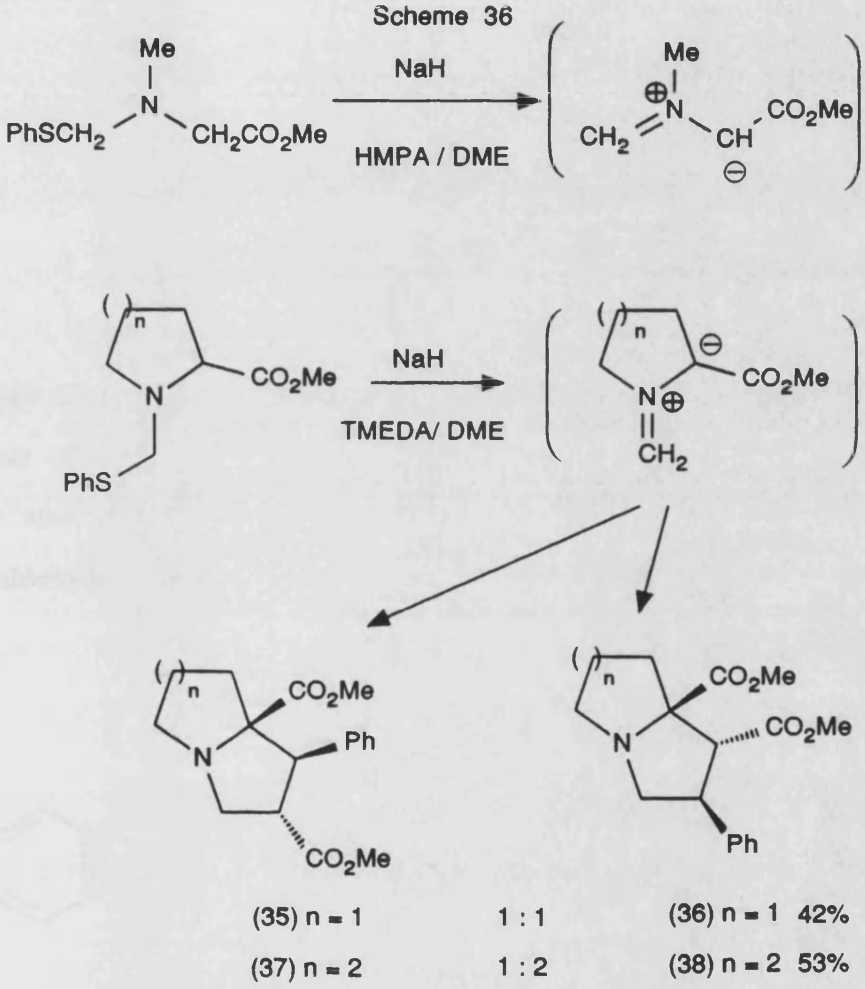
Recently[31], this N-alkylation/deprotonation sequence has been demonstrated by the N-alkylation of 1-benzyl-2-imidazoline (32), and deprotonation with the mild base (DBU), in the presence of a reactive dipolarophile (Scheme 35).

Scheme 35



An interesting variation of this technique has been exploited by Achiwa[32] who used sodium hydride to generate the ylide from an N-phenylthiomethyl derivative (a masked iminium ion of α-amino esters) (Scheme 36).

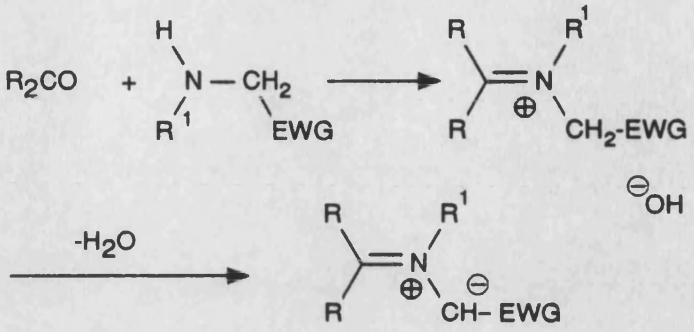
Scheme 36



This method has been applied to the generation of both acyclic and heterocyclic ylides and in the latter system cycloadditions using methyl cinnamate afforded the substituted pyrrolizidines (35) and (36), and the indolizidines (37) and (38) in good yields.

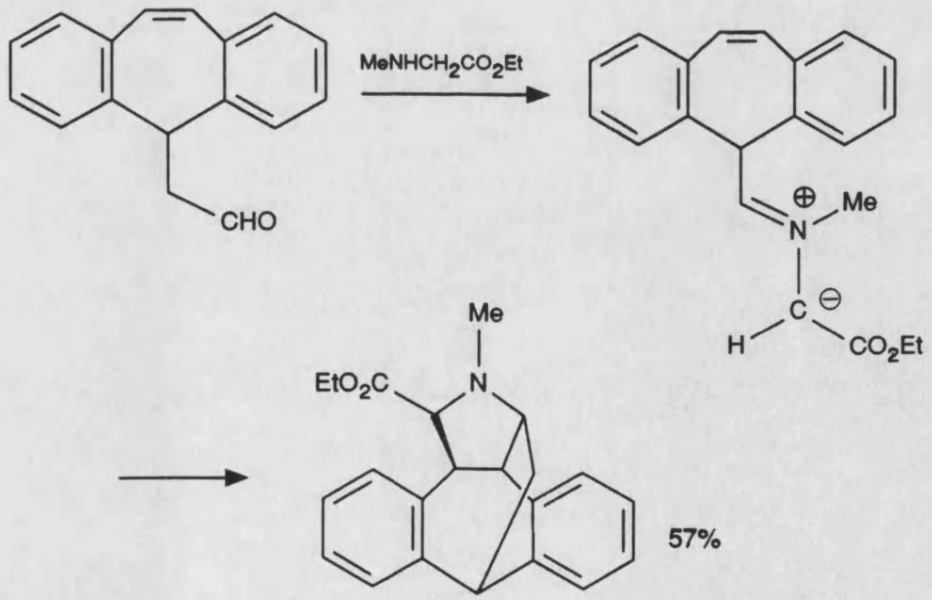
The simplest and most general of these deprotonation-based routes to azomethine ylides is the condensation of N-substituted α-amino esters with carbonyl compounds (Scheme 37).

Scheme 37



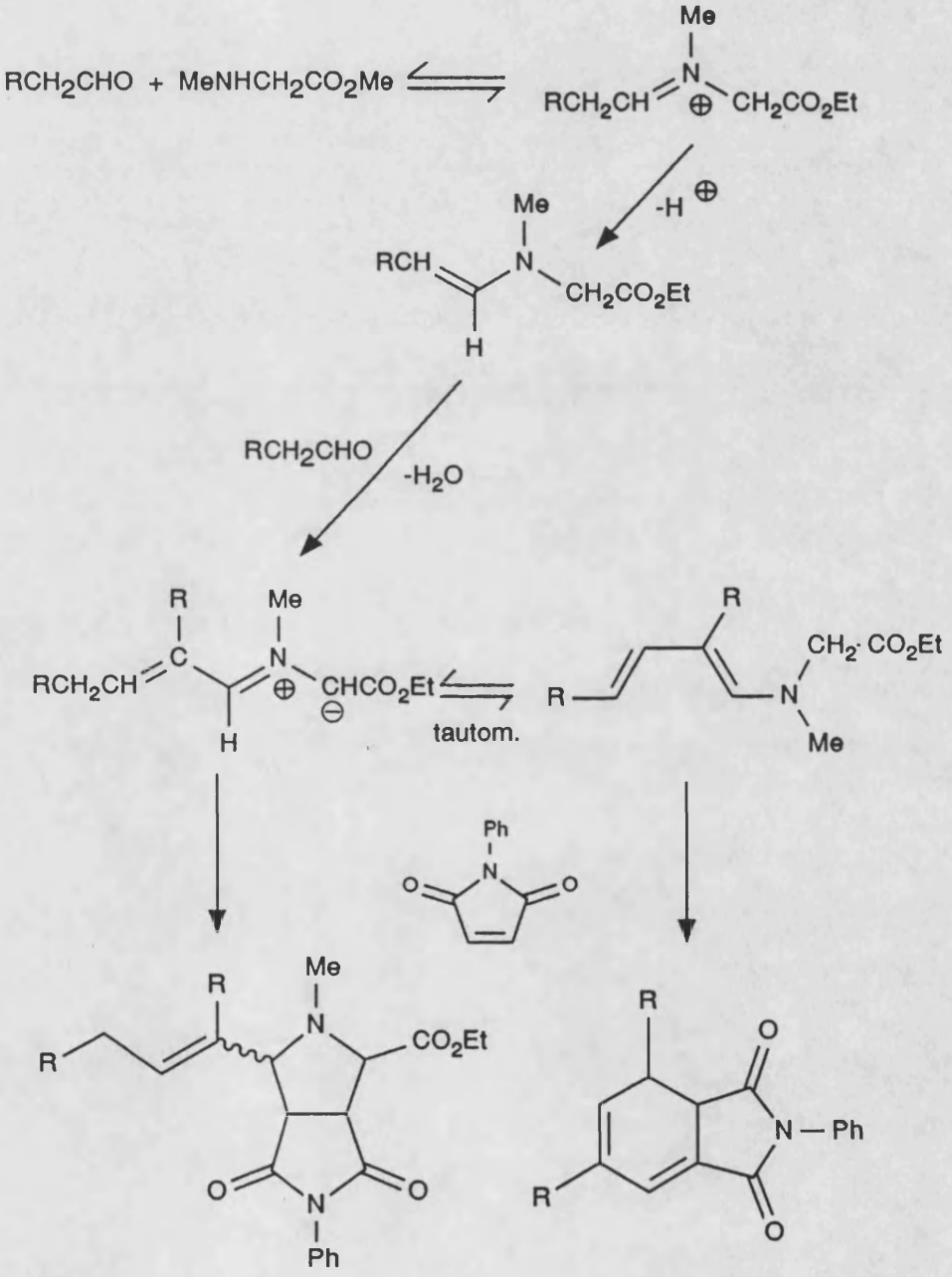
In 1983 Confalone et al[6a] applied this method to the generation of ylides capable of undergoing a subsequent intramolecular cyclisation (Scheme 38). They also demonstrated the intramolecular reaction of the O-(allyloxy)-benzaldehyde with N-substituted α-amino esters.

Scheme 38



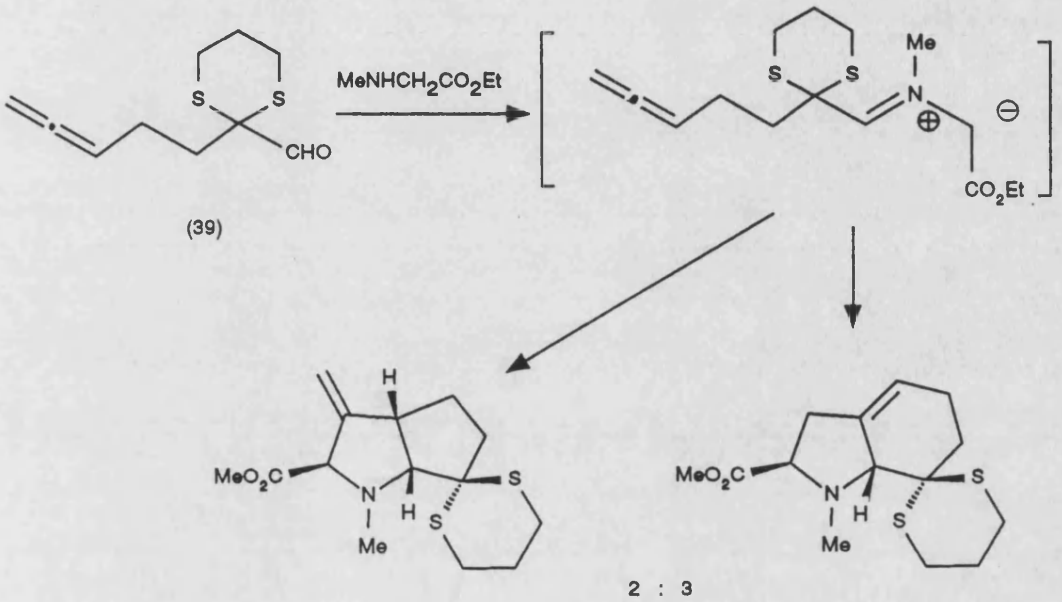
There are, however, problems associated with this chemistry when applied to aliphatic aldehydes[14], which either involve tautomerisation or further condensation reactions and result in the generation of new ylides or dienes. These pathways are exemplified in Scheme 11 and Scheme 39.

Scheme 39

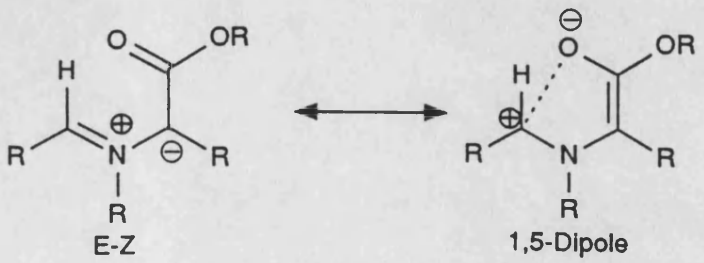


This problem has been neatly circumvented by Confalone[33] through the use of the 1,3-dithiane moiety; a good illustration of this method is shown in Scheme 40 and involves the use of an allenyl residue as the dipolarophile.

Scheme 40

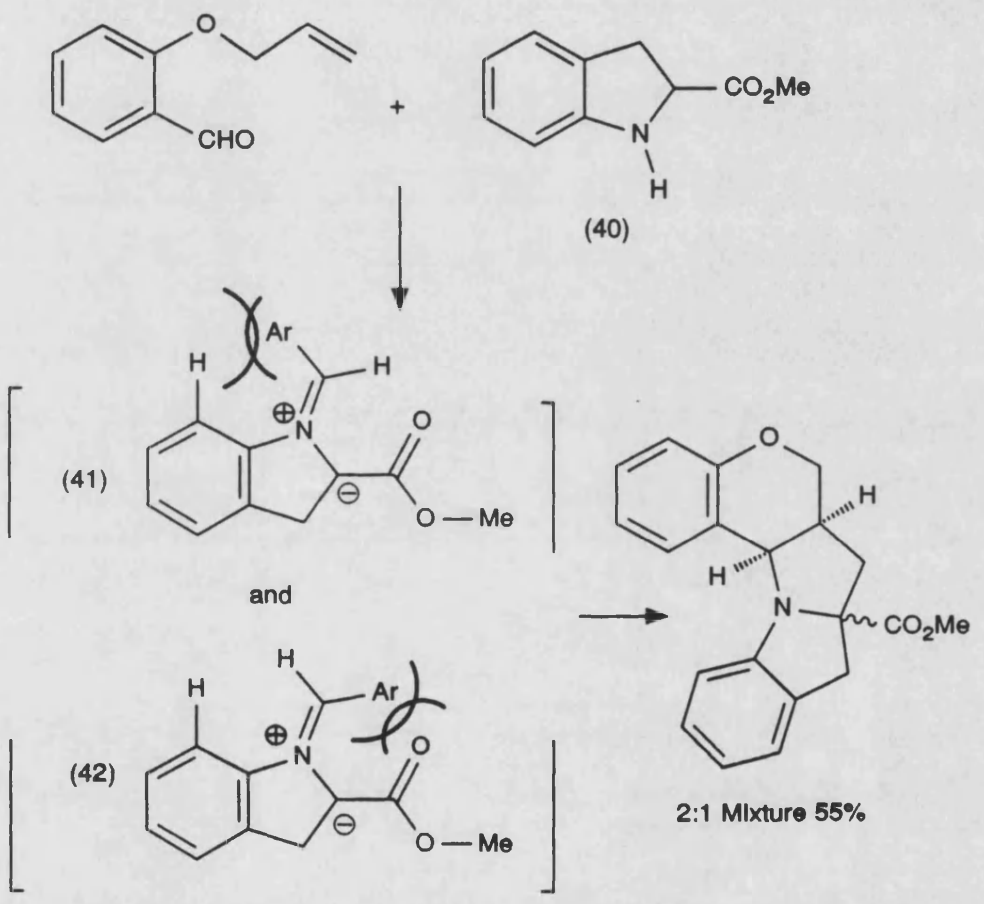


The stereochemical properties of an azomethine ylide generated in this way are also of interest in terms of their future synthetic utility. The stereochemistry of N-substituted azomethine ylides stabilised by the ester moiety is very different from the N-unsubstituted stabilised ylides. In the latter case, hydrogen bonding dictates the dipole stereochemistry, whereas with N-substituted ester-stabilised ylides the (E-Z) anti-ylide is normally trapped, due to a stabilising 1,5-dipole interaction:



The intramolecular cycloaddition reaction of the imines of cyclic secondary α-amino esters (40) has recently been investigated[6b] (Scheme 41).

Scheme 41

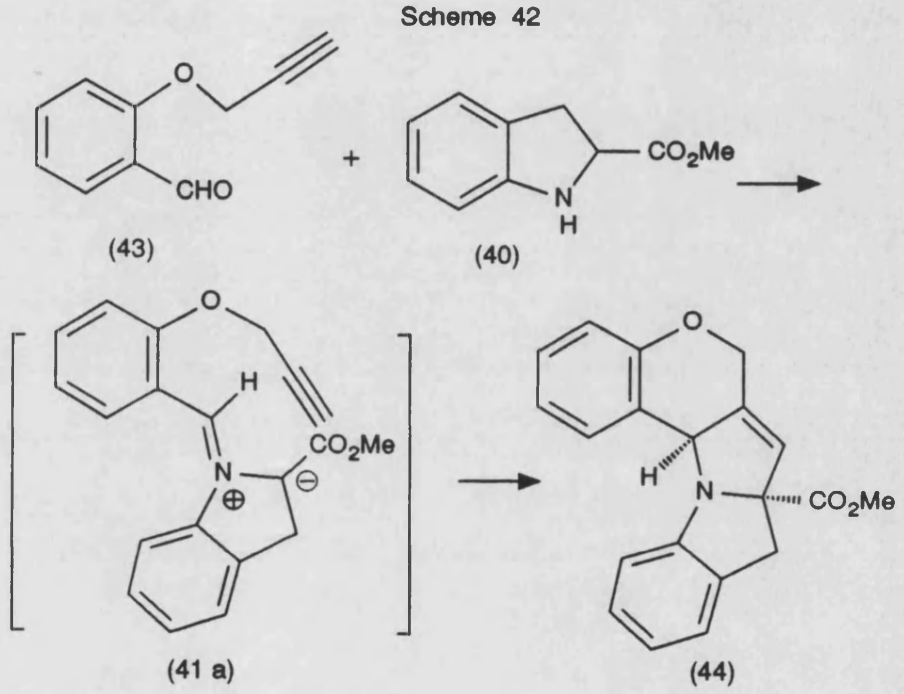


An investigation of this reaction by the intermolecular cycloaddition of NPM indicated that dipole formation was non-stereospecific, because neither of the intermediate dipoles (41) nor (42) were favoured, due to the adverse steric interactions. A similar result was observed for the intramolecular cycloaddition reaction, which showed little selectivity.

The reaction between (43) and the cyclic amino ester (40) gave only one product (44) (Scheme 42). Because neither of the two possible intermediate dipoles (41) nor (42) were favoured in the intermolecular cycloaddition reaction

with NPM, two products were expected from the intramolecular reaction involving (43), but the alkyne reacted solely with the ylide type (42), which was attributed to a more favourable alignment of the alkyne (see 41 a).

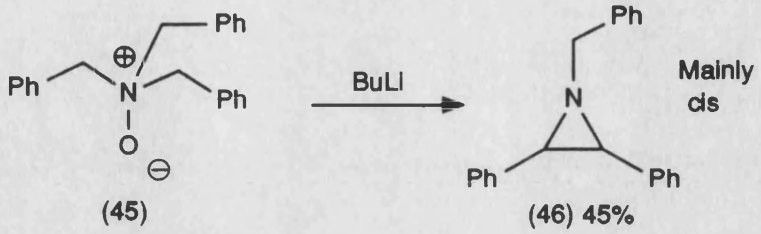
Scheme 42



Generation of Azomethine Ylides by Elimination Process Involving N-oxides of Tertiary Amines

The generation of extremely reactive, unstabilised azomethine ylides from N-oxides using a strong base, was first observed by Takayama and Nomoto in 1982[34]. These authors were unable to trap the ylide by a cycloaddition reaction, but the aziridine (46) was isolated (Scheme 43).

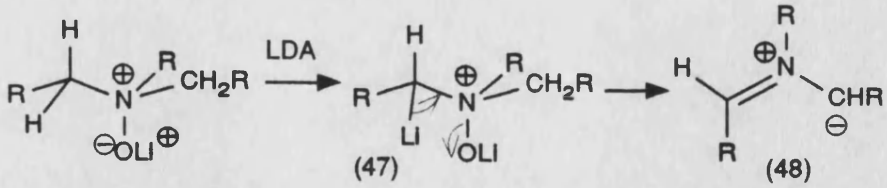
Scheme 43



(45) (46) 45%

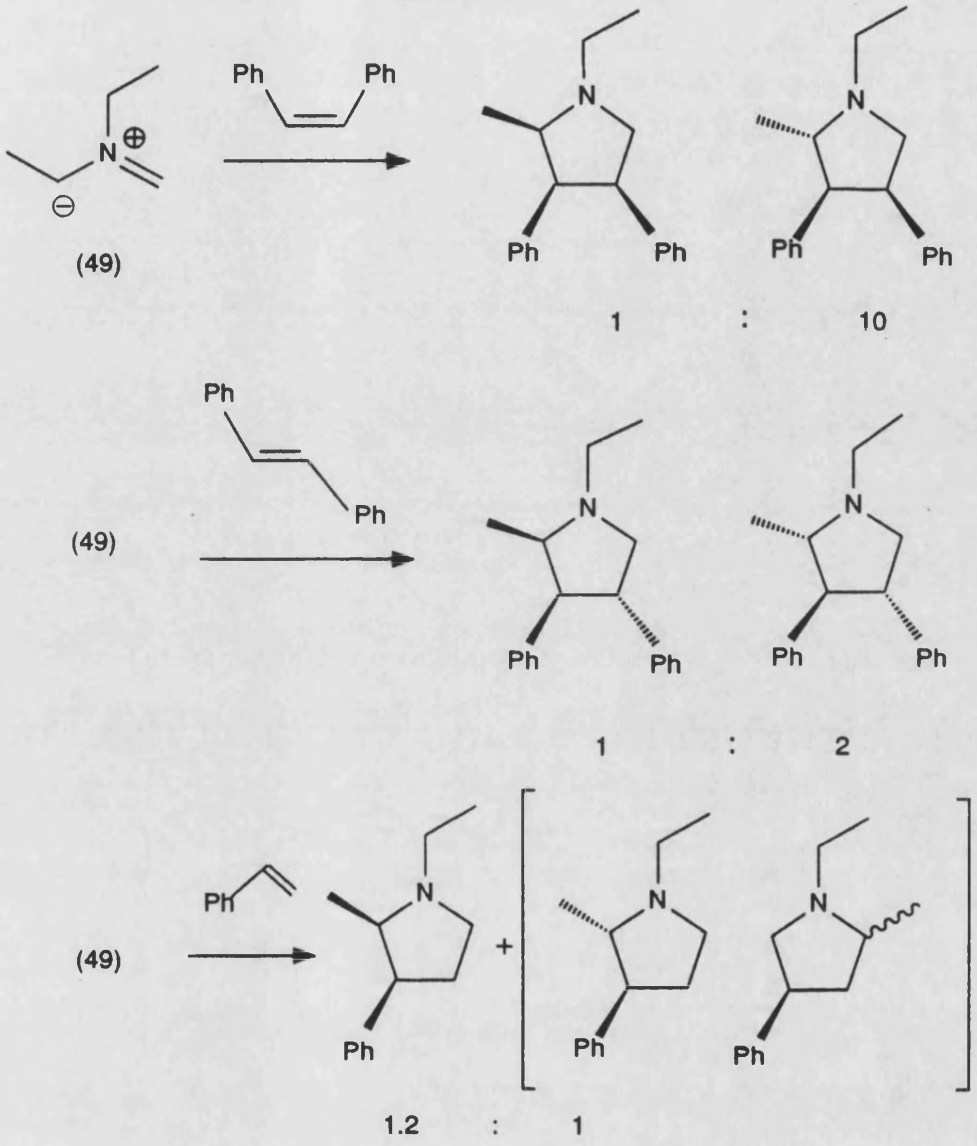
Recently Roussi et al[35] extended the use of this methodology and trapped the ylides with a large number of dipolarophiles.

The proposed mechanism for the generation of this dipole involves two equivalents of base. O-Lithiation of the N-oxide is followed by α-deprotonation, and subsequent elimination of Li_2O to generate the 1,3-dipole (48).



The high reactivity of these unstabilised azomethine ylides was demonstrated by trapping the 1,3-dipole with unactivated olefins such as hex-1-ene, cyclopentene and cyclohexene. Roussi also demonstrated that the ylide (49) undergoes stereospecific cycloaddition to (E)/(Z)-stilbene and although the ylide was readily trapped by styrene, this process did not show a high degree of stereo- or regioselectivity (Scheme 44). The remarkable reactivity of dipoles formed by the N-oxide route is quite unique, and is not fully understood.

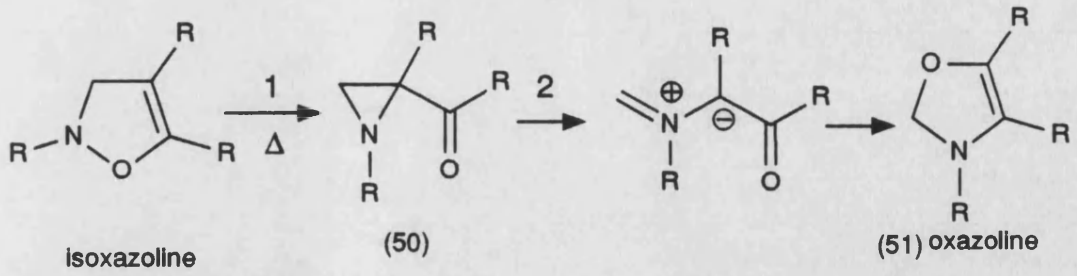
Scheme 44



Thermal Cleavage of Isoxazolines

The thermal N-O bond cleavage in 4-isoxazolines was first demonstrated by Baldwin[36] to proceed via acyl aziridines (50) to give 4-oxazolines (51) (Scheme 45).

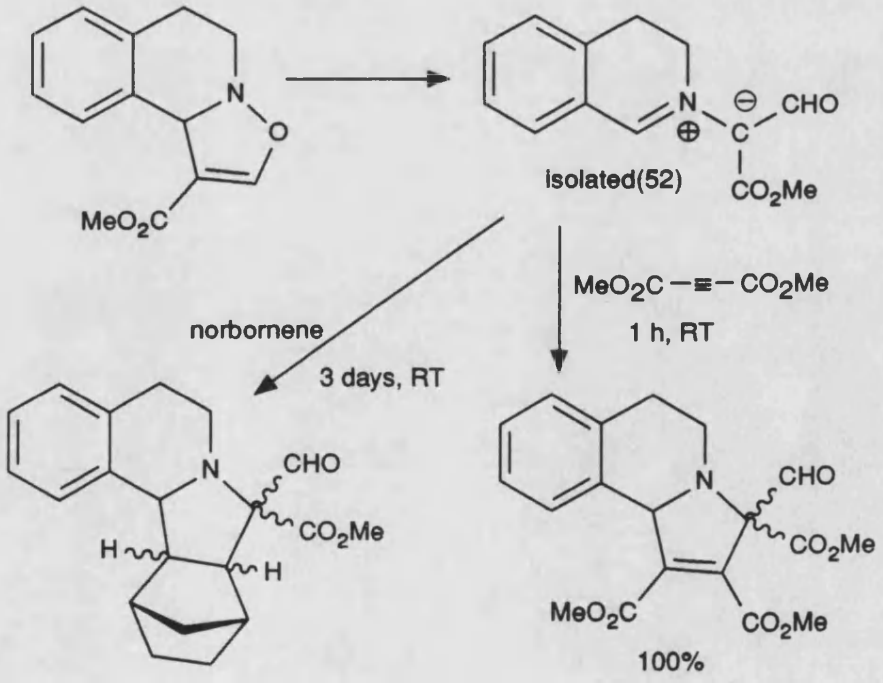
Scheme 45



Baldwin recognised step (2) as being related to the well-established thermal ring opening of aziridines to give azomethine ylides and given the ready availability of isoxazolines from nitrones and activated alkynes, this is a relatively flexible synthetic route to azomethine ylides.

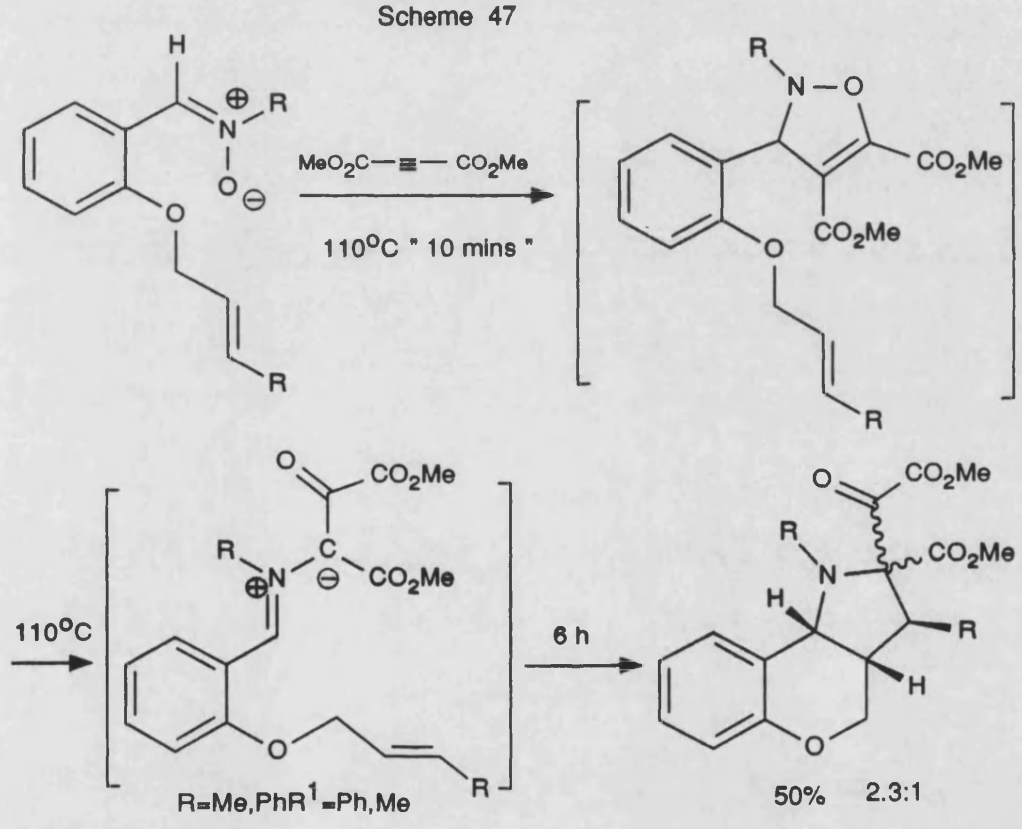
Huisgen[37] isolated the highly stabilised azomethine ylide (52) generated from a 4-isoxazoline and this dipole which was trapped in high yield using either DMAD or the unactivated dipolarophile, norbornene. This was the first isolable azomethine ylide that did not incorporate an aromatic nucleus (Scheme 46).

Scheme 46



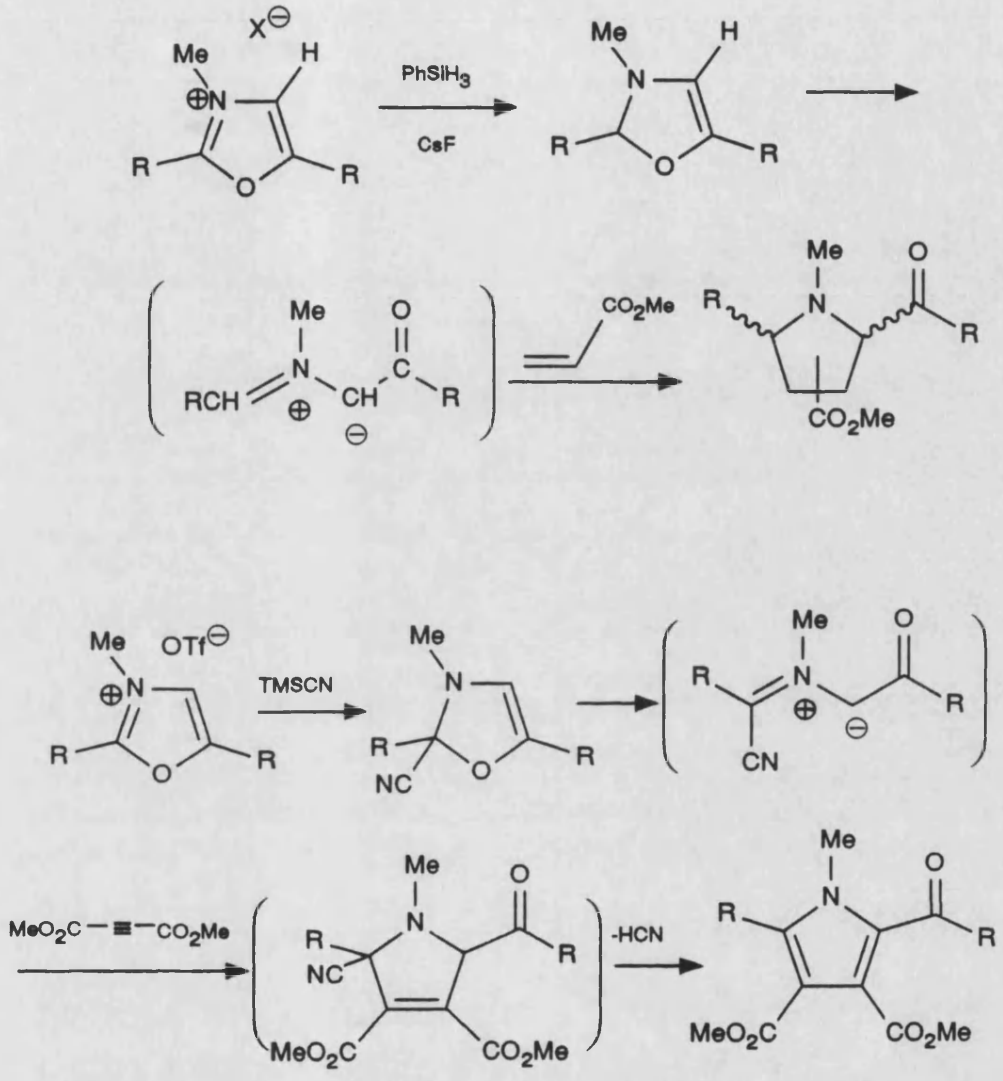
The intramolecular cycloaddition of an unactivated dipolarophile has also been demonstrated[6c]. An initial intermolecular 1,3-dipolar cycloaddition of a nitrone moiety to DMAD formed the 4-isoxazoline, which upon heating generated the azomethine ylide, and subsequently underwent an intramolecular 1,3-dipolar cycloadditon with an unactivated dipolarophile. This one-pot double 1,3-dipolar cycloaddition reaction is a good example of the synthetic utility of 1,3-dipoles (Scheme 47).

Scheme 47



Although azomethine ylides can be generated via isoxazolines, this method is limited due to the relative inaccessibility of the required precursors. However many of these problems have been overcome by the procedure developed by Vedejs[38] (Scheme 48) which is a useful synthetic route to substituted pyrroles.

Scheme 48



As shown above, this route has been extended[39] to include $CN^{\ominus}$, in addition to $H^{\ominus}$ as the nucleophile component.

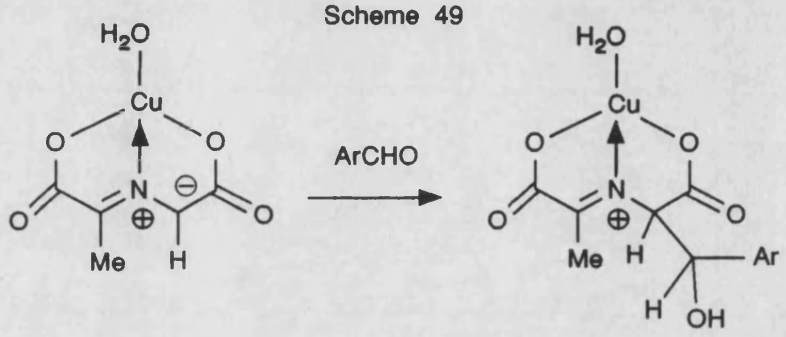
Oxazolines have already been mentioned as the intermediates in the decarboxylation route to azomethine ylides and are believed to be responsible for the excellent stereospecificity of this decarboxylation route (Scheme 23).

N-Metallation of Imines

This methodology involves the complexation of a metal, to an imine nitrogen atom. On complexation of the metal, the acidity of the α-protons of the imine is

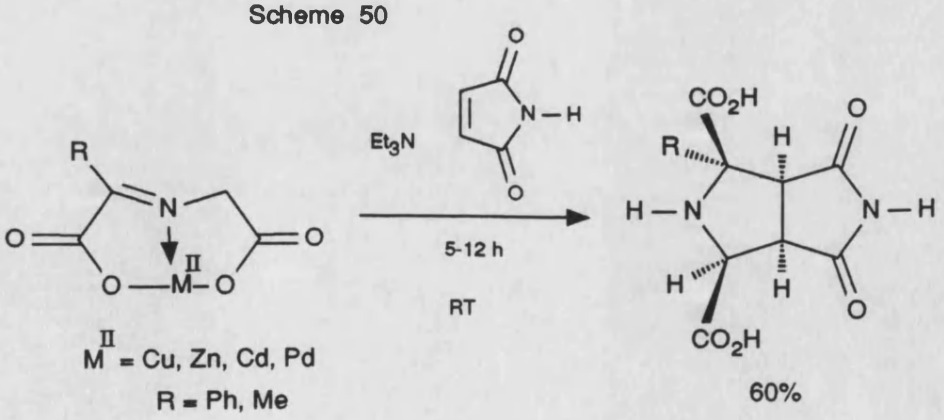
increased, enabling even a weak base to effect deprotonation to generate an azomethine ylide. The first ylides formed by this method were reacted with aldehydes[40] (Scheme 49). Later, Casella et al[41] used more activated dipolarophiles as traps, though poor selectivity was observed, which was presumably due to isomerisation of the cycloadduct during the demetallation step.

Scheme 49



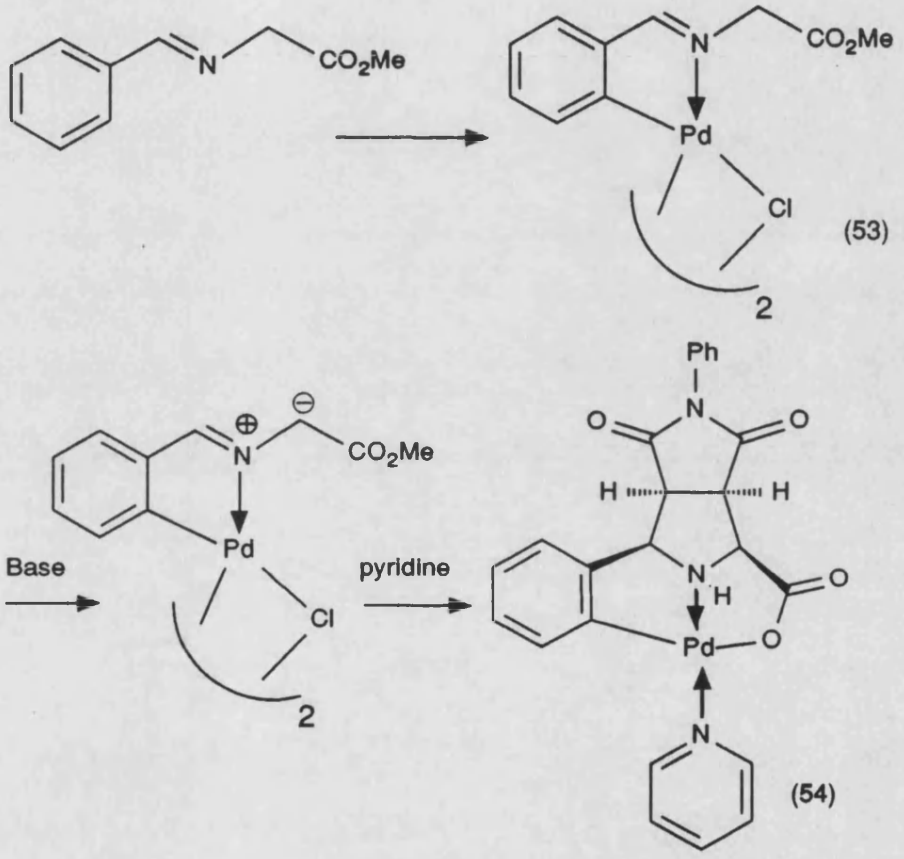
Stereoselective reactions via N-metallation have been demonstrated by Grigg[42] (Scheme 50) who demonstrated that short reaction times and the use of ion-exchange resin for the work-up suppressed stereoisomerisation of the cycloadducts.

Scheme 50



Ortho-palladation has been used to generate ylides from suitable aromatic imines[43] (Scheme 51).

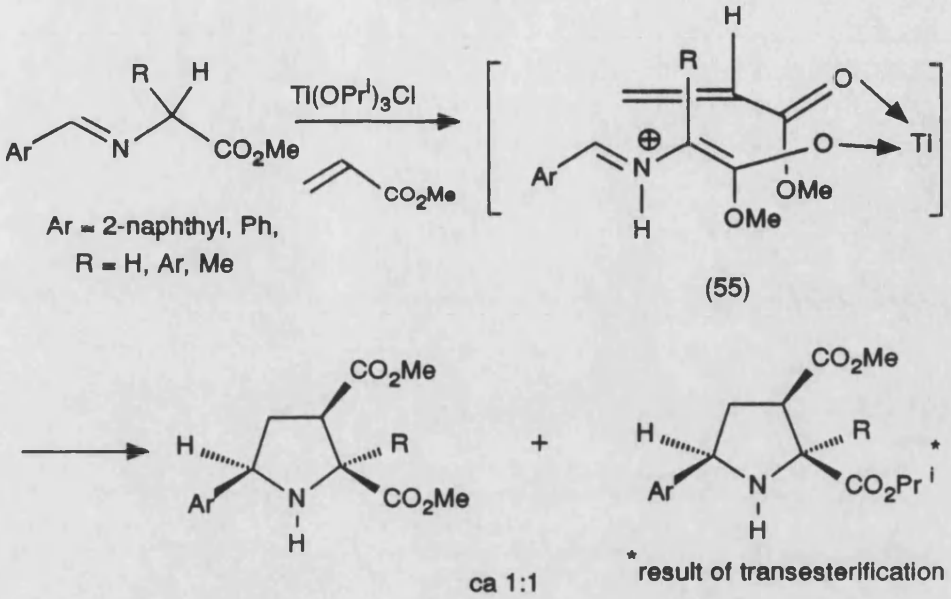
Scheme 51



Palladated dimers, such as (53), could be isolated and when deprotonations were conducted in the presence of NPM, the cycloadducts were also obtained as dimers, however the use of pyridine as solvent allowed access to the "monomeric" cycloadduct (54).

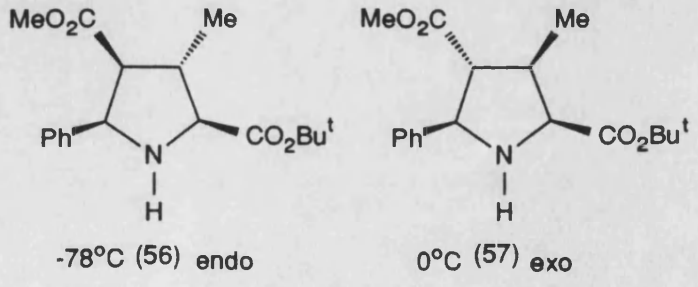
Some other recent advances in the N-metallation route to azomethine ylides have been made. Grigg[44] has studied the Ti(IV) complexes of imines, which could be deprotonated with triethylamine and subsequently trapped with methyl acrylate (Scheme 52).

Scheme 52



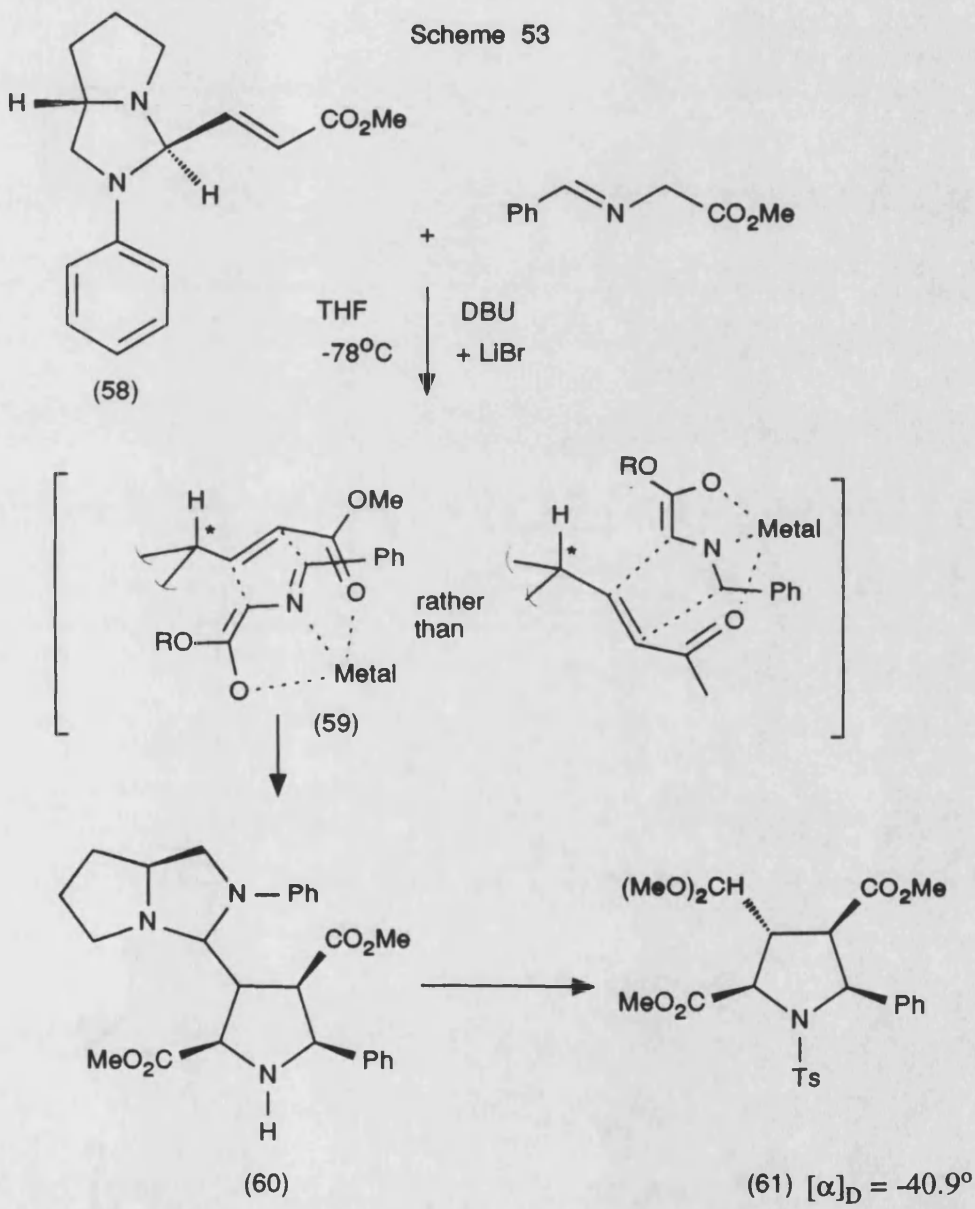
Of particular interest is the regiochemistry of the adducts obtained by this process which is opposite to that usually observed with uncomplexed dipoles. The formation of a tight complex (55) between dipole and dipolarophile was invoked to explain this reversal of the normal regiochemistry, but unfortunately attempts to use a chiral titanium complex to promote the asymmetric cycloaddition reaction failed.

Subsequently other unusual examples of stereo- and regioselectivity have been observed by Kanemasa et al[45] with titanium complexes. A change in temperature has a dramatic effect on the stereoselectivity of the reaction. At -78°C endo-adducts (56) were the sole products, whereas at 0°C only exo products (57) were obtained. Similar observations were made when methyl acrylate and methyl methacrylate were employed as dipolarophiles.



In a later communication, the same group[46] reported a very efficient asymmetric cycloaddition reaction, based on the use of a chiral dipolarophile (58) and an N-metallated azomethine ylide (Scheme 53).

Scheme 53

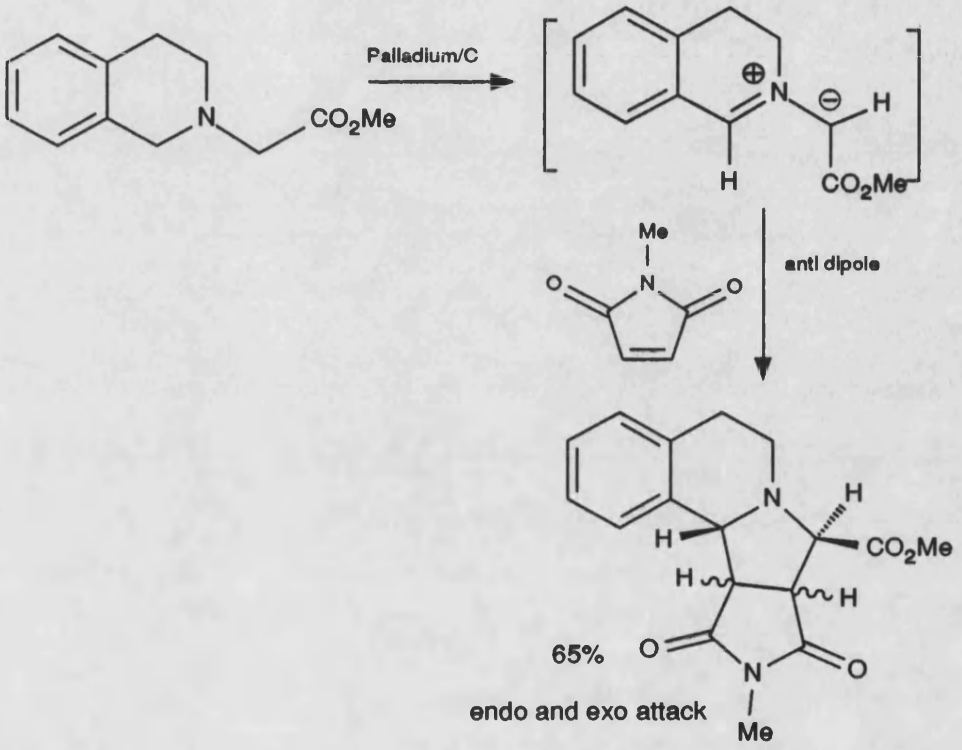


The single diastereomer (60) was obtained via selective diastereofacial attack via (59) and the removal of the chiral auxiliary was efficiently accomplished to give (61) in 85% yield and in enantiomerically pure form.

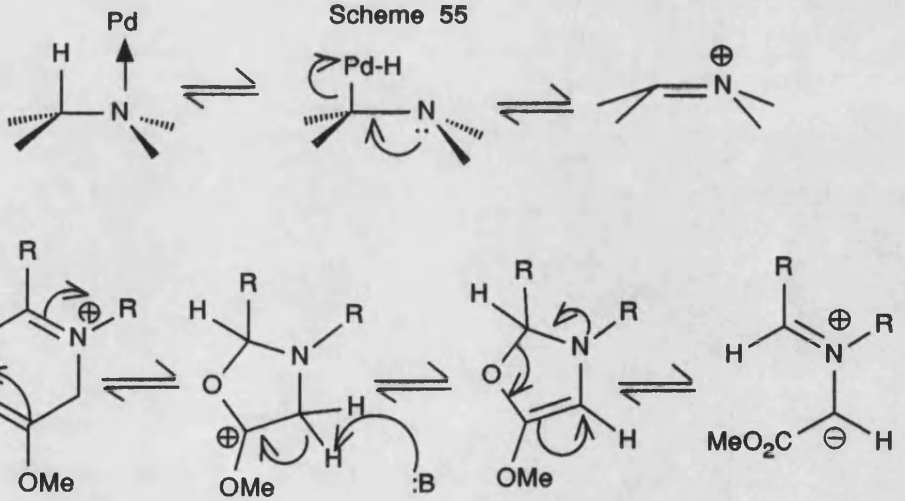
Miscellaneous routes

a) The dehydrogenation of N,N-disubstituted α-amino esters using palladium black provides access to azomethine ylides[47] (Scheme 54) and the mechanism suggested by Grigg to account for this process is shown in Scheme 55.

Scheme 54

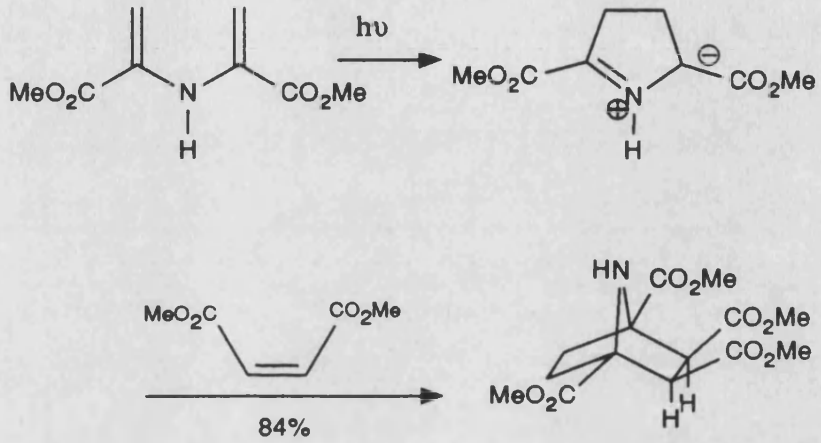


Scheme 55



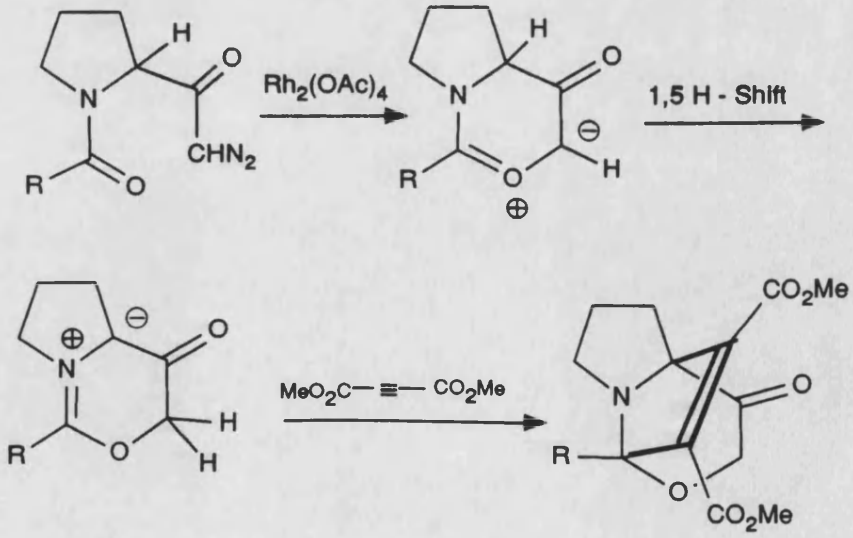
b) Cyclic azomethine ylides have been generated by the photochemical cyclisation of divinylamines[48] (Scheme 56). The stereospecificity of this reaction has been demonstrated with maleates and fumarates as dipolarophiles.

Scheme 56



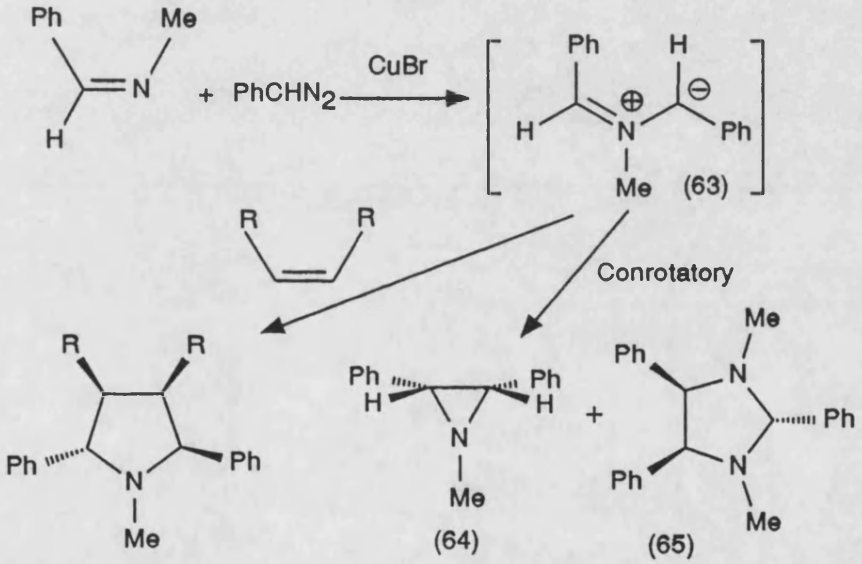
c) Padwa et al[49] recently described a novel $Rh_2(OAc)_4$-induced process for the generation of azomethine ylides via metallo-carbenes (Scheme 57).

Scheme 57



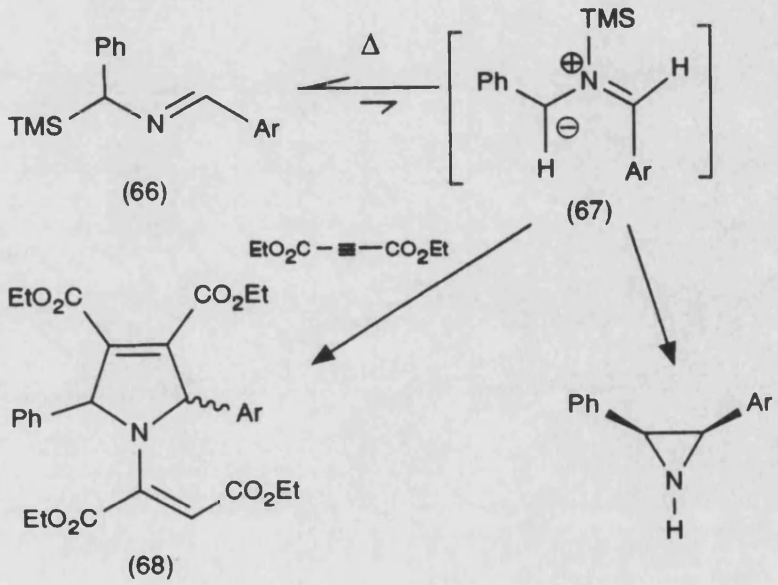
The insertion of a metallo-carbene into an imine nitrogen lone pair has been demonstrated[50] to give an azomethine ylide (63), which undergoes a cycloaddition reaction with suitable dipolarophiles (Scheme 58). In the absence of such dipolarophiles, conrotatory cyclisation and dimerisation occurs to give a mixture of (64) and (65).

Scheme 58



d) The thermal rearrangement of aryl-substituted N-(silylmethyl) imines (66) to give the anti-azomethine ylide (67) has been demonstrated[51] (Scheme 59). Once again, the ylide may be trapped by dipolarophiles or, in the absence of such a trap, cyclisation to give the cis-aziridine is observed.

Scheme 59

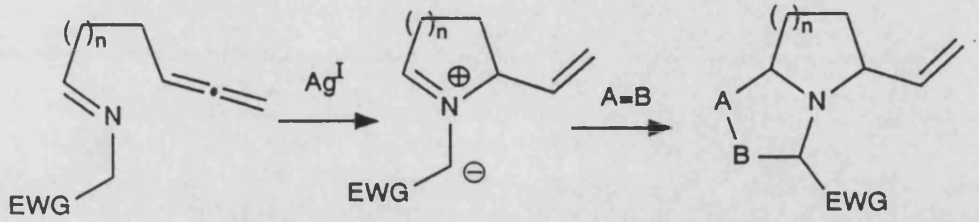


(66) (67) (68)

New Approaches to the Generation of Azomethine Ylides

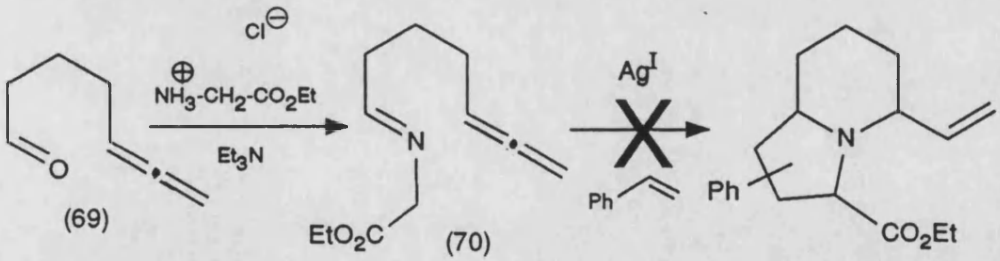
Our objective in this phase of the programme was to generate azomethine ylides via heterocyclisation (Scheme 60) based on Ag(I)-catalysed cyclisation of a nitrogen nucleophile to an allene-based π-system using methodology similar to that previously described for the generation of nitrones[52].

Scheme 60



The preparation of the requisite aliphatic allenic imine (70) was accomplished in a straightforward fashion, however, this intermediate was unstable and decomposed on storage. Treatment of freshly prepared (70) with Ag(I) in the presence of styrene, produced a complex mixture of products, none of which could be characterised (Scheme 61).

Scheme 61

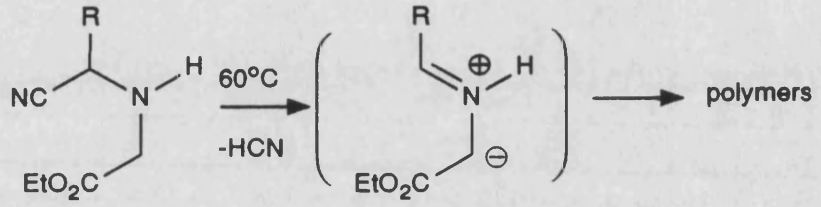


We were not, however, so surprised at this result, since other workers had previously commented on the relative instability of aliphatic imines.

Cyanoamines as a Source of Azomethine Ylides

In an effort to overcome the limitations associated with aliphatic imines as precursors for azomethine ylides, we turned our attention to cyanoamines. This was prompted by the observation that N-cyanoalkyl glycine esters (71) cannot

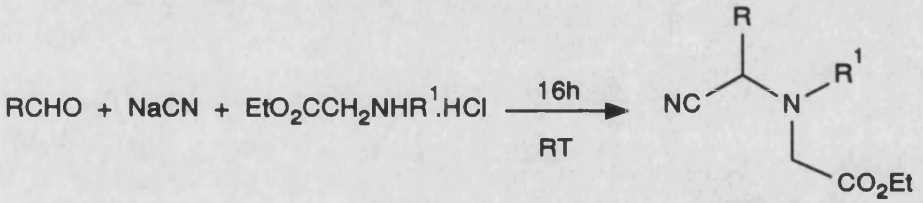
be distilled, due to decomposition accompanied by the evolution of HCN[53]. We postulated that a possible intermediate for such a decomposition pathway might be the 1,3-dipole (72). Therefore the cyanoamine might provide a stable, masked equivalent of an azomethine ylide.



(71) (72) possible intermediate

We initially conducted model studies on a range of cyanoglycine and sarcosine esters, prepared using the Strecker reaction[53] (Scheme 62).

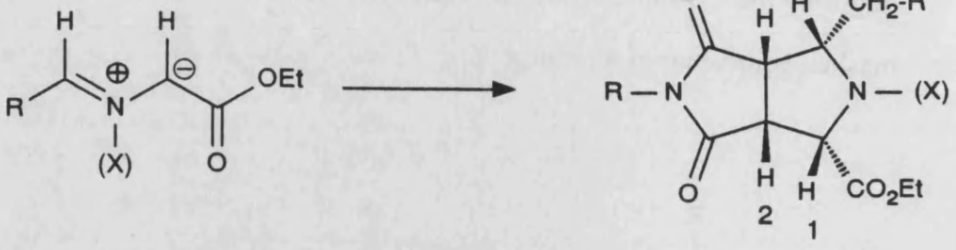
Scheme 62



(73 - 77)

Table 1

Aldehyde	Aminoester		
R	R^1	Product	Yield %
$^nC_6H_{13}$	H	(73)	80
$^nC_6H_{13}$	Me	(74)	35
$^tC_4H_9$	Me	(75)	50
CH≡C-$(CH_2)_4$	H	(76)	50
CH≡C-$(CH_2)_4$	Me	(77)	70

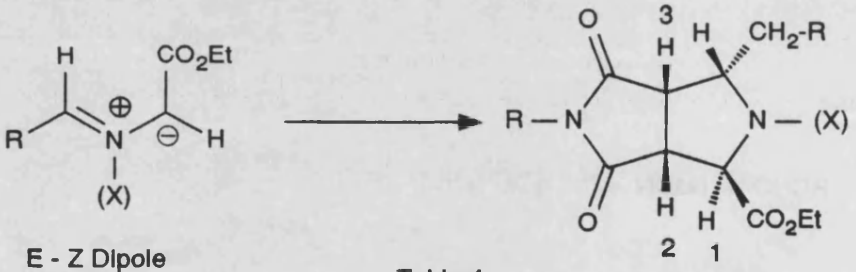


E- E Dipole

Endo adduct

Table 3

R	X	1	2	3
(81b) $CH{\equiv}C(CH_2)_3$	Me	3.9 d, J8Hz	3.5 t, J8Hz	3.0 dd, J8Hz
(80b) $CH{\equiv}C(CH_2)_3$	D	4.1 d, J8Hz	3.5 t, J8Hz	3.05 dd, J8Hz
(79b) $C_5H_{11}{}^n$	Me	3.8 d, J9Hz	3.5 t, J9Hz	3.00 dd, J9Hz
(78b) $C_5H_{11}{}^n$	D	4.1 d, J8Hz	3.5 t, J8Hz	obscured



E - Z Dipole

Endo adduct

Table 4

R	X	1	2	3
(81a) $CH{\equiv}C(CH_2)_3$	Me	4.0 s	3.2 d, J7.5Hz	3.3 t, J7.5Hz
(79a) $C_5H_{11}{}^n$	Me	3.95 s	3.2 d, J8Hz	3.3 t, J8Hz

The cyanoamines were heated in toluene in the presence of a dipolarophile, (NEM) which efficiently trapped the azomethine ylides as cycloadducts (a) or (b). The initial set of reactions were carried out at 110°C for 4 days, (Table 2 entries 1 and 2), but a more efficient method was developed which involved heating the mixture at 180°C in a sealed tube for only 1-2 days.

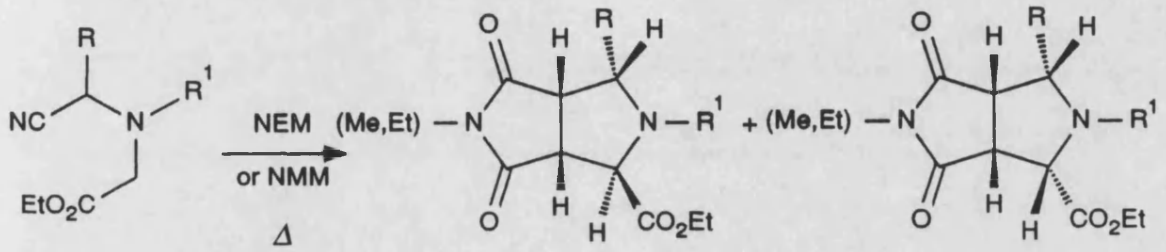


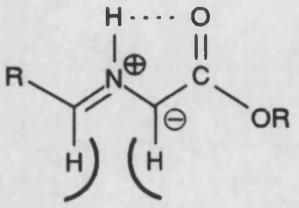
Table 2

R	R^1	Temp/°C	Time Days	Product	Ratio	Yield %
$^nC_6H_{13}$	H	110	4	(78 a:b:c)	1:3:1	25
$^nC_6H_{13}$	Me	110	4	(79 a:b)	2.1:1	68
$^nC_6H_{13}$	Me	180	2	(79 a:b)	2.2:1	70
$^tC_4H_9$	Me	180	7	-	-	0
CH≡C- $(CH_2)_4$	H	180	1	(80 b)	0:1	56
CH≡C- $(CH_2)_4$	Me	180	2	(81 a:b)	1:1	76

The stereochemistry of the cycloadducts was assigned on the basis of the ^1H NMR spectra, and the spectroscopic data are summarised in Tables 3 and 4.

Previous workers have established that the rate of reaction of N-substituted maleimides with azomethine ylides is faster than the rotation of the dipole, so stereomutation is not generally observed. Based on this report, and the stereochemical outcome of our model studies, we can draw some conclusions about the stereoselectivity of this route for the generation of azomethine ylides.

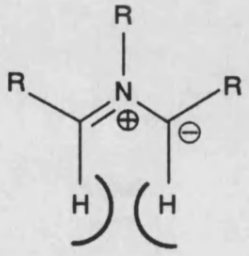
For N-unsubstituted ylides (generated at 180°C) only one product (80 b) was isolated in 56% yield after a reaction time of 24 h, which suggests that the (E-E) dipole (82) is formed stereoselectivly. This has been previously explained in terms of strong hydrogen bonding stabilising the stereoisomer with minimal steric interactions.



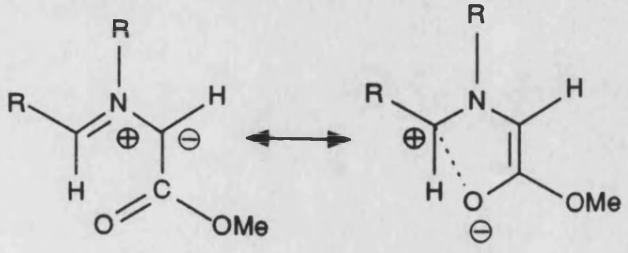
(82)
E-E

minimal
steric
interactions

The generation of N-substituted azomethine ylides via this methodology is not stereospecific, but only two of the possible dipoles are generated (see Introduction, Scheme 4). Unlike the N-unsubstituted ylides, no intramolecular hydrogen bonding can occur, therefore other factors must be important. The minimal steric interaction of the (E-E) dipole (82) would account for its preferred formation and the (E-Z) dipole (83) is stabilised by a 1,5-dipole interaction. The other two possible isomeric dipoles (Z-Z) and (Z-E) suffer from destabilising steric interactions.



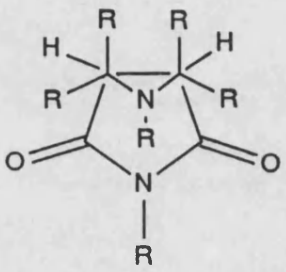
(82) (E - E)



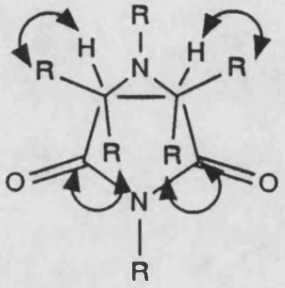
(83) (E - Z)

1,5-dipole
interaction

All cycloadducts were formed by endo cycloaddition, which is a result consistent with the work of other groups and has been explained in terms of a combination of secondary orbital interactions and steric interactions.

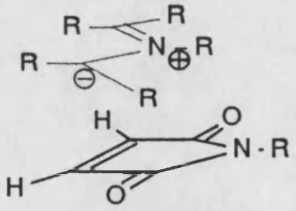


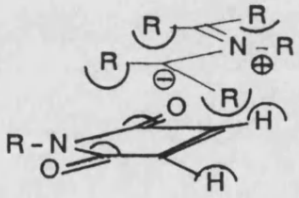
Endo



Exo

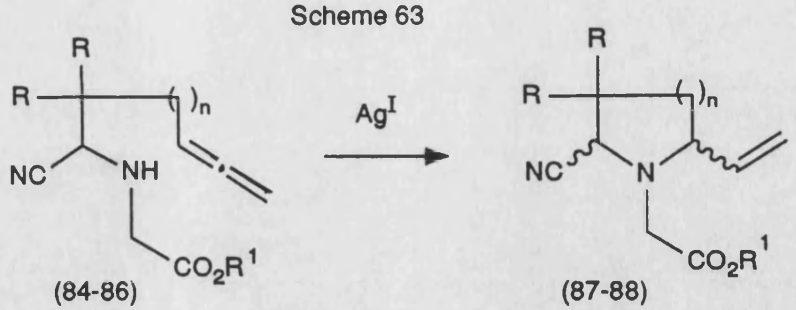
near eclipsed repulsions





Having conducted model studies, we next turned our attention to the Ag(I)-mediated cyclisation of allenic cyano amines (84-86, Table 5)(Scheme 63). These reactions were best conducted at -30°C, and although (84) and (85) underwent smooth cyclisation, attempts to apply this methodology to the six-ring series based on (86) failed. This was not too surprising due to the unfavourable entropy associated with larger ring formation and the decreased nucleophilicity of the nitrogen centre as a consequence of the nearby cyano and ester moieties [see later results with cyanohydrins (Scheme 99)].

Scheme 63

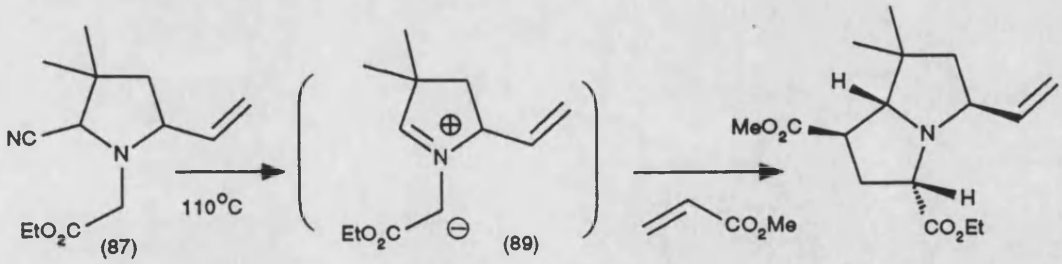


(84-86) (87-88)

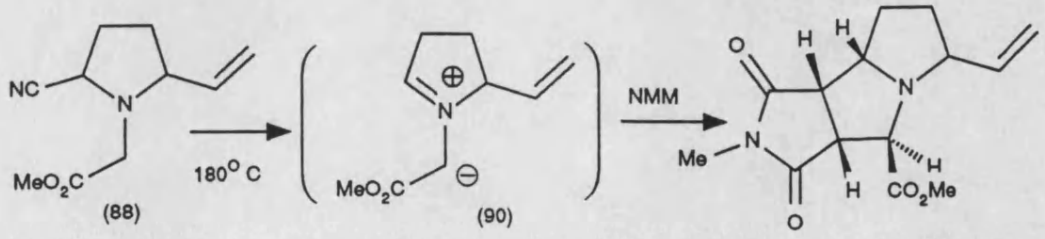
Table 5

	R	R^1	n		n	Yield %
(84)	Me	Et	1	(87)	1	40
(85)	H	Me	1	(88)	1	25
(86)	H	Me	2	-	2	0

Cyclisation of (84) was, however, rapid which is presumably a reflection of the accelerating influence of the gem-dialkyl effect. In the case of cyanoamine (85), a number of other products were also observed which could not be identified, but resulted from competing side reactions. Thermolysis of (87) and (88) in the presence of either methyl acrylate or N-methylmaleimide, led to the elimination of hydrogen cyanide and the resulting dipoles (89) or (90) respectively were trapped to give (91) 10% and (92) 60%.



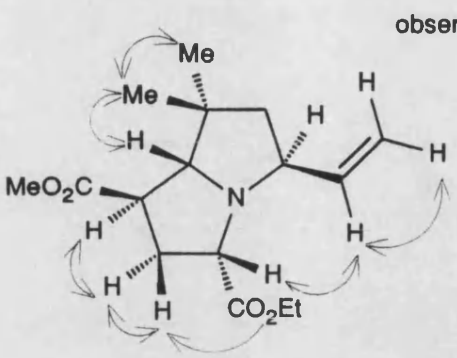
(91) 10%



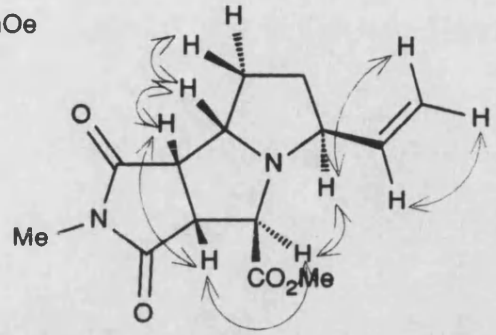
(92) 60%

The stereochemistry of the cyclic adducts (91) and (92) was assigned by nOe experiments.

observed nOe



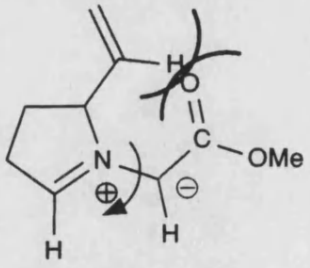
(91)



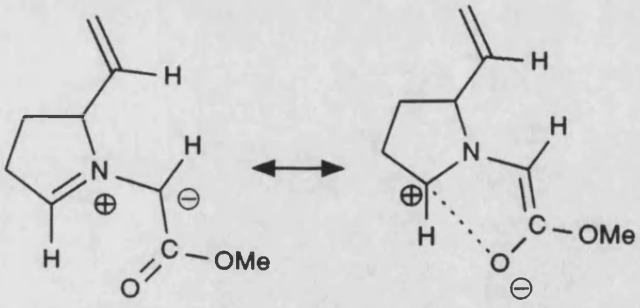
(92)

The product (92) results from the stereoselective formation of the (E-Z) anti-dipole (93) followed by face-selective addition of the dipolarophile in an endo sense. From our previous work on N-substituted acyclic dipoles formed by this methodology, we have established that the reaction is normally non-stereospecific, with the formation of the the two (E-E) and (E-Z) dipoles. An investigation of this N-substituted cyclic dipoles reveals that the (E-Z) (93) isomer has relatively few steric interactions compared with the (E-E) dipole, and with the additional 1,5-dipole-stabilising interaction, is likely to be preferred (Scheme 64).

Scheme 64



(E-E) dipole



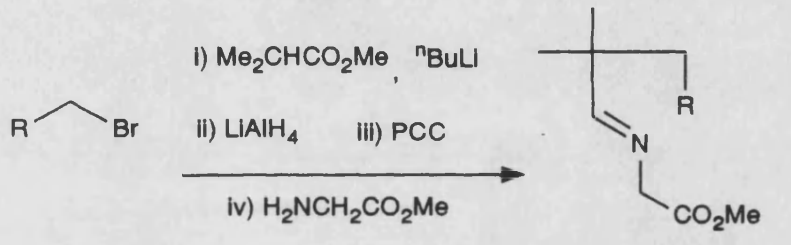
(93) (E-Z) dipole

Due to the low yield of (91), very little can be claimed for this reaction regarding regio- and stereocontrol. The sole product was derived from exo-attack of the (E-E) dipole, however, stereomutation cannot be ruled out due to the relative unreactivity of the dipolarophile.

Intermolecular Cycloaddition Reactions of Unsaturated Aliphatic Imines

It is apparent from previous workers that aliphatic imines are rather unstable[14], and the thermal generation of azomethine ylides from such imines causes tautomerisation to enamines[14], and then polymerisation. To prevent such destruction the use of the gem-dimethyl[17d] or the 1,3-dithiane[14] moiety has been employed to replace enolizable hydrogens and we have prepared a range of gem-dimethyl imines (94 a,b,c) (Scheme 65).

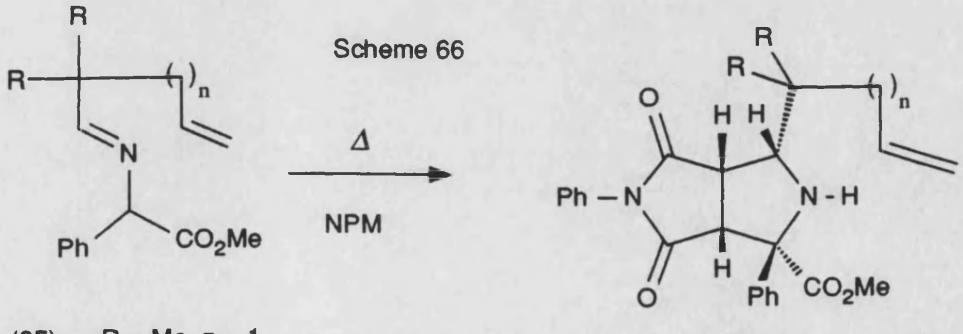
Scheme 65



(94 a) R = CH_2 - CH=CH_2
(94 b) R = CH=C=CH_2
(94 c) R = CH_2 - C ≡ CH

Grigg[17d] has recently shown that the alkenyl derivatives (95 a,b,c) undergo tautomerisation to give the corresponding dipoles which were trapped by N-phenylmaleimide (130°C, xylene), but unfortunately the intramolecular reaction of (95 a) failed (Scheme 66).

Scheme 66

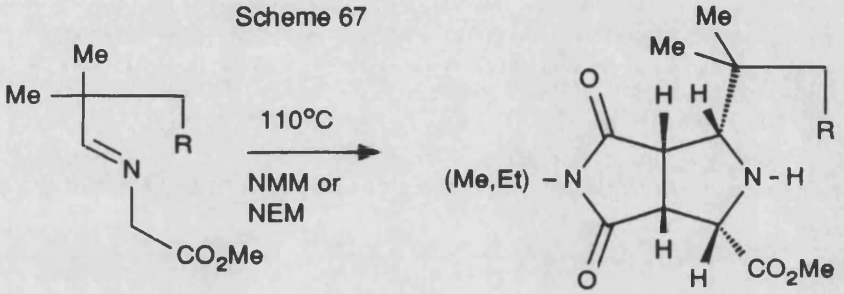


(95) a R = Me n = 1
b R = H n = 2
c R = H n = 3

a 95%
b 79% Single isomer
c 88%

We have studied the thermal generation of the azomethine ylides from imines (94a,b,c) at 110°C for 5-15 h, in the presence of an activated dipolarophile (N-methylmaleimide) and obtained the cycloaddition products (96 a,b,c) as single isomers (Scheme 67). Our results, which are in agreement with Grigg's observations, that this tautomerisation route to azomethine ylides is stereoselective.

Scheme 67



(94 a) R = CH_2 - CH= CH_2

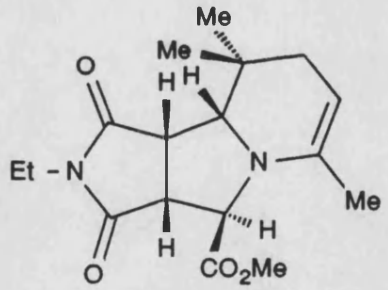
(94 b) R = CH= C= CH_2

(94 c) R = CH_2 - C ≡ CH

(96 a) R = CH_2 - CH= CH_2 82%

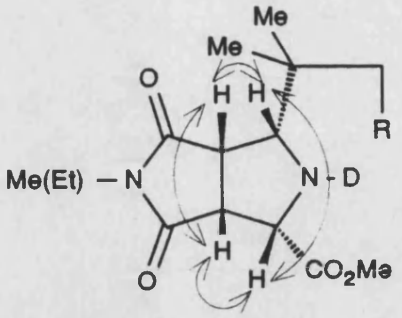
(96 b) R = CH= C= CH_2 60%

(96 c) R = CH_2 - C ≡ CH 12% + (d)



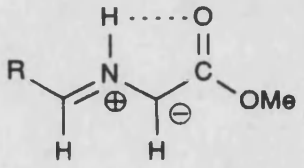
(96 d) 54%

The stereochemistry of all the products (96 a,b,c and d) was assigned by nOe experiments. Cycloadducts (96 a,b,c) arise from the (E-E) dipole (82).



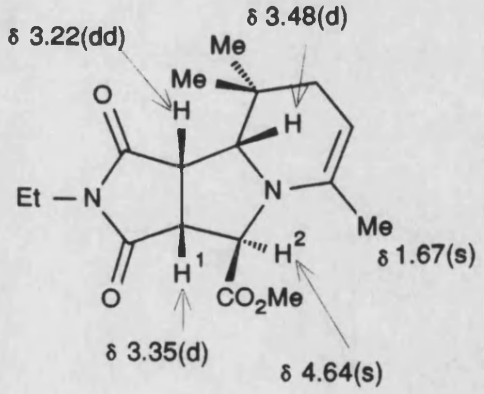
R = CH=C=CH$_2$
Observed n.O.e

(96 a,b,c)



(82) (E-E) dipole

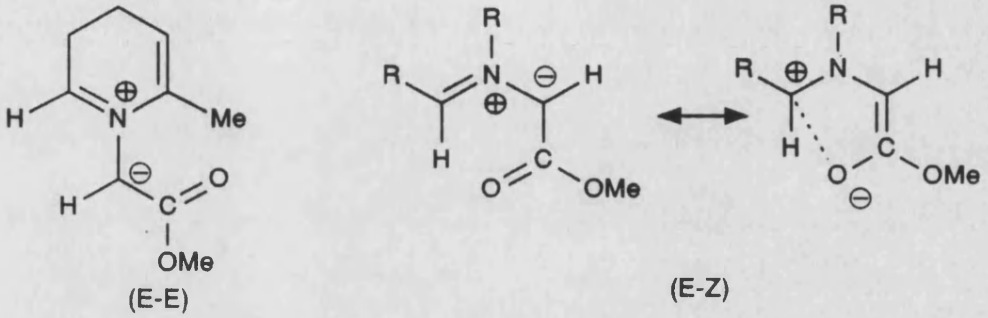
In the case of the alkynyl derivative (94 c), the major product obtained on thermolysis in the presence of NMM was (96 d), which was isolated in 60% yield. Clearly, this product has arisen by a second cyclisation step involving the alkynyl moiety and the structural assignment of (96 d) was based on a combination of COSY and nOe analysis.



(96 d)

From molecular modelling, the predicted dihedral angle between H^1 and H^2 was 115.7°, which would give a vicinal coupling constant J=1.7 Hz (-observed value J=0Hz). The stereochemistry is not that expected from the N-unsubstituted dipole (E-E) with an ester-stabilising moiety, but is the product derived form the

(Ė-Z) dipole, which is normally favoured for N-substituted ester-stabilised dipoles. From the stereochemistry of the product it could be inferred that either the amine-alkyne interaction must prevent the N-H from hydrogen bonding, or that the cyclisation takes place prior to dipole formation.



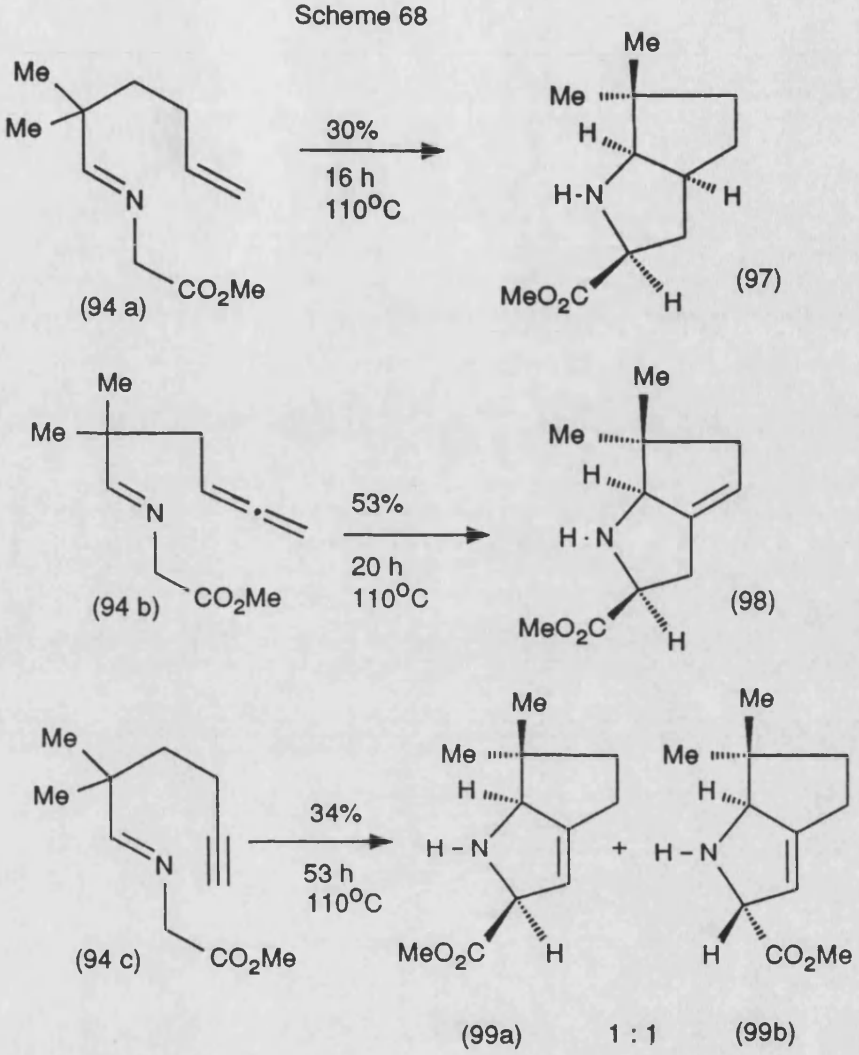
(E-E) (E-Z)

Attempts to achieve cyclisations of the allenic or alkyne cycloadducts (96 a,c) using Ag(I) were unsuccessful. When the thermal generation of the 1,3-dipole was conducted in the presence of a less activated dipolarophile (methyl acrylate), the intermolecular product (96 a) was not obtained, but a small amount of the intramolecular cycloaddition product (97) was observed (Scheme 68). This observation prompted us to look more closely at the intramolecular cycloadditions of these compounds.

Intramolecular Cycloaddition of Unsaturated Aliphatic Imines

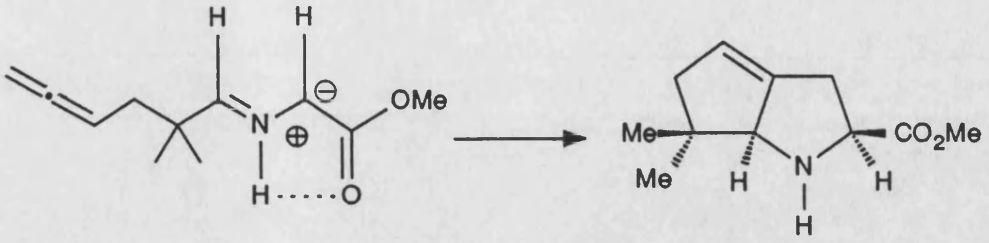
The intramolecular reaction of unactivated dipolarophiles with azomethine ylides has previously failed,[5] with a few noticeable exceptions[17] . Encouraged by the intramolecular reaction of (94 a) we turned our attention to the allene and alkyne moieties (94 b) and (94 c). Our investigation of the intramolecular cycloaddition reaction of unsaturated aliphatic imines is outlined in Scheme 68.

Scheme 68



Due to the unreactivity of the dipolarophiles used in the intramolecular reactions, both the kinetically and/or the thermodynamically-favoured dipoles could be trapped as a result of competing dipole stereomutation.

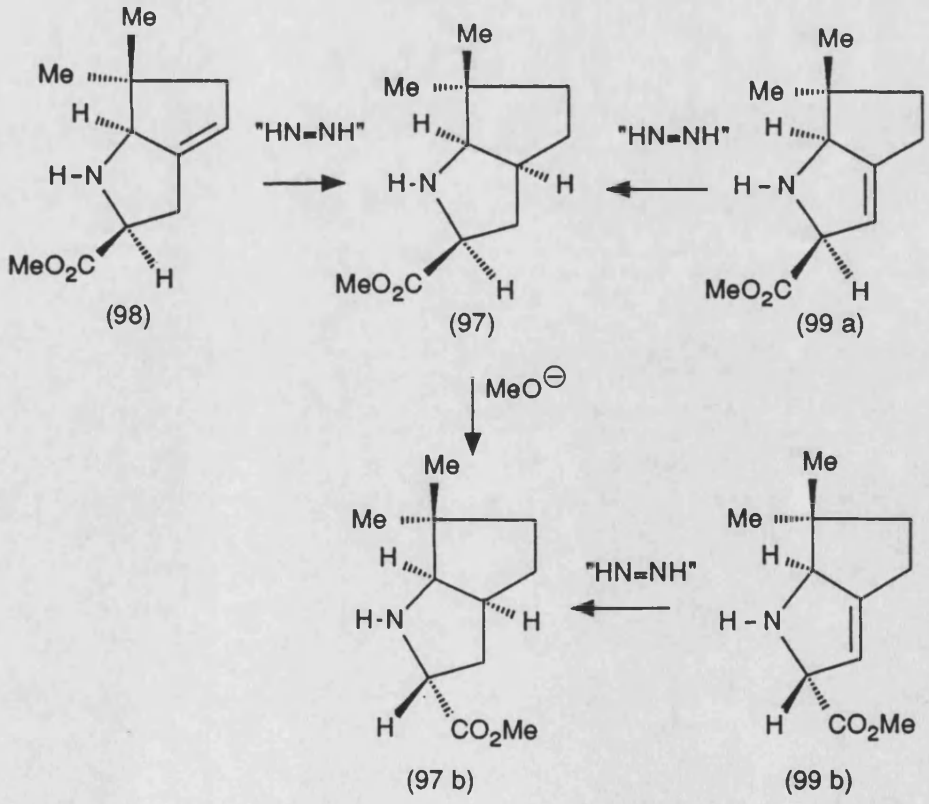
The two cycloadducts (97) and (98) produced from the alkene and allene precursors (94 a) and (94 b) were obtained from the dipole (E-E) exclusively, which is the expected kinetic dipole formed from N-unsubstituted azomethine ylide, as a result of intramolecular hydrogen-bonding.



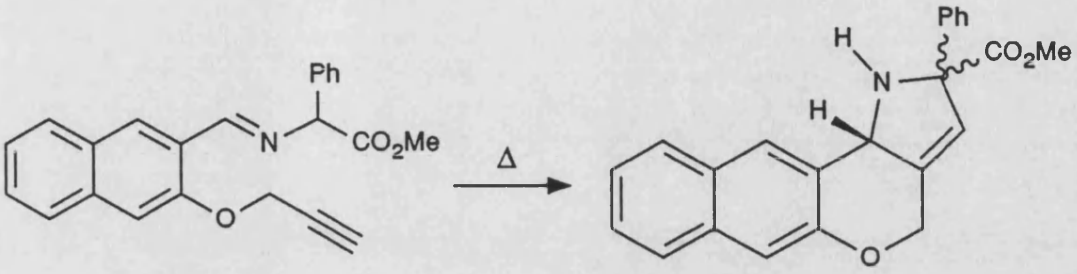
(E-E) H-bond (98)

By contrast, the longer reaction time involved for the alkyne (94 c) gave a 1:1 mixture of products (99 a) and (99 b) derived from the kinetic and thermodynamic dipoles. The stereochemistry of the constrained amino esters (98) and (99 a,b) was assigned on the basis of two straightforward chemical transformations. Reduction with di-imide and base-induced epimerisation of (97) by sodium methoxide gave (97 b), which involved the conversion of the kinetic product (97) to the thermodynamically more stable product (Scheme 69).

Scheme 69



Grigg[17d] has reported that alkynes undergo intramolecular reactions with azomethine ylides non-selectively, but there appear to be no examples of unactivated aliphatic alkyne intramolecular cycloadditions in the literature.

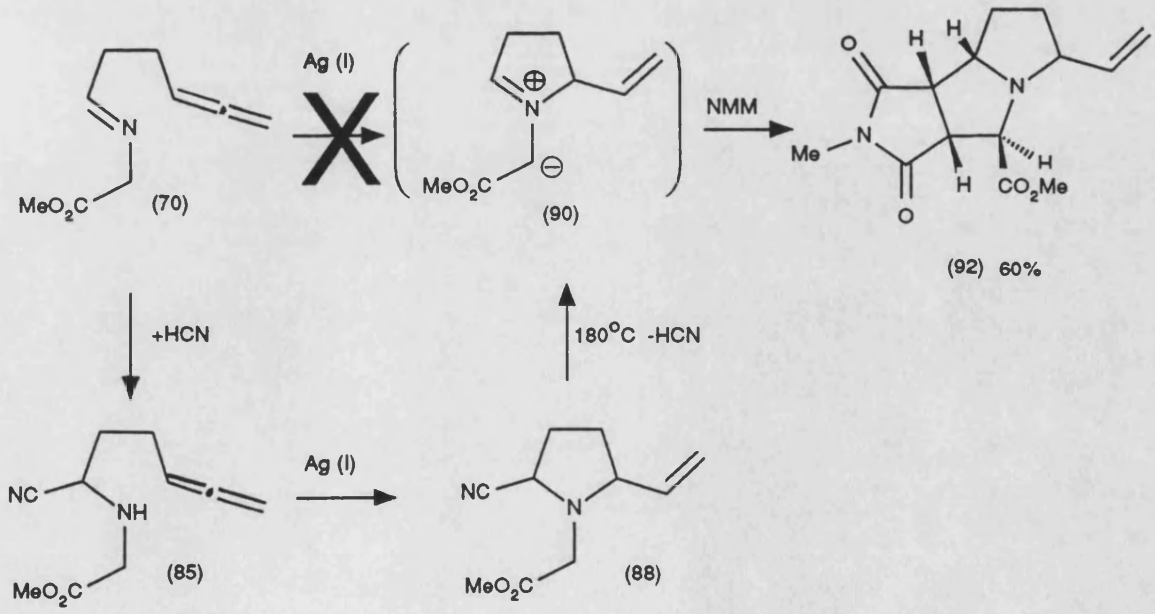


3:1 mixture

The allene moiety has only once been used as a trap for an azomethine ylide, as previously mentioned[6a].

Conclusion

We were unsuccessful in our attempts to generate azomethine ylides via the Ag(I)-mediated cyclisation of allenic imine (70). However, this problem was overcome by use of the corresponding HCN adducts and we were successful in generating and trapping the azomethine ylide (90).



This novel method, involving the elimination of HCN for the generation of azomethine ylides, is complementary to the tautomerisation route developed by Grigg[10] and offers stereoselective (E-E) dipole formation from N-unsubstituted cyanoamines. In previous work, involving the tautomerisation of imines, β-hydrogens cannot normally be tolerated because of competitive enamine formation, but our route does not suffer from any such drawbacks. When acyclic N-substituted cyanoamines are used, this reaction pathway proceeds via the non-stereoselective generation of the ylide generating both the (E-E) and (E-Z) dipoles. When a cyclic N-substituted cyano amine was employed, the stereoselective formation of the (E-Z) dipole was established by trapping with N-methylmaleimide.

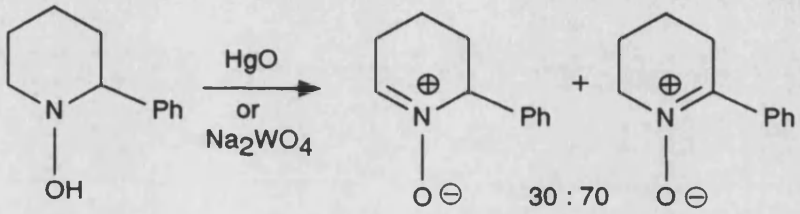
We were also able to use the tautomerisation method for the synthesis of a range of simple constrained amino esters via intramolecular cycloaddition of unactivated alkenes, allenes and alkynes as shown in Scheme 68.

New Approaches to the Generation of Cyclic Nitrones

Background

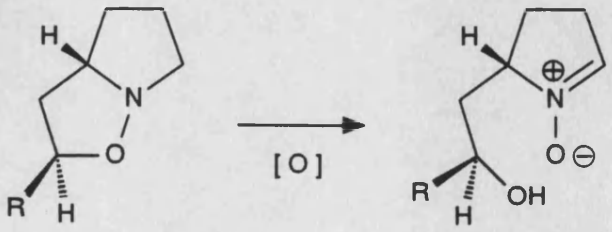
The use of nitrones in both intra- and intermolecular cycloadditions frequently embodies a high degree of both regio- and stereochemical control, making the chemistry of this 1,3-dipole an interesting and important area to study. A general preparation of nitrones involves the oxidation[54] of N,N-disubstituted hydroxylamines (Scheme 70), although this route does suffer from the disadvantage that there is little regiochemical control in the dipole-forming step.

Scheme 70

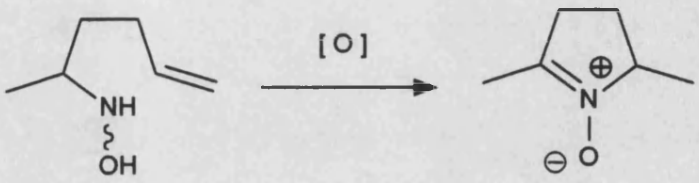


Regiospecific dipole formation was first achieved by Le Bel[55] using the stereospecific oxidation of isoxazolines and this chemistry was subsequently developed and applied to a range of synthetic problems by Tufariello[56](Scheme 71).

Scheme 71

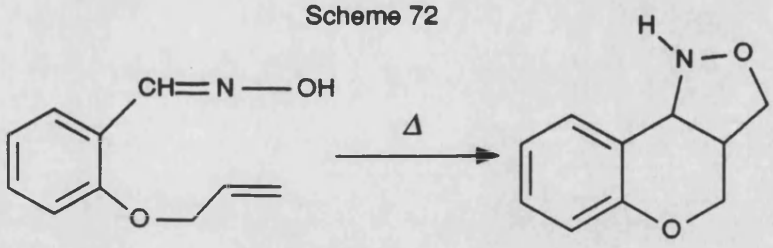


The oxidative cyclisation of δ-unsaturated hydroxylamines to generate stable nitrones has been successfully employed by House[57] and St.C.Black[58].



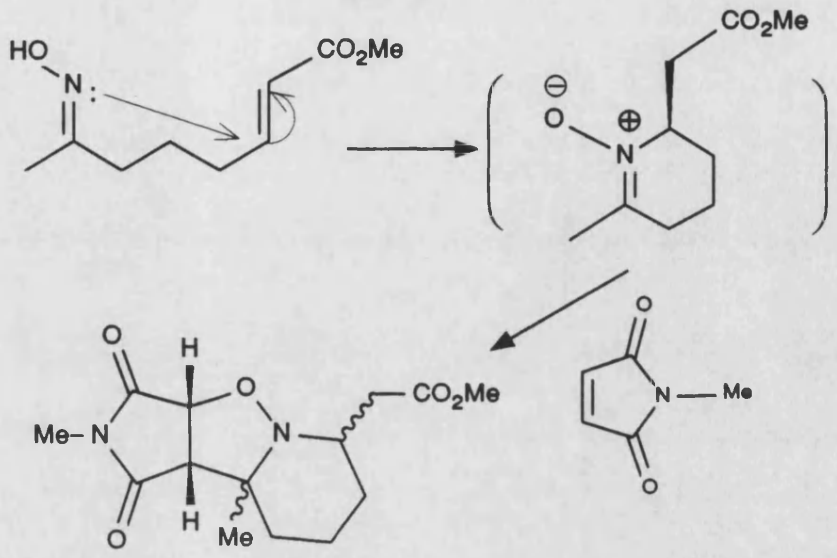
The condensation of N-monosubstituted hydroxylamines with carbonyl compounds is also an efficient route to nitrones. Oppolzer[59] has utilised a 1,2-prototropic shift to generate a nitrone intermediate from an oxime. This dipole was trapped in an intramolecular fashion by an unactivated dipolarophile, although the 1,4-addition reactions of the dipolarophile often predominates (Scheme 72).

Scheme 72



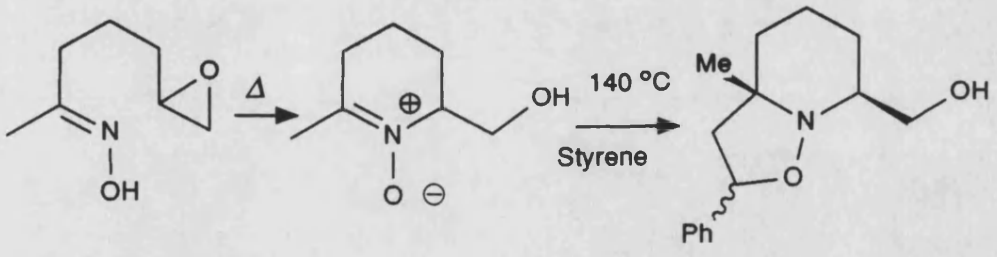
The addition of hydroxylamine to activated acetylenes affords nitrones which can be subsequently trapped. Padwa[60] demonstrated this approach in an intramolecular sense and this technique has been extended by Grigg and co-workers[61] using activated alkenes (Scheme 73).

Scheme 73



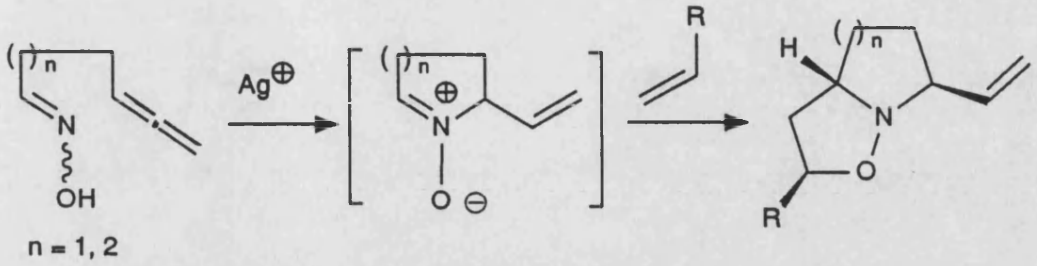
Grigg and his co-workers[62] also developed a route which involved the cyclisation of oximes, to generate nitrones via intramolecular attack on an epoxide (Scheme 74). These methods are related and complement the methodology developed by Gallagher et al[52] involving Ag(I)-mediated cyclisations (Scheme 75).

Scheme 74



We have previously found[52] that the Ag(I)-induced cyclisation of allenic oximes is a useful method for the regioselective formation of cyclic nitrones (Scheme 75). The alkenyl-substituted nitrone was trapped with a range of dipolarophiles to give predominantly attack of the 1,3-dipolarophile in an exo sense from the opposite face to the alkenyl residue.

Scheme 75

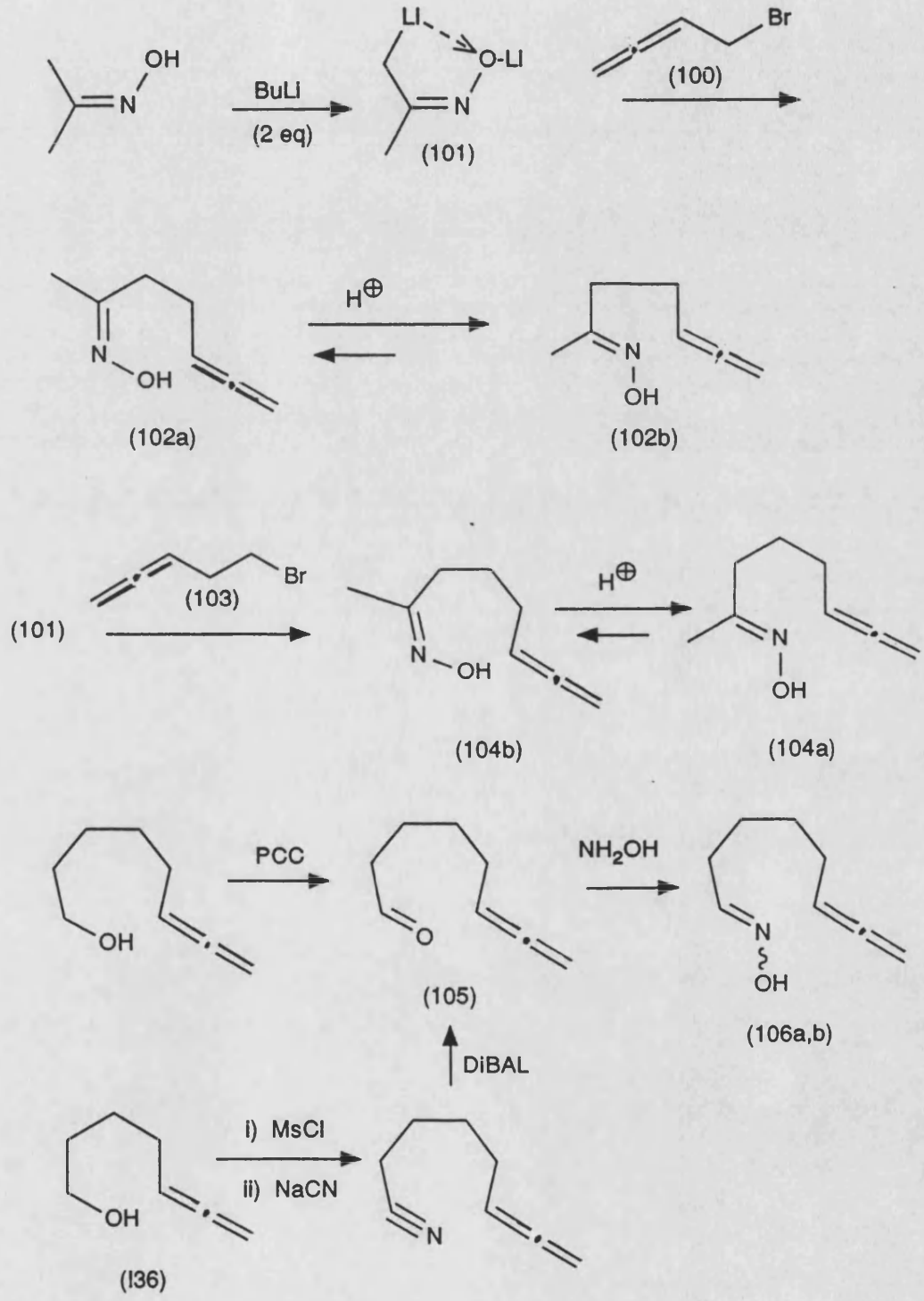


We hoped to be able to extend the Ag(I)-mediated cyclisation procedure to include allenic ketoximes and the formation of larger ring nitrones. An investigation into other π-systems which might be capable of undergoing this cyclisation was also studied, using alkynyl and alkenyl-substituted oximes.

Synthesis of Allenic Oximes

In an effort to probe the scope of the Ag(I)-induced allenic oxime cyclisation/nitrone formation, a range of allenic ketoximes and an ϵ-allenic aldoxime were prepared as shown in Scheme 76. The volatile 4-bromobuta-1,2-diene (100) was prepared via the literature procedure of Landor[63] in multigram amounts from buta-1,2-dien-4-ol. Alkylation of the dianion[64] (101) of acetone oxime with 4-bromobuta-1,2-diene (100) gave the allenic ketoxime (102 a,b). The (E)- and (Z)- octa-6,7-dien-2-one oximes (104 a,b) were prepared via a similar alkylation of the dianion of acetone oxime with 5-bromopenta-1,2-diene (103) and the (E)- and (Z)-octa-6,7-dienal oxime (106 a,b) were either prepared from the corresponding allenic alcohol by oxidation (PCC) followed by oxime formation or from the alcohol (136).

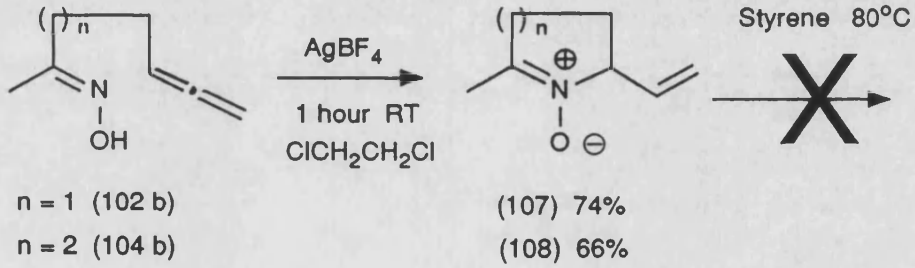
Scheme 76


OH
N
BuLi
(2 eq)
Li
O-Li
N
(101)
Br
(100)
H⊕
N
OH
(102a)
N
OH
(102b)
(101)
Br
(103)
N
OH
(104b)
H⊕
N
OH
(104a)
OH
PCC
O
(105)
NH2OH
N
OH
(106a,b)
DiBAL
OH
i) MsCl
ii) NaCN
N
(136)

Ag(I)-Mediated Cyclisation of Allenic Oximes

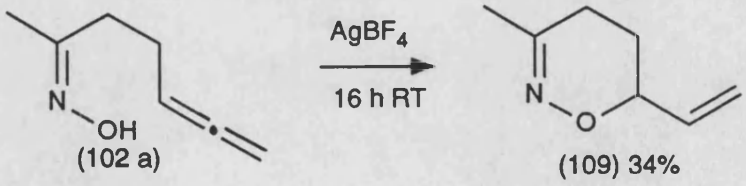
The Ag(I)-induced cyclisation of the (E)-allenic ketoximes (102 b) and (104 b) proceeded rapidly, via the nitrogen, to afford the nitrones (107) and (108) respectively in a 74% and 66% yield (Scheme 77). Attempts to trap the nitrone (107) with styrene at 80°C for 12 hours were unsuccessful, only starting material was recovered. Grigg[62a] has subsequently trapped similar methyl-substituted cyclic nitrones by carrying out the reaction at 140°C for 8 hours (Scheme 73) but due to time constraints we did not examine these conditions.

Scheme 77



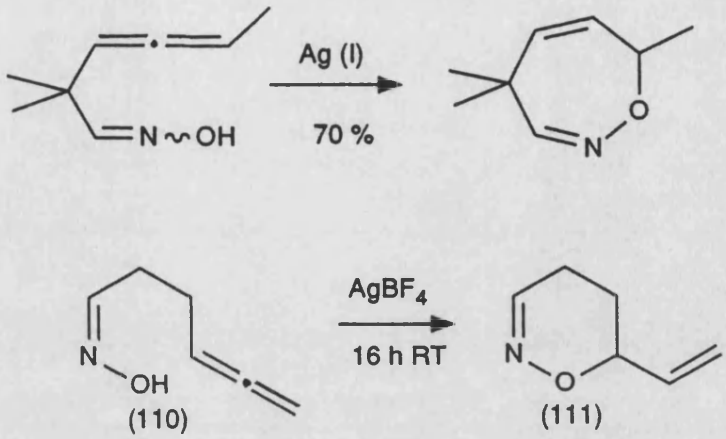
The (Z)-ketoxime (102 a) slowly cyclised via oxygen with Ag(I) to give the dihydrooxazine (109) (Scheme 78).

Scheme 78



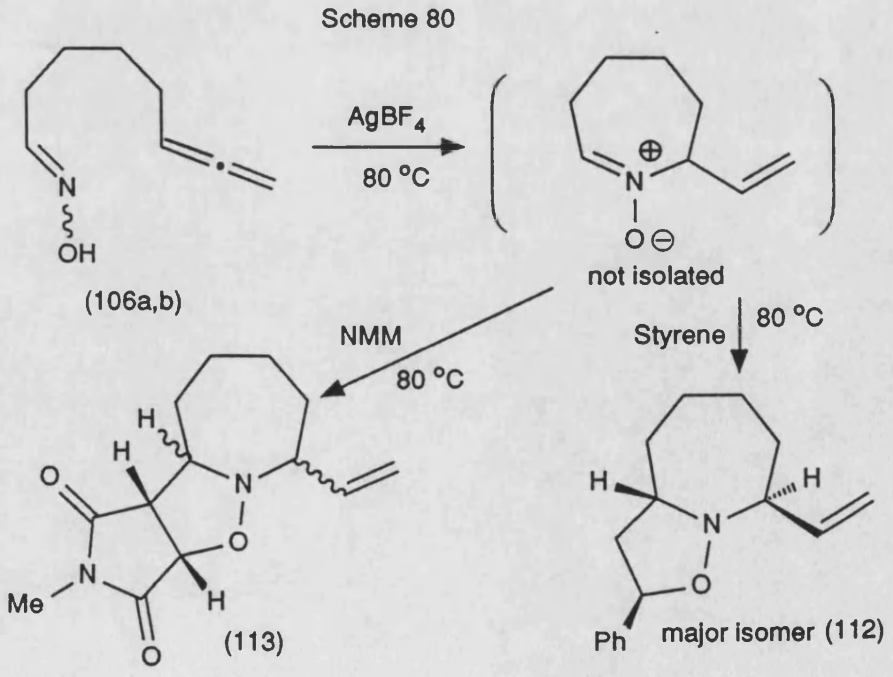
A similar cyclisation via oxygen onto an Ag(I)-activated allene moiety has been observed with the gem-dimethyl β-allenic oxime[65] but in this example it is the terminal carbon of the allenic moiety that undergoes nucleophilic attack, (Scheme 79). Aldoxime (110) has also been observed to cyclise[52] via oxygen to give the unstable oxazine derivative (111)(Scheme 79).

Scheme 79



An extension of the five- and six-membered ring cyclisation of (E)-aldoximes to the formation of a seven-membered cyclic nitrone was also examined. A mixture of (E)- and (Z)-aldoxime (106 a,b) was reacted with Ag (I) at 80°C and the formation of a very polar component was observed by tlc. Although attempts to isolate the intermediate nitrone failed, it was trapped with styrene to give the cycloadduct (112) (20%) as a 5:1 mixture (Scheme 80).

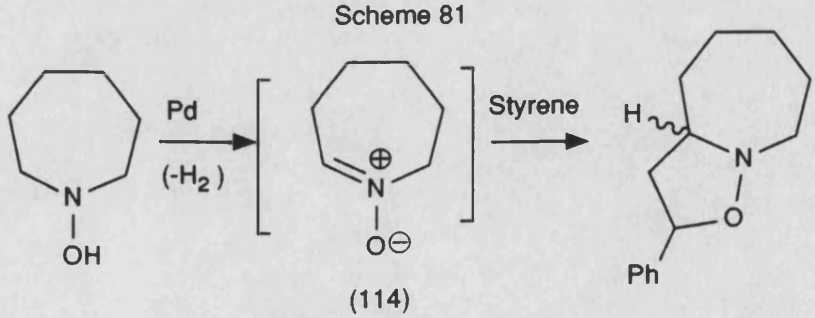
Scheme 80



With a more efficient dipolarophile (N-methylmaleimide) the seven-membered nitrone was more readily trapped to give (113) as a 2:2:1 mixture of isomers in a 60% yield (Scheme 80).

The poor yield obtained when styrene is used as the dipolarophile, is possibly not a reflection of the efficiency of the cyclisation reaction but rather the instability of the seven-membered cyclic nitrone. This is not surprising bearing in mind the relative instability of the corresponding six-membered ring analogue compared with the five-membered ring, which could be isolated. The yield obtained with the more reactive dipolarophile (NMM) is a better reflection of this cyclisation reaction. Presumably under the reaction conditions ($AgBF_4$, 80°C) there is rapid (E)⇌(Z)-isomerisation, so separation of the isomers is unnecessary. In one preparation of the parent 3,4,5,6-tetrahydro-2H-azepine-1-oxide[66], dehydrogenation of N-hydroxyazepine with Pd(0) at 80°C produced the dipole (114) which was subsequently trapped with styrene (Scheme 81). The stereochemistry of the major isomer (112) obtained by trapping with styrene was assigned by nOe experiments but the minor isomer could not be fully characterised and efforts to separate the isomers by flash chromatography were unsuccessful. The stereochemistry of the three isomers (113) obtained from the trapping experiment with NMM could not be fully determined.

Scheme 81

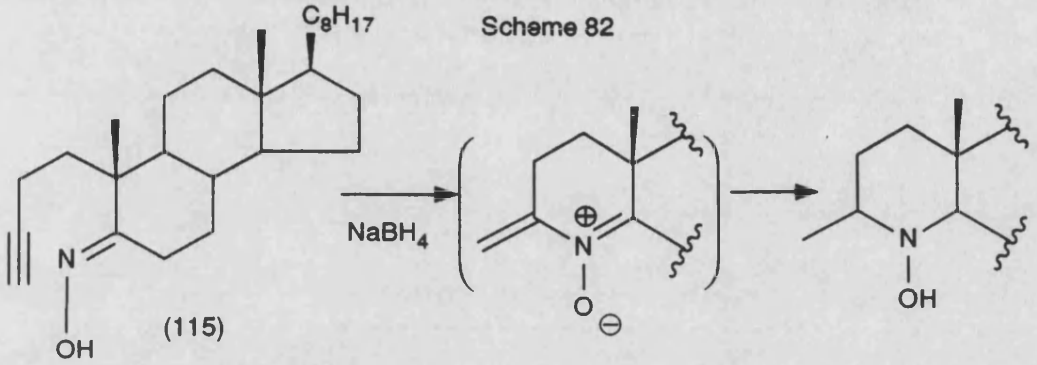


(114)

Generation of Nitrones via the Cycloaddition of Oximes to other π-Systems

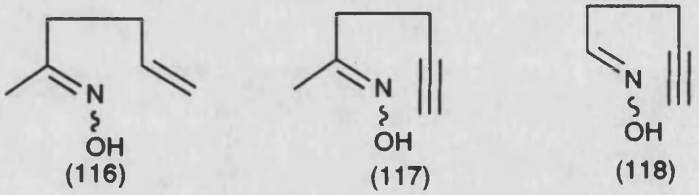
The cyclisation of oximes to other π-systems to generate nitrones has been achieved previously. The very unusual and unique reaction of the oxime (115) with $NaBH_4$ has been suggested[67] to proceed via a nitrone (Scheme 82).

Scheme 82



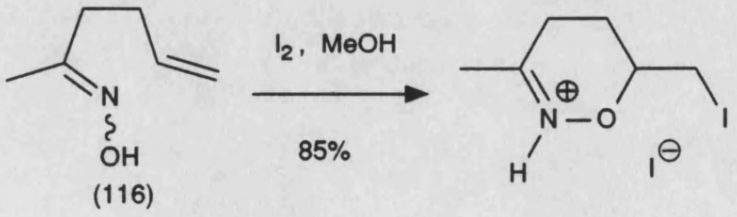
We hoped to be able to extend the Ag(I)-mediated oxime cyclisation procedure involving the allene π-system to incorporate alkynyl and alkenyl-substrates.

The synthesis of the alkenyl and alkynyl oximes (116-118) was straightforward. Alkylation of the dianion of acetone oxime with allyl bromide gave (116)[64] and a similar procedure involving propargyl bromide gave (117). Alkylation of the dianion of acetaldoxime with propargyl bromide gave (118).

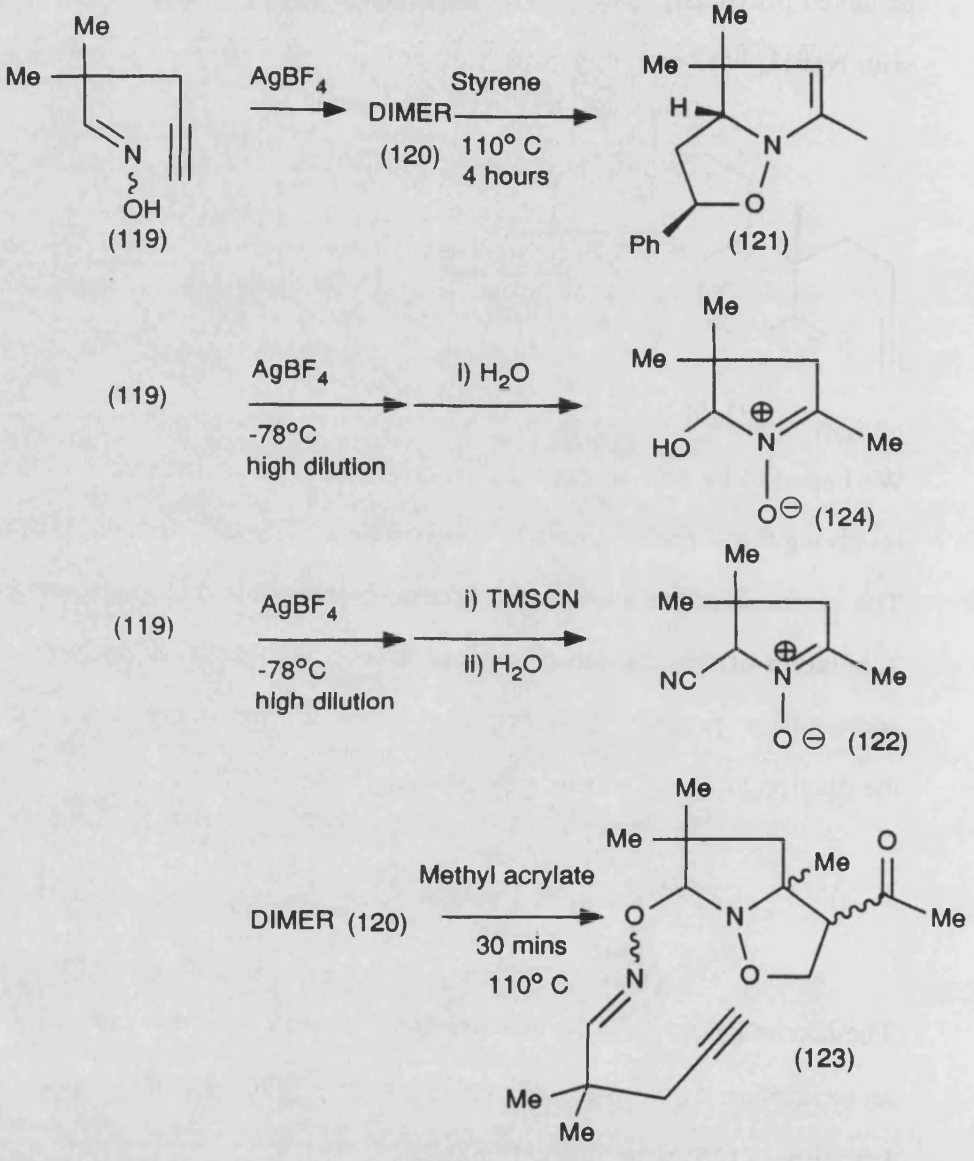


The alkene ketoxime (116) has previously been cyclised[68] using iodine to give an oxazinium derivative (Scheme 83), but we found that the (E)- and (Z)-alkene ketoximes (116) were unreactive towards Ag(I)-induced cyclisation even after 4 days at room temperature.

Scheme 83



Scheme 85

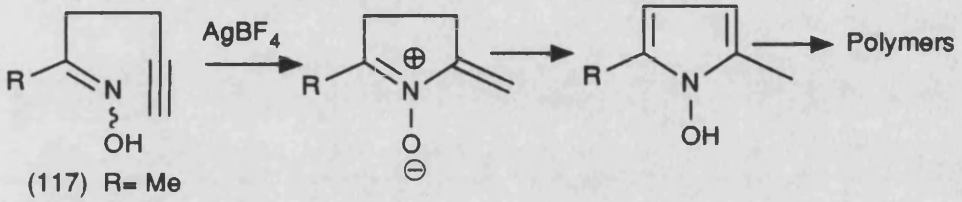


(119) $AgBF_4$ high dilution →

i) benzaldehyde oxime	Liquid
ii) 2-napthaldehyde oxime	Liquid
iii) 9-anthraldehyde oxime	Solid

When (117) and (118) were treated with Ag(I) a multicomponent mixture was obtained, even when the reaction was conducted at -78°C. Aromatisation of the cyclised product and subsequent polymerisation might account for this result (Scheme 84).

Scheme 84



(117) R= Me
(118) R= H

To avoid the possibility of side reactions diverting the course of the cyclisation sequence, we examined the dimethyl-substituted alkynyl oxime (119) which was prepared using a literature procedure[69]. Aldoxime (119) readily reacted with Ag(I) at -78°C to give after 3 h a dimer, assigned as (120), in 80% yield. The dimer (120) was heated for 4 h at 110°C in the presence of styrene, adduct (121) was isolated in a low (4%) yield along with recovered starting oxime (119) in 30% yield (Scheme 85). Reaction of oxime (119) with Ag(I) under pseudo-high dilution conditions, via syringe pump addition, gave on aqueous work up, a product which has been tentatively assigned (124)(Scheme 85). Under the same dilute conditions, addition of TMSCN after the cyclisation and aqueous work up gave the cyano adduct (122) in 12% yield (Scheme 85).

The "dimeric" nitrone (120) was trapped with methyl acrylate to give a single product (123) after 30 mins at 110°C, the precise stereochemistry of (123) was not determined. The structure of (120) will be discussed below but we wanted to probe this cyclisation process and try and obtain crystalline derivatives for X-ray crystallographic analysis. We attempted to generate "mixed" analogues of the dimer (120), and oxime (119) was reacted with Ag(I) in the presence of benzaldehyde oxime and 2-naphthaldehyde oxime. Both reactions gave products which were isolated as oils and failed to crystallise. Reaction with

9-anthraldehyde oxime, however, gave a crystalline solid. Despite exhaustive efforts, we were unable to obtain crystals suitable for X-ray crystallographic analysis owing to extensive crystal twinning.

The structures of the unknown compounds (120) and (124) could not therefore be unambiguously determined, but full spectral analysis of the dimer (120) was obtained and the high resolution accurate mass spectroscopy enabled the molecular formula to be determined: $C_{14}H_{22}N_2O_2$. Full ^{13}C and ^{1}H data will be discussed later (Table 6). The ^{1}H spectrum of (124) was very broad, the mass spectrometry indicated a molecular ion of the nitrone + H_2O (corresponding to $C_7H_{13}NO_2$). The structure of (122) was assigned by ^{13}C and ^{1}H NMR spectroscopy and ^{13}C -^{1}H correlation experiments confirmed the structure. A comparison of the δ_C and δ_H of the dimer (120) and the nitrone (122) obtained via TMSCN workup, indicated these two compounds were very similar.

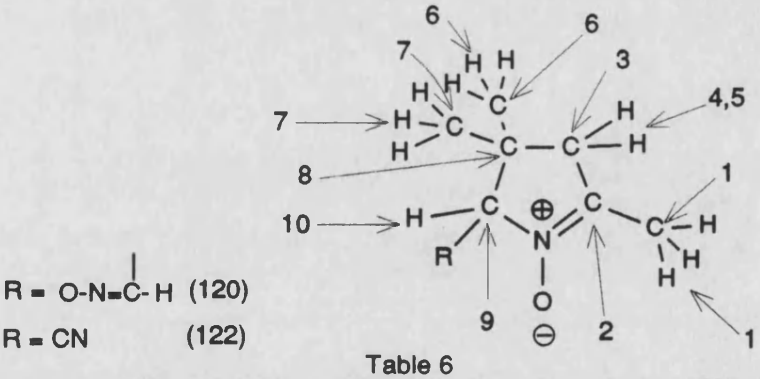
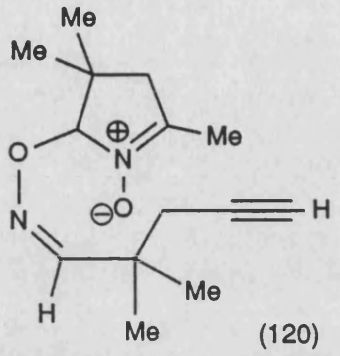


Table 6

Number	CN (122)		DIMER (120)		DIMER - CN	
	δ_C	δ_H	δ_C	δ_H	$\Delta\delta_H$	$\Delta\delta_H$
1	12.9	2.08	12.8	2.08	-0.1	0
2	145.5	-	146.7	-	-1.2	-
3	46.8	-	46.5	-	+0.3	-
4	-	2.68	-	2.65	-	+0.03
5	-	2.59	-	2.34	-	+0.25
6	27.3	1.32	28.1	1.19	-0.8	+0.13
7	25.5	1.40	21.7	1.13	+3.8	+0.27
8	36.5	-	36.7	-	+0.2	-
9	73.5	-	106.9	-	-33.4	-
10	-	4.59	-	5.12	-	-0.53

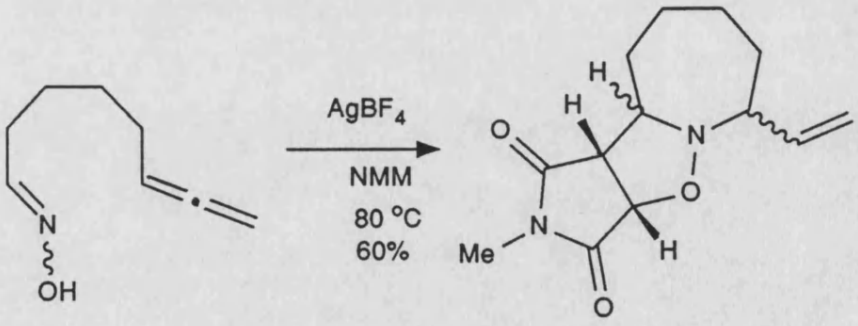
Based on the above information, we have tentatively suggested the following structure for the dimer (120):



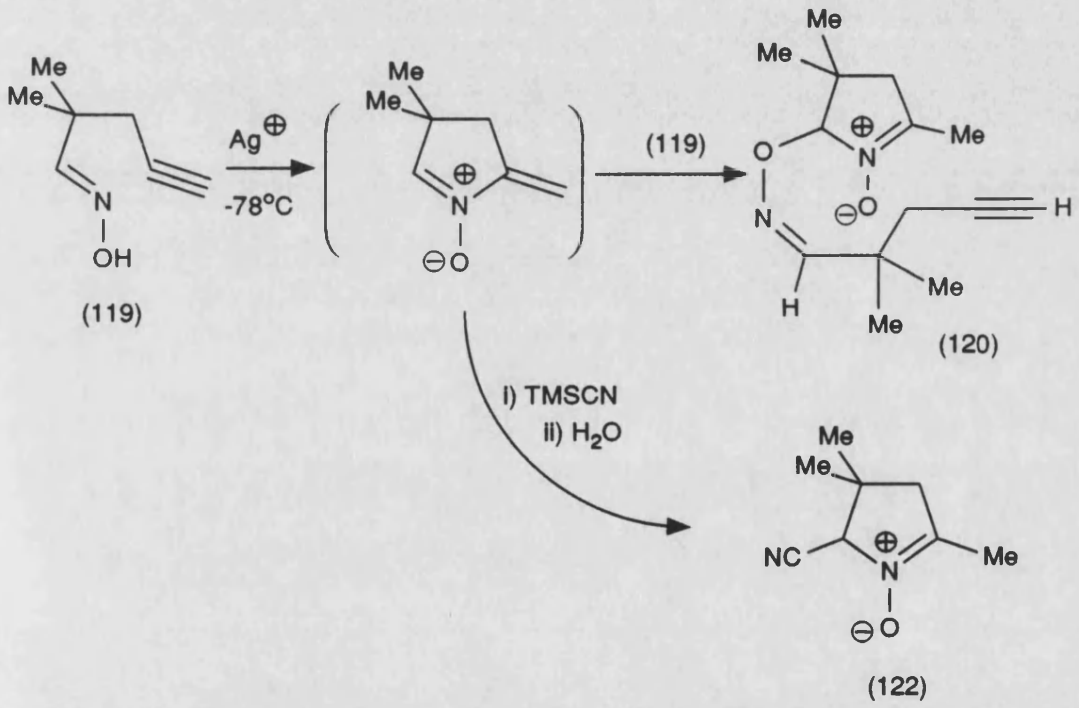
(120)

Conclusion

We have demonstrated that the Ag(I)-mediated cyclisations of allenic oximes is not limited to the use of aldoximes to form only five- and six-membered rings. We were unable to trap the stable nitrones generated from the ketoximes although similar nitrones have subsequently been trapped by Grigg et al. The formation of the unstable seven-membered nitrone is an efficient cyclisation process and it can be readily trapped with dipolarophiles.



This Ag(I)-mediated cyclisation procedure is not limited to allenic oximes, but has been extended to alkynes. Unfortunately, so far only one specific gem-dimethyl oxime (119) gives a characterisable product (120), which thermally decomposed in the presence of a dipolarophile to give the cycloadduct (121). A monomer can also be obtained from this oxime (119), under dilute conditions. This monomer cannot be isolated, due to its high reactivity, but can be quenched cleanly with TMSCN to give (122).



Allene-Based Electrophile-Mediated Heterocyclisations

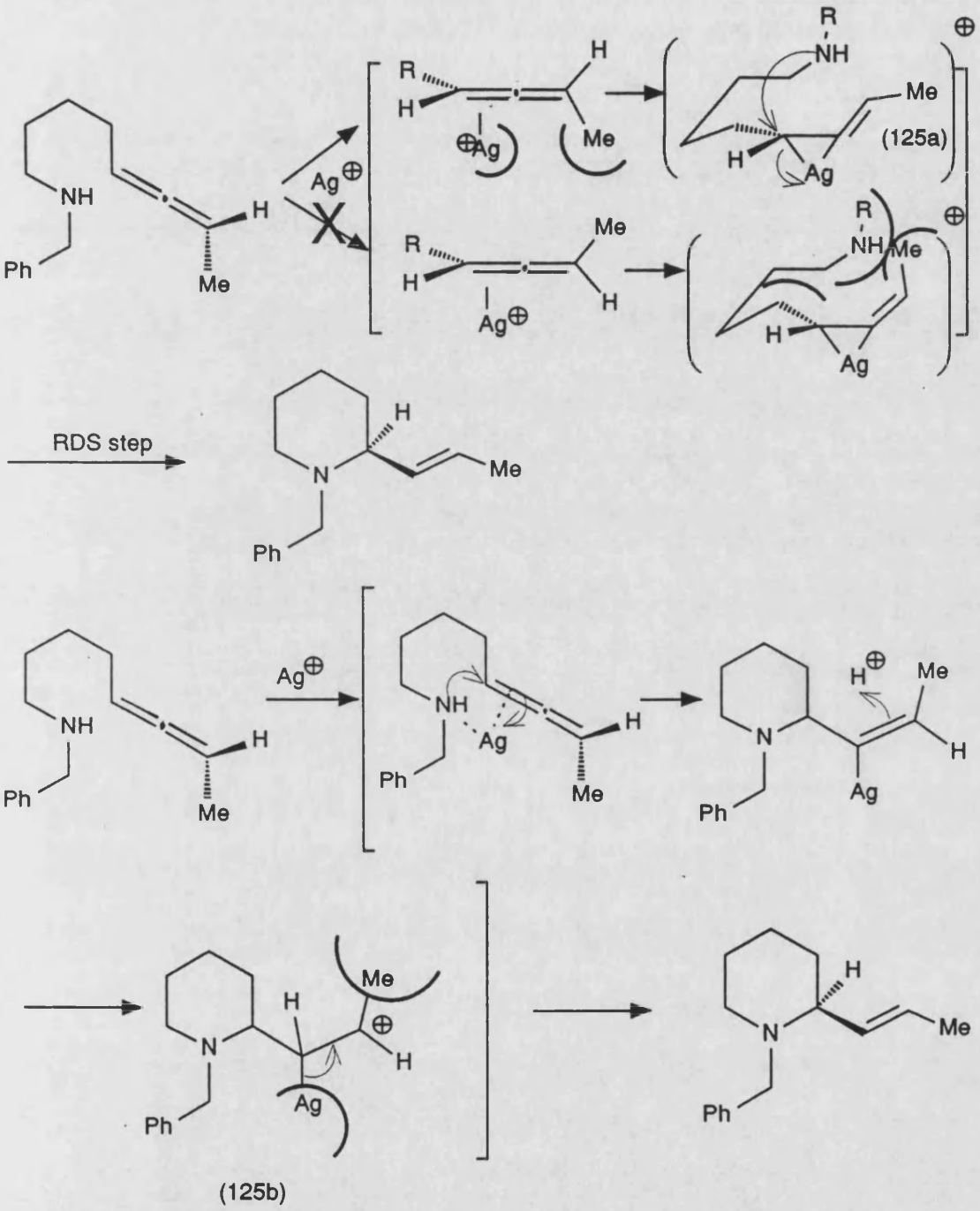
Background

In 1979 Claesson et al[70] established the ability of catalytic amounts of silver(I) to activate the allene moiety towards nitrogen and oxygen nucleophiles, inducing heterocyclisation. Since this initial observation various groups have exploited this mild catalytic process and the range of nucleophilic substrates used with Ag(I) has been extended to include alcohols[71], amides[72], amines[73], imines[74] and oximes[65,75]. Some of the cyclisation reactions have only been demonstrated when the gem-dimethyl moiety has been present and the cyclisation of γ- and δ-allenes has only been demonstrated with a limited range of other electrophiles, such as Pd(II)[76], Hg(II)[77] and Ag(I).

Silver(I)-Mediated Cyclisation of γ- and δ-Allenic Amines

The precise nature of the silver(I)-allene interaction and subsequent nucleophilic heterocyclisation is not fully understood. In previous studies[72b] it has been observed that chiral allenic residues treated with silver(I) undergo an asymmetric cyclisation to give the E-double bond geometry. The intermediate (125 a) was proposed, based on the known interaction of Hg(II) with chiral allenes[78], where the rate determining step is the addition of the nucleophile to the activated π-system. For such a mechanism the approach of the metal electrophile to the less hindered face of the allene is unfavoured, because of considerable steric interactions involved in the rate determining cyclisation step. An alternative mechanism, which is difficult to ignore, is the direct interaction between Ag(I) and the basic nitrogen to induce the cyclisation, where the steric interactions in the intermediate (125 b) dictate the stereochemistry of the double bond (Scheme 86).

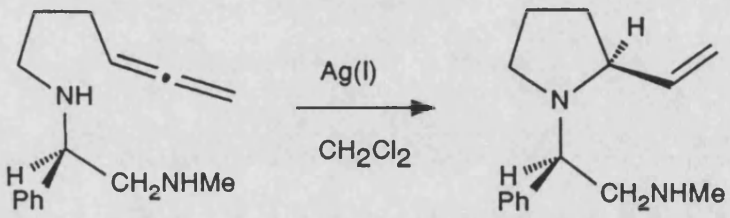
Scheme 86



In an effort to probe the nature of the intermediate and extend the synthetic value of this cyclisation reaction, Gallagher and co-workers[79] examined a series of allenic amines, carrying an asymmetric centre on the nitrogen (Scheme

87). On treatment with Ag(I)(0.5eq) the products were formed in 81% d.e, but Pd(II)-mediated cyclisation was less selective (43%d.e). From these observations a tentative theory based on face-selective addition of silver(I) to form a π-complex/metallocyclopropane complex with one of the π-bonds of the allene moiety has been suggested. Interaction between the asymmetric centre on the nitrogen and the silver complex might account for the selectivity.

Scheme 87

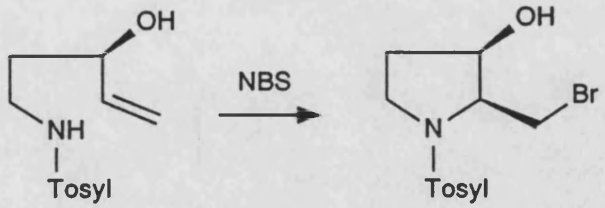


81% d.e

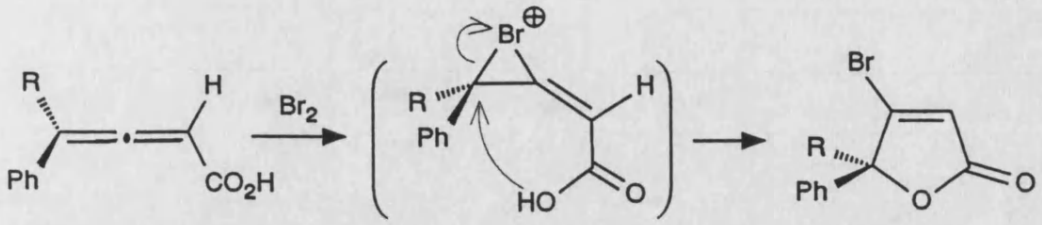
Bromonium Ion-mediated Cyclisation of Allenic Amines

N-Bromosuccinimide, unlike silver(I), will induce cyclisation with alkenes[80] (Scheme 88).

Scheme 88

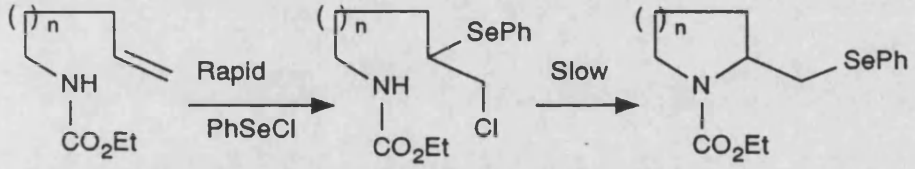


Bromine has previously been used to give optically active bromolactones from chiral α-allenic carboxylic acids[81], presumably via the intermediacy of the bromonium ion:



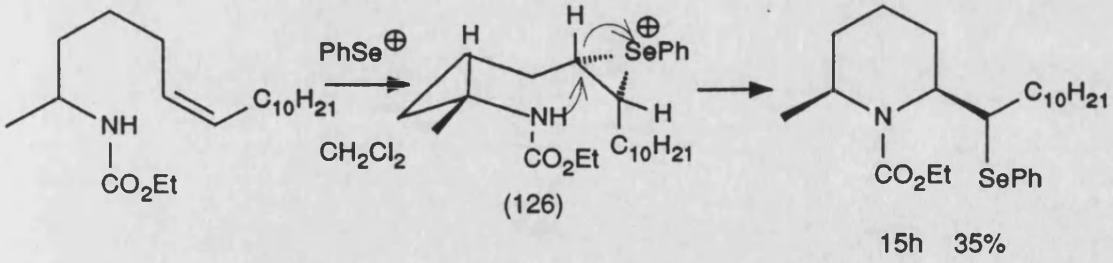
Phenylseleno Ion-mediated Cyclisation of Allenic Amines

Phenylselenyl chloride will activate alkenes towards intramolecular nucleophilic cyclisation[82].

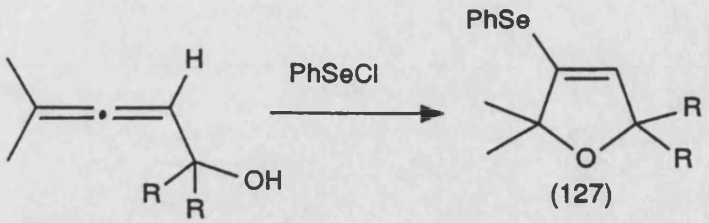


Due to the stereochemical outcome of the reaction, the intermediate (126) has been postulated (Scheme 89).

Scheme 89



Phenylselenyl chloride also induces cyclisation in a of range of α-allenic alcohols[83] to produce dihydrofurans (127) in high yields, although the reaction of monosubstituted allenes under the same conditions is more sluggish.



(127)

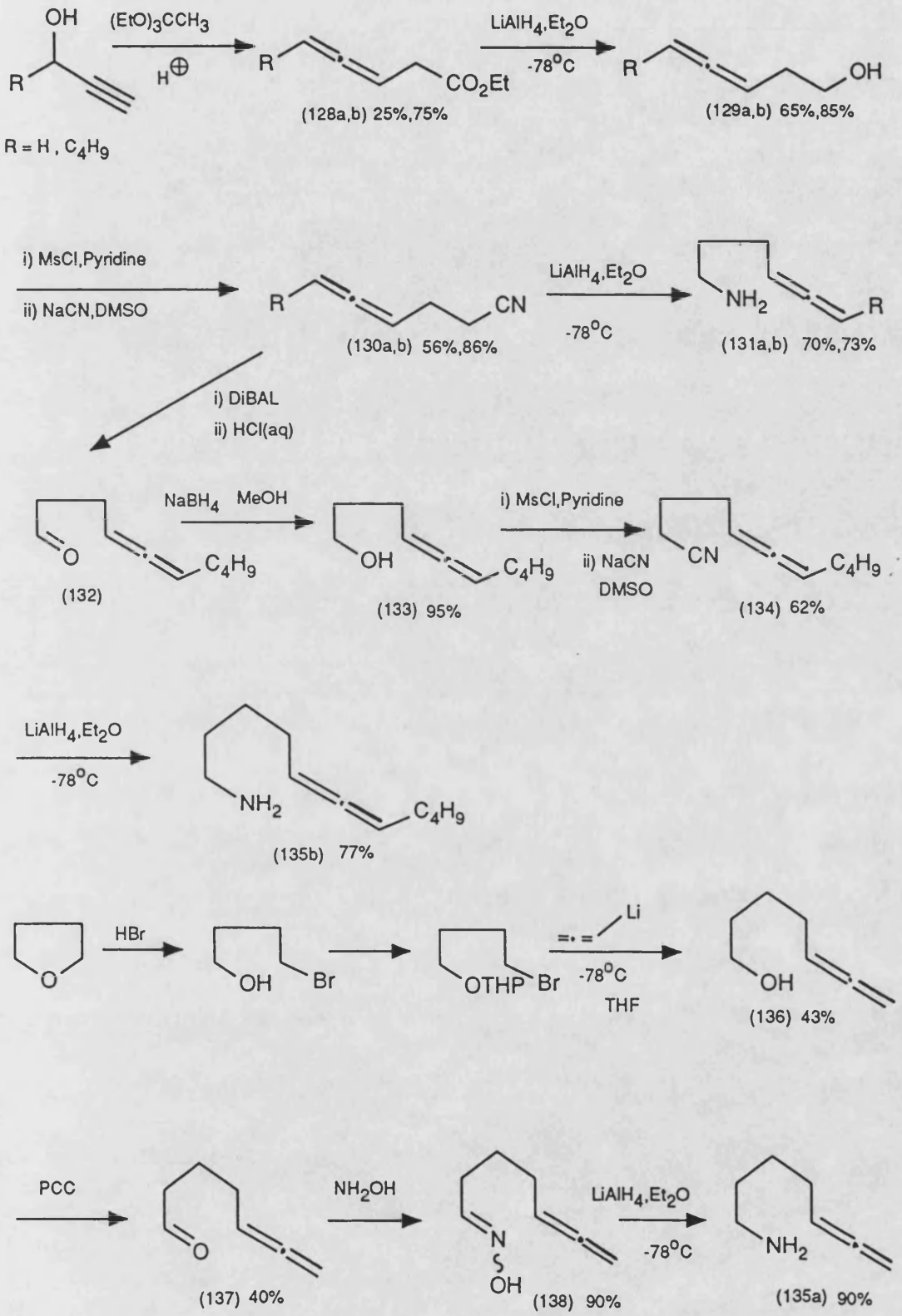
Our initial objective in this area was to extend the scope of the electrophile-induced heterocyclisation reaction of allenic substrates carrying oxygen or nitrogen nucleophiles and we also planned to probe the range of electrophiles (E^+) that would induce such heterocyclisations.

Studies with Allenic Amines

Synthesis of Allenic Amines

A range of N-substituted allenic amines (131 a,b) and (135 a,b) were readily prepared in moderate yields as shown in Scheme 90. Multigram quantities of the β-allenic ethyl esters (128 a,b) were prepared via the Claisen rearrangement methodology developed by Crandall and Tindell[84]. Reduction ($LiAlH_4$ -78°C) of the esters followed by mesylation of the corresponding alcohols (129 a)[85] and (129 b) and cyanide displacement gave the allenic nitriles (130 a)[86] and (130 b). The reduction ($LiAlH_4$) of the nitriles (130 a,b) allowed access to the corresponding mono-substituted allene (131 a)[87] and 1,3-disubstituted allenic amine (131 b). The homologation of nitrile (130 b) was conducted via standard methodology. Reduction (DiBAL) and aqueous work up gave aldehyde (132) which was further reduced ($NaBH_4$) to the alcohol (133). Cyanide displacement of the corresponding tosylate produced nitrile (134) which upon reduction ($LiAlH_4$) gave the disubstituted 5,6-dienyl amine (135 b).

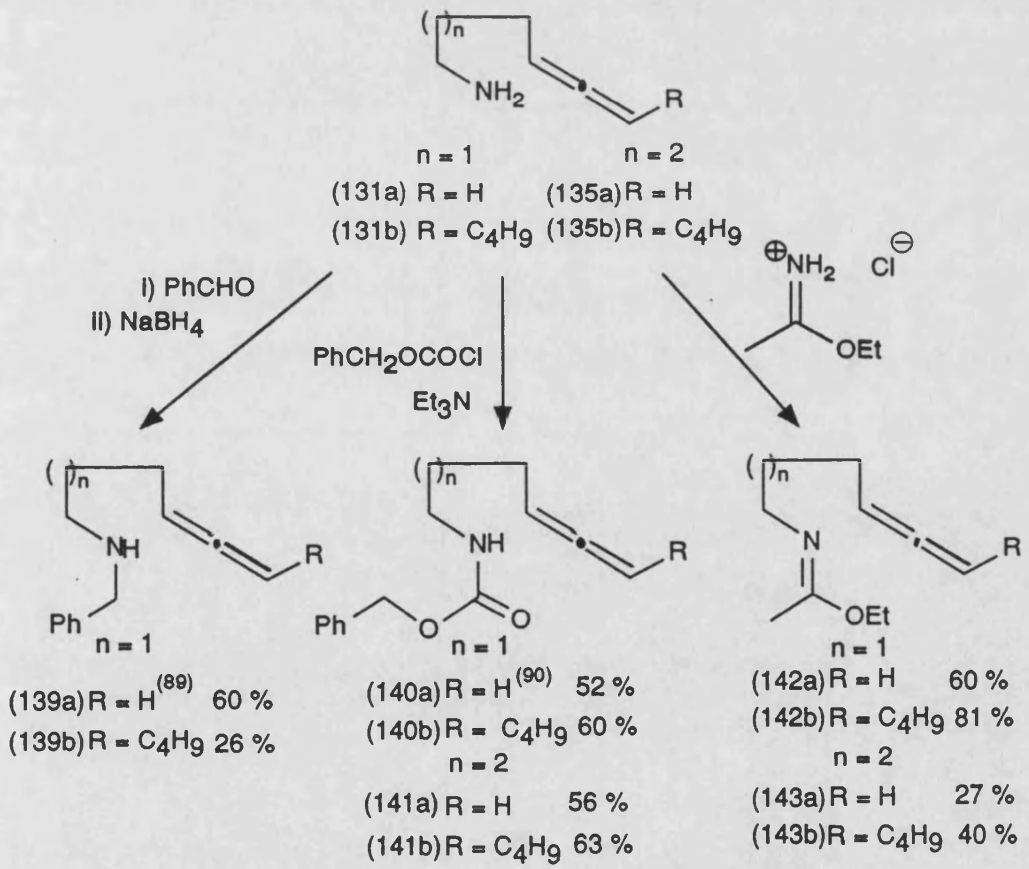
Scheme 90


OH
(EtO)3CCH3
H⊕
R
CO2Et
(128a,b) 25%,75%
LiAlH4,Et2O
-78°C
OH
(129a,b) 65%,85%
R = H , C4H9
i) MsCl,Pyridine
ii) NaCN,DMSO
CN
(130a,b) 56%,86%
LiAlH4,Et2O
-78°C
NH2
(131a,b) 70%,73%
i) DiBAL
ii) HCl(aq)
O
C4H9
(132)
NaBH4 MeOH
OH
(133) 95%
i) MsCl,Pyridine
ii) NaCN
DMSO
CN
(134) 62%
LiAlH4,Et2O
-78°C
NH2
(135b) 77%
HBr
OH
Br
OTHP
Br
Li
-78°C
THF
OH
(136) 43%
PCC
O
(137) 40%
NH2OH
N
OH
(138) 90%
LiAlH4,Et2O
-78°C
NH2
(135a) 90%

The monosubstituted 5,6-dienyl amine (135 a) was readily accessible from hepta-5,6-dien-1-ol (136) and this alcohol was prepared in multigram quantities as described by Bransma[87], by alkylation of lithioallene with the THP-protected 5-bromopentanol. Oxidation of (136) using pyridinium chlorochromate (PCC) gave aldehyde (137), which was converted to the target primary amine (135 a)[89] by oxime formation (138)[88] and subsequent reduction ($LiAlH_4$) .

Since we have previously observed that the cyclisation of primary allenic amines with Ag(I) was not very efficient (probably due to the formation of an insoluble silver-amine complex and/or oxidation), these intermediates were converted to a range of N-substituted derivatives (139-143) as shown in Scheme 91.

Scheme 91

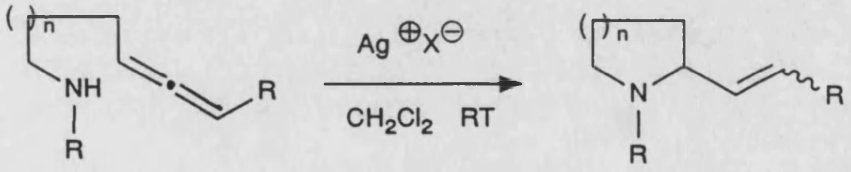


The N-benzyl protected allenic amines (139 a,b) were prepared by reducing the imines prepared from benzaldehyde. N-Acylation with benzylchloroformate allowed access to the benzyloxycarbonyl-protected amines (140 a,b) and (141 a,b) and using standard methods[90], ethyl acetimidate. HCl reacted with amines to give (142 a,b) and (143 a,b).

Silver (I)-Mediated Cyclisation of N-Substituted γ- and δ-Allenic Amines

We have examined the influence of both the effect of the counterion of the Ag(I) and the substitution on nitrogen on the outcome of five- and six-membered ring cyclisations (Scheme 92). Although only a catalytic amount of Ag(I) is required, in practice we used one equivalent to increase the rate of cyclisation.

Scheme 92



Pyrrolidines n = 1					
R^1	R	$X^{\ominus}$	Product	Time/h	Yield [i]
(140a) CBZ	H	BF_4	(144a)[91]	2	85%
(140a) CBZ	H	SO_3CF_3	(144a)[91]	2	80%
(140b) CBZ	C_4H_9	BF_4	(144b)	2	50%
(139a) $PhCH_2$	H	BF_4	(145a)[92]	2	55%
(139b) $PhCH_2$	H	SO_3CF_3	(145a)[92]	2	66%

Piperidines n = 2					
R^1	R	$X^{\ominus}$		Time/days	Yield
(141a) CBZ	H	BF_4	(146a)	5	70%[ii]
(141b) CBZ	C_4H_9	BF_4	(146b)	14	80%[ii]
$PhCH_2$	Me	BF_4			80%

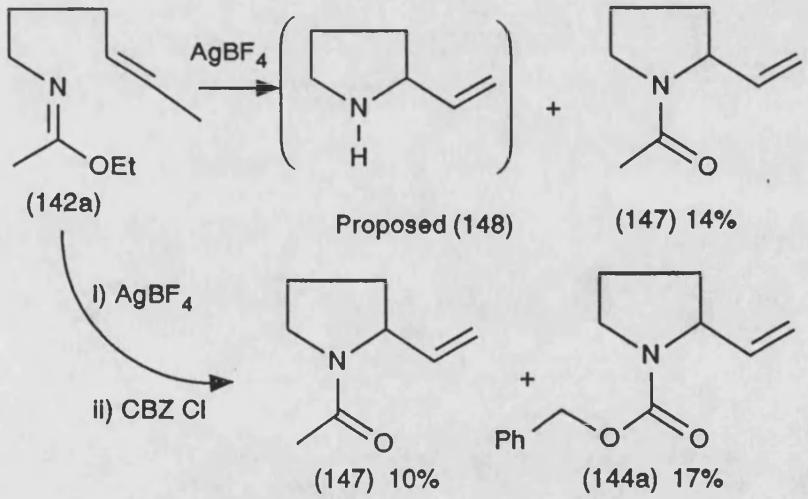
i) Isolated yields after chromatography
ii) Yield corrected for recovered starting material.

*The $AgNO_3$ induced cyclisation has previously been reported.[96]

The (E/Z) stereochemistry of the alkenyl residue in (144 b) and (146 b) could not be assigned, because the relevant region in the ^1H NMR spectrum was complex due to resonance associated with the amide group. However, previous workers have demonstrated that Ag(I)-mediated cyclisation does show a marked preference for the formation of the (E)-double bond geometry[72b].

The more nucleophilic imidate (142 a) gave, on treatment with $AgBF_4$, a complex mixture of products. Amide (147) was the only product that could be isolated from the mixture, however, we postulate that one of the other components could be the secondary amine (148). When the reaction mixture was treated prior to workup with benzyl chloroformate, two compounds were isolated (147) and (144 a) (Scheme 93).

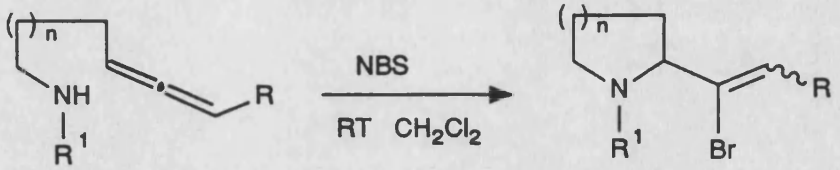
Scheme 93



Bromonium Ion-Mediated Cyclisation of Allenic Amines

A range of allenic amines was treated with NBS (1 equivalent) to explore the bromonium ion-mediated cyclisation of γ- and δ-allenic amines. NBS was used rather than Br_2 as a source of $Br^{\oplus}$ to avoid simple addition across the π-system (Scheme 94).

Scheme 94



n=1 Allenic amines	R^1	R	Product	Time	Yield
(140a)	CBZ	H	(148a)	14 days	55%
(140b)	CBZ	C_4H_9	(148b)	6 days	50%
(139b)	$PhCH_2$	C_4H_9	-	4 days	0%

Although cyclisation of (140 a,b) was observed with NBS, the reaction was considerably slower than when Ag(I) was used as the electrophilic trigger.

We also briefly investigated the effect of solvent on the rate of this reaction and found that 1,2-dichloroethane increased the rate of cyclisation, but the reasons underlying this effect are not clear (Table 7). This methodology is, however, limited since all attempts to form a six-membered ring, even under the rate-enhancing conditions (1,2-dichloroethane) were unsuccessful.

Table 7

Solvent	Product:Starting[(a)] Material	% of reaction[(b)] Mixture being product
CH_2Cl_2	1 : 3.7	21% (148 b)
$ClCH_2CH_2Cl$	1.2 : 1	54% (148 b)

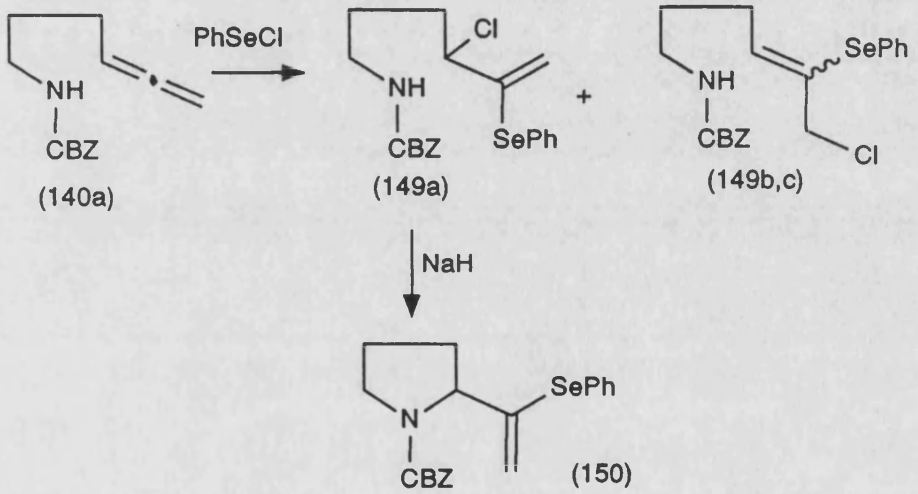
(a) determined by ^{1}Hnmr

(b) after 5h at RT

Phenylseleno Ion-mediated Cyclisation of Allenic Amines

As observed previously, PhSeCl reacts rapidly with the allenic moiety, to give three addition products (149 a,b,c) which were isolated in approximately equal amounts (Scheme 95). Although cyclic products were not observed under these conditions, treatment of (149 a) with NaH resulted in rapid cyclisation to give (150) in 41% yield for the cyclisation process.

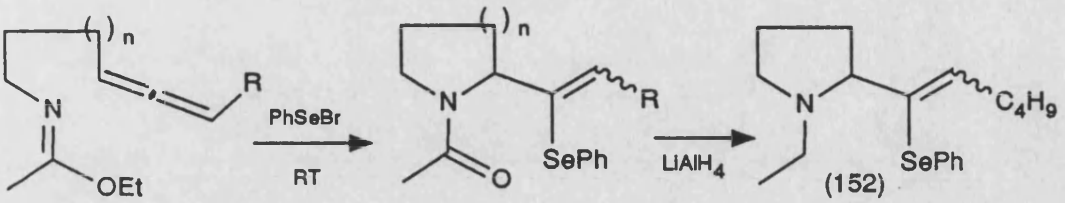
Scheme 95



It was hoped the problem associated with addition of $Cl^{\ominus}$ could be circumvented by using the less nucleophilic counterion ($SO_3CF_3^{\ominus}$) but when $PhSeSO_3CF_3$[93] was employed at -78°C a very complex mixture of products was obtained, from which only diphenyl diselenide could be identified.

The more nucleophilic imidate moiety has been employed by other workers[94] within the area of PhSeBr-induced alkenyl cyclisations. However, in our hands the allenic cyclisation was accomplished only in the case of the five-membered rings and once again the formation of the corresponding six-membered ring was not observed, presumably because of a sizeable kinetic barrier.

The ^1H NMR of (151 b) was very complex, but reduction ($LiAlH_4$) of the amide gave (152) with a simple and more readily analysed ^1H NMR spectrum.



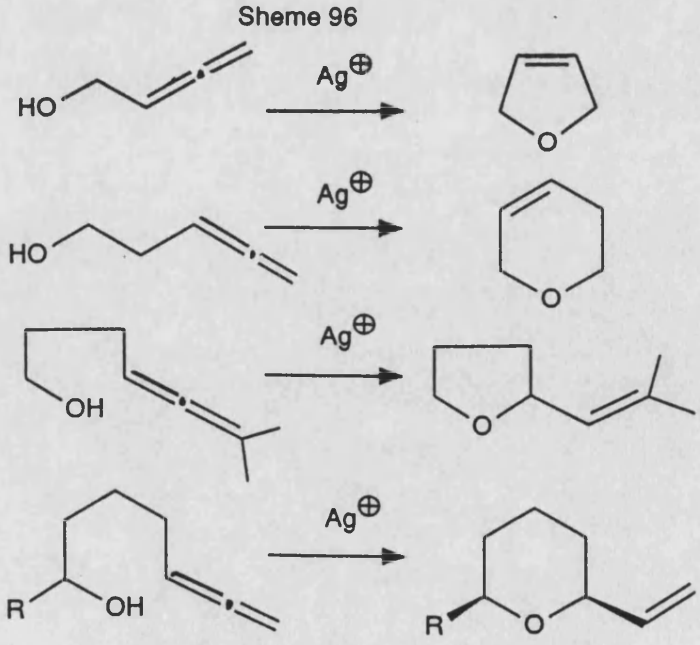
imidate	R	n	Time/h	Product	Yield
(142a)	H	1	5	(151a)	42%
(142b)	C_4H_9	1	5	(151b)	50%
(143a)	H	2	24	-	0
(143b)	C_4H_9	2	24	-	0

Use of Oxygen as the Nucleophile Component

Background

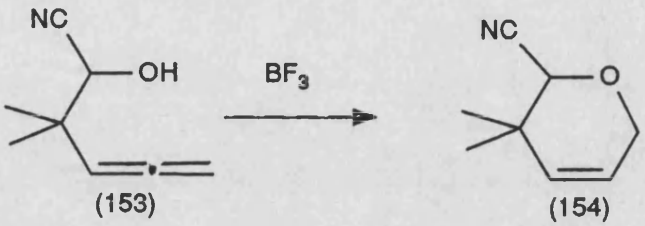
It is apparent from earlier work[70] that Ag(I)-mediated cyclisation of allenic alcohols is a very efficient process (Scheme 96).

Sheme 96



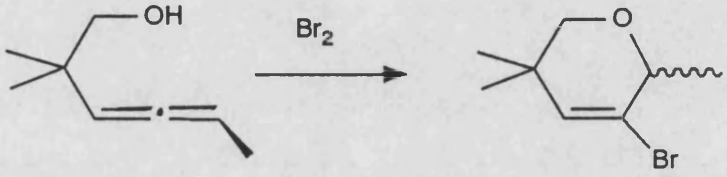
R = H, Me, Bu^t, $^cC_6H_{11}$, Ph, and $CH{=}CH_2$

Grimaldi reported the cyclisation[95] of the gem-dimethyl allenic cyanohydrin (153) with BF_3, but attempts to effect the cyclisation with $AgBF_4$ failed[95].



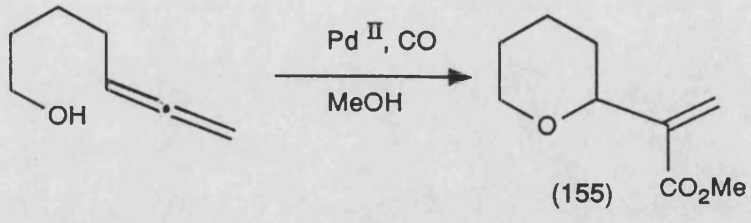
(153) (154)

The cyclisation of allenic alcohols has been observed under a variety of other circumstances. Bromine has been successfully employed to achieve such cyclisations[96].

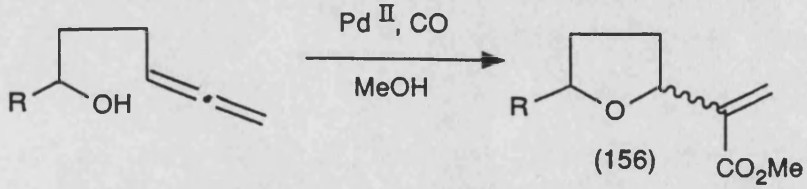


As previously mentioned, PhSeCl-induced cyclisations of α-allenic alcohols has also been demonstrated. Cyclisation of δ- and γ-allenic alcohol has been achieved using palladium(II)-based electrophiles, under carbonylating conditions to give tetrahydropyrans (155) and tetrahydrofurans (156)[76,77](Scheme 97).

Scheme 97



(155)

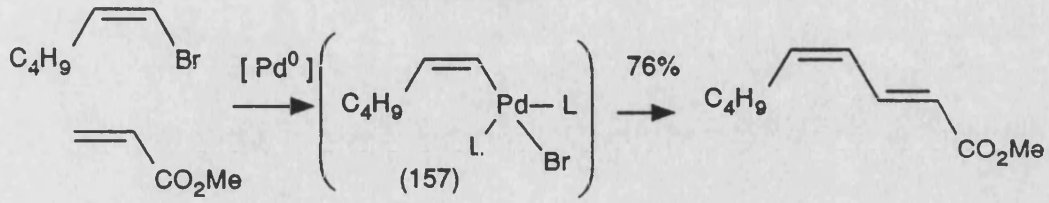


(156)

Heck[97] has demonstrated the use of palladium, in the coupling of vinyl halides with alkenes (Scheme 98). The reaction is believed to proceed via a vinyl

palladium species (157) generated by the oxidative addition of the vinyl halide to the palladium (0) catalyst.

Scheme 98

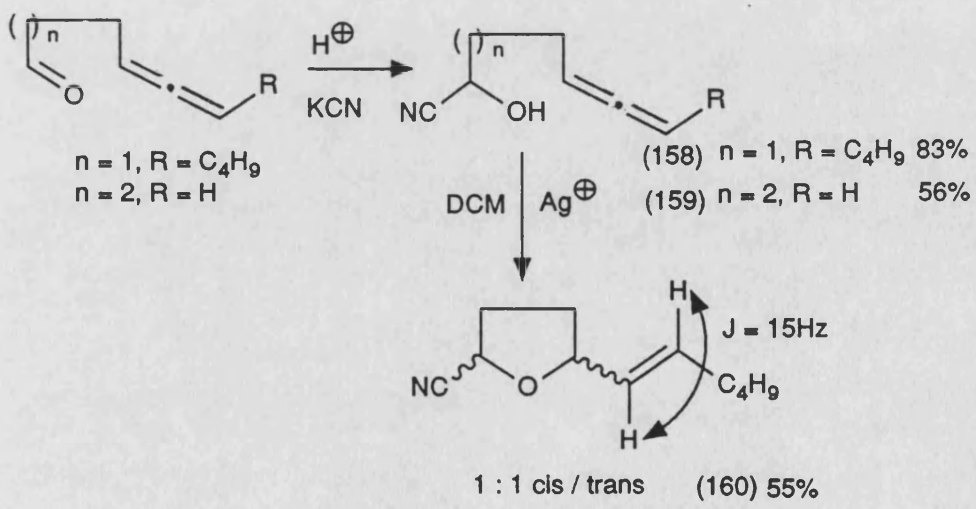


We hoped to be able to explore the scope and limitations of the cyclisation of allenic alcohols and then apply Heck-type chemistry, based on the assumption that palladium(II) reacts with allene to form, after cyclisation, a vinyl palladium species related to (157). These efforts are described below.

Studies with Cyanohydrins

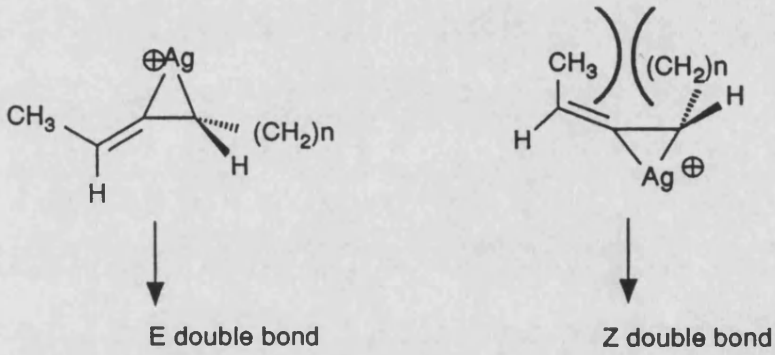
The failure to observe a Ag(I)-mediated cyclisation of the cyanohydrin (153) as reported by Grimaldi[95] was somewhat surprising and we felt that this result merited closer examination. With this in mind, we investigated the Ag(I)-mediated cyclisation of the cyanohydrins (158) and (159) which could be readily prepared by standard methodology (Scheme 99).

Scheme 99



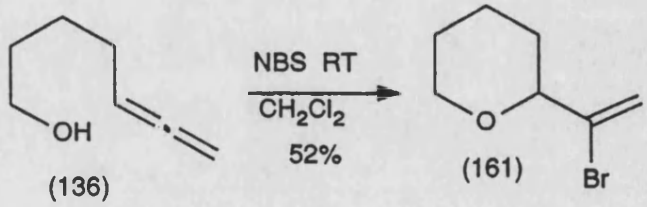
The 2,5-disubstituted tetrahydrofuran (160) was formed as a 1:1 mixture of cis- and trans-isomers, both with the same (E)-double bond geometry (Scheme 99). Attempts to extend this methodology to the corresponding disubstituted tetrahydropyran was, however, unsuccessful.

The (E)-double bond geometry is to be expected if the reaction proceeds via a metallocyclopropane intermediate, owing to steric interactions.



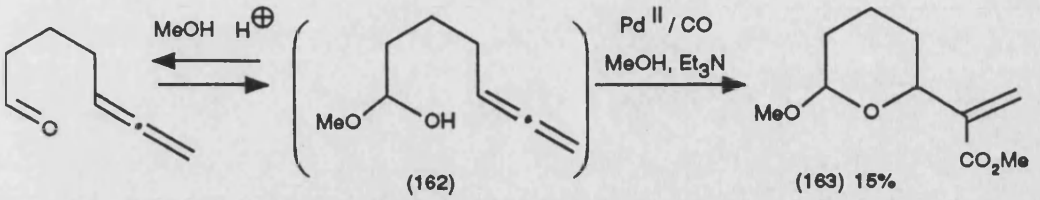
Studies with Alcohols

Hepta-5,6-dien-1-ol (136) readily cyclised with N-bromosuccinimide to give the tetrahydropyran (161) in a moderate 52% yield.



Phenylselenyl bromide also reacted with the allenic alcohol (136), but no cyclic products could be isolated.

As previously mentioned the, palladium (II)-induced cyclisation/ carbonylation of the δ-allenic alcohol (136) is a relatively facile reaction and this process has been extended to the cyclisation of the hemiacetal (162) under standard palladium(II) carbonylating conditions, to give a (3:1) mixture of the disubstituted tetrahydropyran (163).



We investigated the Heck-type reactions of Pd(II) with hepta-5,6-dien-1-ol (136) under various conditions (Scheme 100):

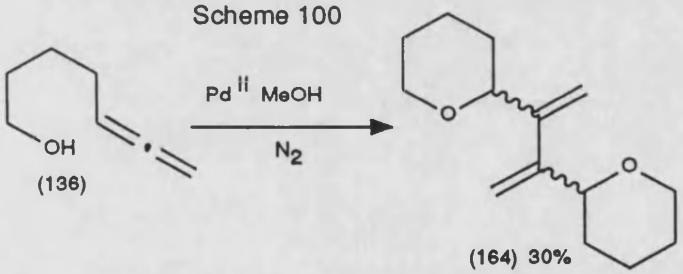
(i) Absence of CO.

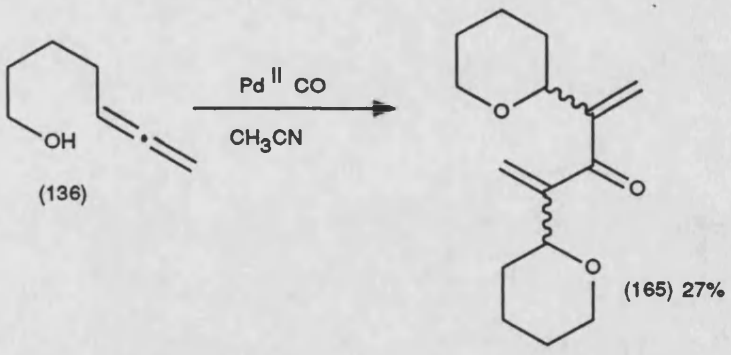
(ii) Absence of MeOH.

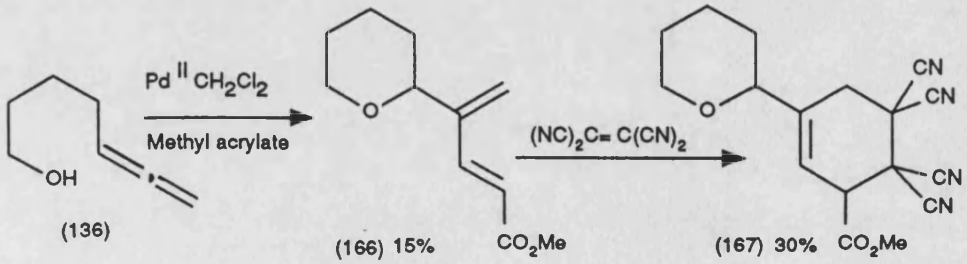
(iii) Replacement of CO with methyl acrylate.

When the cyclisation reaction was attempted in the absence of CO, the dimeric product (164) was obtained as a 1:1 mixture of diastereoisomers.

Scheme 100



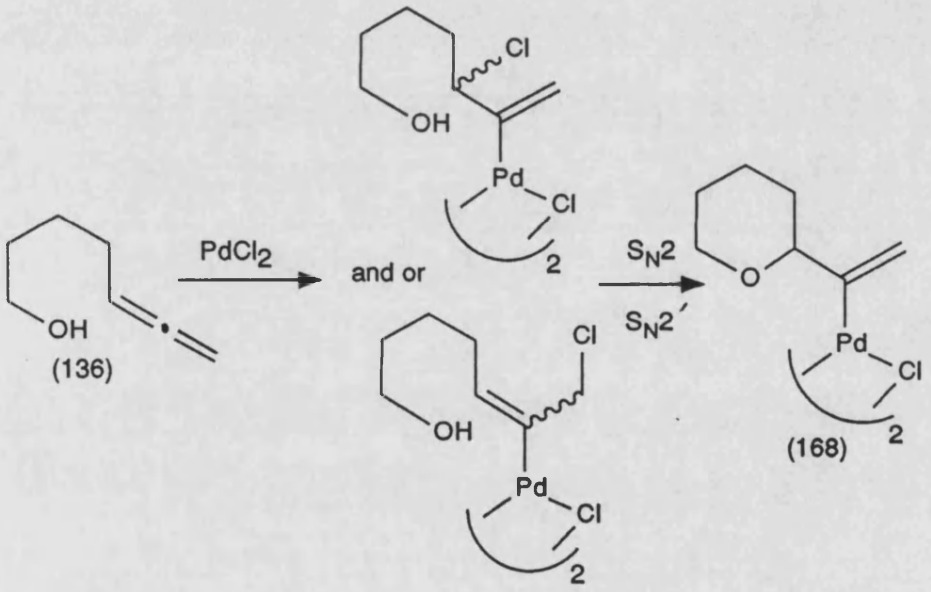




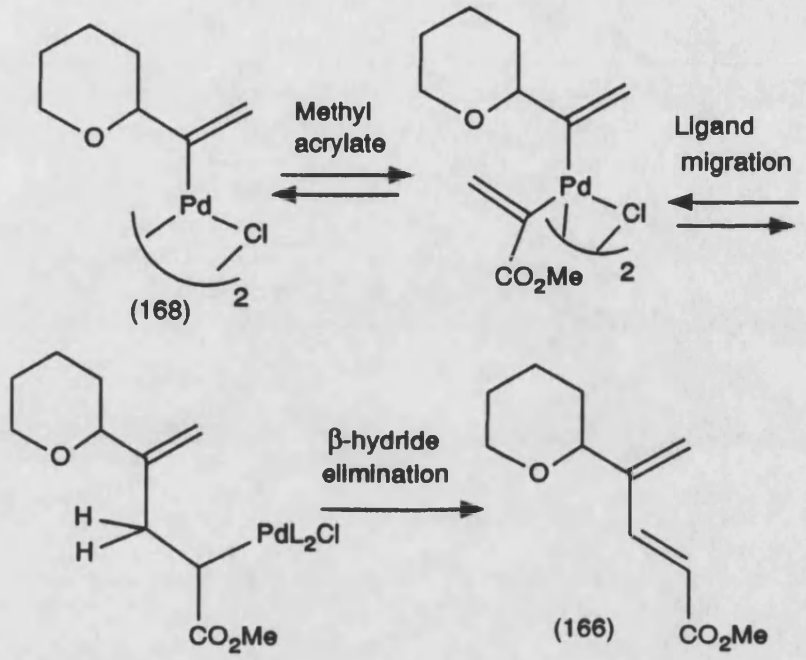
When the reaction was conducted in the absence of MeOH, the ketone (165) was obtained as a 1:1 mixture of diastereoisomers. Finally, when CO was replaced by methyl acrylate, the reaction gave a low yield of (166). The structure of (166) was confirmed by Diels-Alder cycloaddition reaction with tetracyanoethylene.

From previous observations[98] the first step may involve the addition of Pd X_2 across one π-bond of the allene. It is likely that the next step could be an S_N2- or S_N2'-like displacement of the chloride to give the cyclic intermediate (168) (Scheme 101).

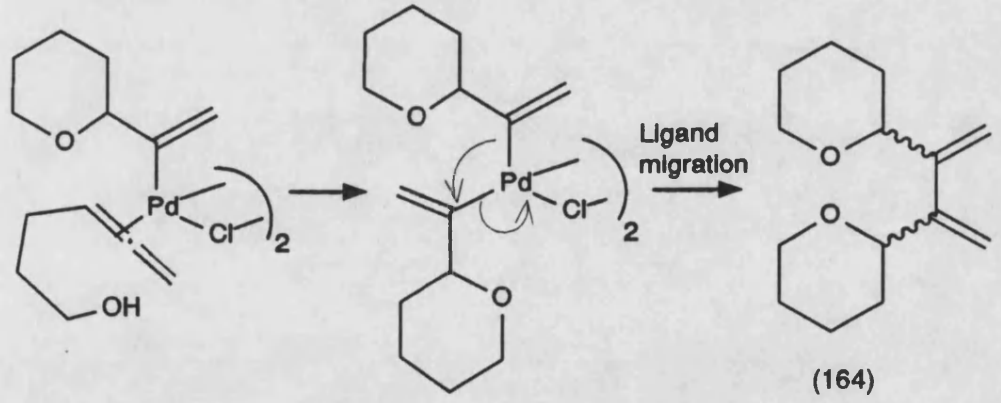
Scheme 101



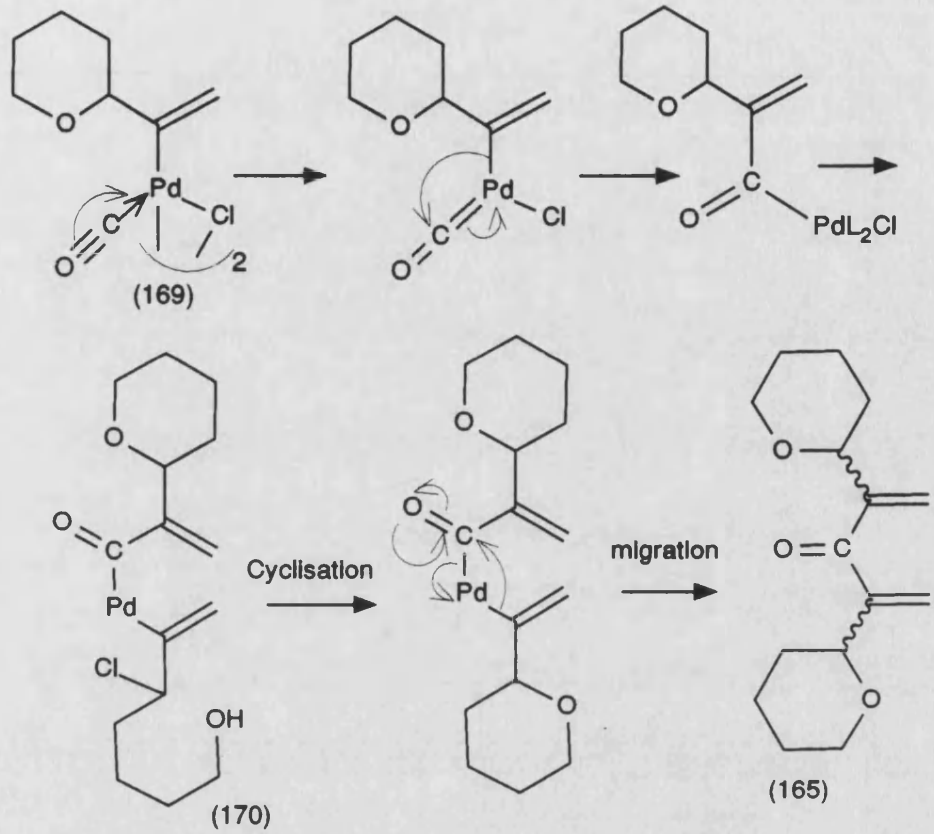
The fate of the cyclic vinyl palladium species (168) depends on the reaction conditions. If methyl acrylate is used, the vinyl palladium (168) forms a complex with the π-bond of the methyl acrylate followed by ligand migration and β-hydrogen elimination to give (166).



If MeOH and CO are absent, (168) can form a complex with the π-bond of another allene-containing molecule to induce a second cyclisation which after ligand migration gives (164).



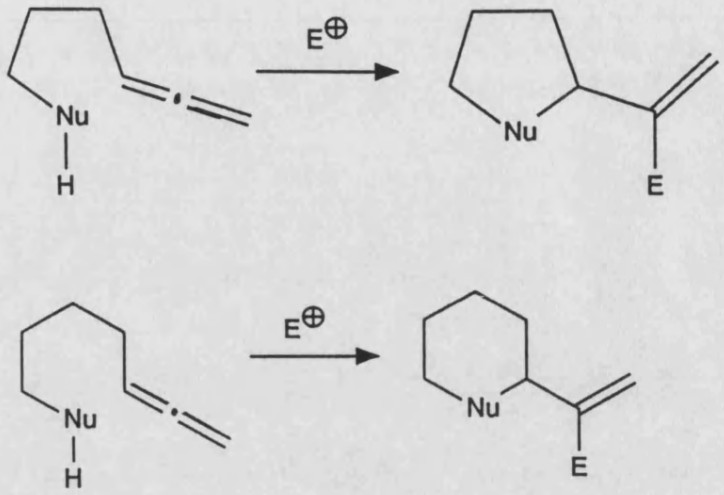
In the absence of MeOH, (168) can react with CO to give a complex (169) which can then complex with the π-system of another allenic alcohol to form (170). After inducing a second cyclisation, ligand migration could lead to the ketone (165).



Conclusion

We have been able to demonstrate the flexibility of the Ag(I) activation of the allene moiety to induce heterocyclisation involving a range of either nitrogen or oxygen nucleophiles. The nature of the counterion ($NO_3^{\ominus}$, $BF_4^{\ominus}$ or $SO_3CF_3^{\ominus}$) for Ag(I) appears to have little effect on the cyclisation processes leading to five-membered nitrogen-containing heterocycles. There is, however, a considerable difference between the rate of cyclisation of γ- and δ-N-benzyloxycarbonyl allenes, with the former being much more efficient. The difference between five- and six-membered ring formation containing the cyanohydrin group is even more marked, with only five-membered rings being formed at a synthetically useful rate.

The $Br^{\oplus}$-induced ring formation of nitrogen-containing five- and six-membered rings showed a similar pattern to the silver(I)-induced cyclisations. In a similar fashion the δ-hydroxyallenes readily cyclised to give tetrahydropyrans. The $PhSe^{\oplus}$-mediated cyclisation was ,however, limited to γ-allenic imidates.



5-MEMBERED RINGS			6-MEMBERED RINGS		
$E^{\oplus}$ Nucleophile	Yield	Rate	$E^{\oplus}$ Nucleophile	Yield	Rate
Ag Nitrogen*	High	Fast	Ag Nitrogen*	High	Slow
Br Nitrogen*	Med.	Slow	Br Nitrogen*	0	-
Se Imidate	Med.	Fast	Se Nitrogen*	0	-
Ag Cyanohydrin	Med.	Med.	Ag Cyanohydrin	0	-
			Ag Alcohol	High	Fast
			Br Alcohol	Med.	Med.
Nitrogen*=amine/carbamate			Se Alcohol	0	-
			Pd Alcohol	High	Fast
			Pd Hemiacetal	Low	Fast

The Pd(II)-mediated cyclisation of δ-allenic alcohols under a range of carbonylating and non-carbonylating conditions always gave cyclic products though in low yields. These reactions do, however, offer a significant level of synthetic value in terms of the level of functionality available in the heterocyclic products.

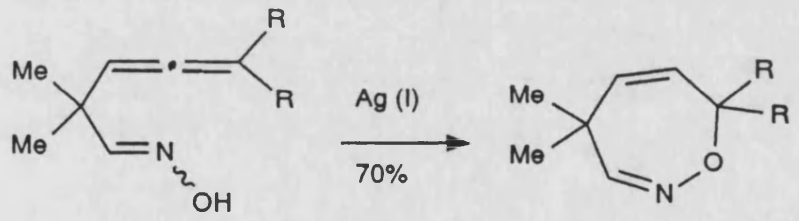
Formation of Medium and Large Rings by Electrophile-Mediated Cyclisation

Background

Before describing our attempts towards the synthesis of medium and large rings by cyclisations involving an activated allenic moiety by internal nucleophilic attack, the prior art for similar cyclisation methodology will be briefly reviewed.

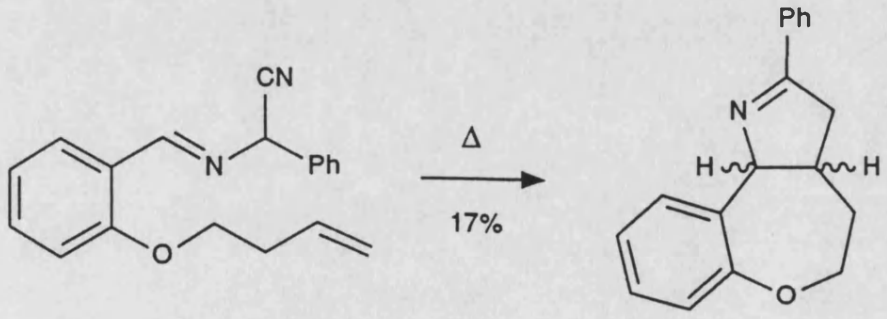
The only Ag(I)-mediated medium ring cyclisation to date was reported by Grimaldi et al[65] (Scheme 102). The scope of this process is somewhat limited, since the gem-dimethyl moiety was present in all cases reported, though it is not clear that this substitution pattern is necessarily required.

Scheme 102



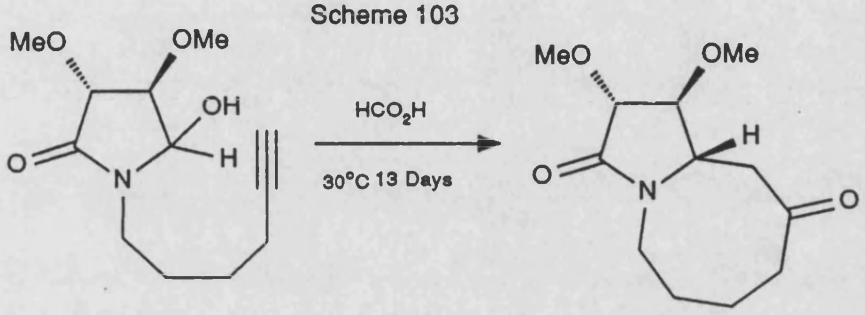
R = - $(CH_2)_5$ - , H, Me, Et.

The intramolecular cyclisations of an azomethine ylide onto alkene to produce seven-membered rings was reported by Tsuge[17c]. Grigg[17d] has also reported a similar cyclisation to give an oxepane in 20% yield. These low yields probably reflect the unfavourable entropy of seven-membered ring closure.

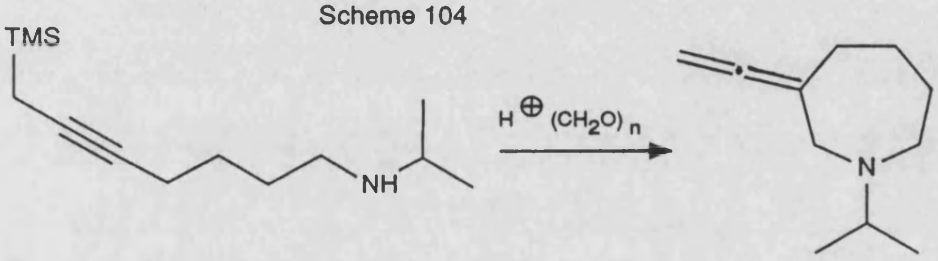


The use of an α-acyliminium-alkyne cyclisation to form an eight-membered ring was reported by Speckamp[99] and Miginiac reported a similar cyclisation in 1987[100] (Schemes 103 and 104).

Scheme 103

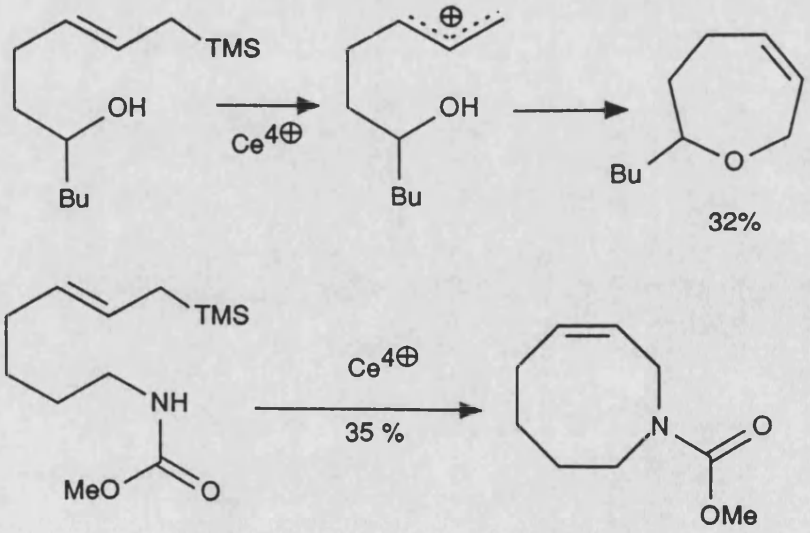


Scheme 104

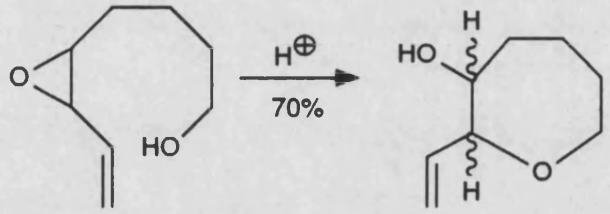


The Ce(IV)-mediated oxidative ring closure[101] of allylsilanes led to oxepanes and azocines, via an allyl cation intermediate (Scheme 105).

Scheme 105

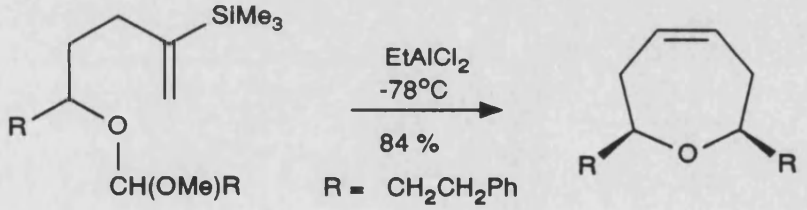


A more efficient epoxide ring opening route to form the larger of the two possible cyclic products, which proceeds via an allyl cation, has been developed by Nicolaou[102].



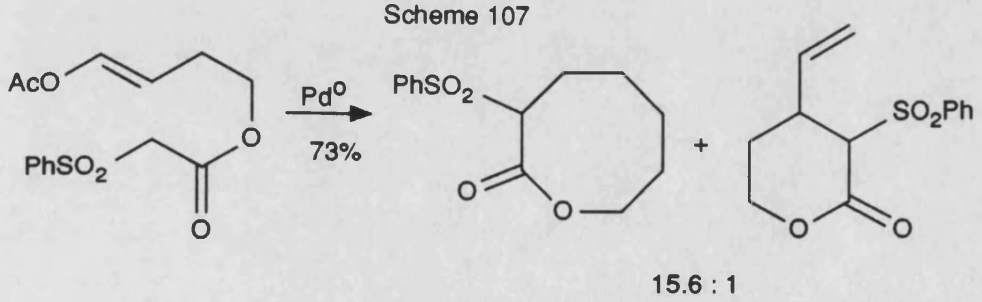
Overman's investigation[103] of the Lewis acid-promoted cyclisation of mixed acetals to form seven-membered cyclic ethers, involved an oxonium cation intermediate (Scheme 106).

Scheme 106



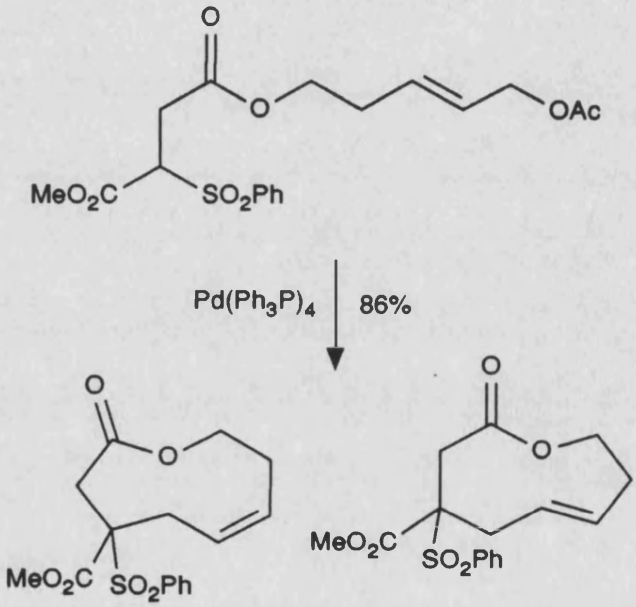
Since Trost's work[104] on the synthesis of macrolides by palladium-induced cyclisation in 1977, his group has extended this methodology and in 1979 they reported[105] the preference of palladium-catalysed cyclisations for the larger of the two possible ring sizes (Scheme 107).

Scheme 107



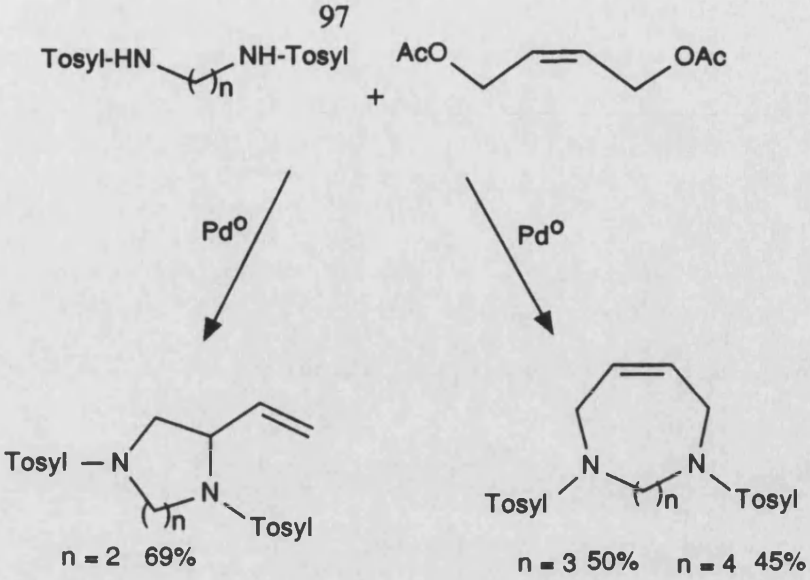
These studies revealed the preference for the formation of 16-, 14-, 12- and 10-membered rings over the possible alternative 14-, 12-, 10- and 8-membered rings respectively. Also 9- and 8-membered lactone formation was preferred to the formation of the corresponding 7- and 6-membered rings.

Scheme 108



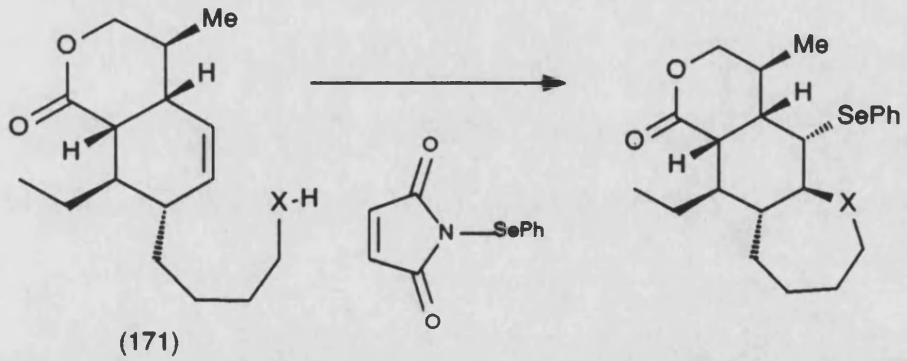
In the reaction depicted in scheme 108 Trost achieved a ratio of 11.5:1 for Z:E double bonds which is to be expected because of the strain in the (E)-isomer. This was in accordance with the acid-catalysed isomerisation of cis/trans double bonds[106], the equilibrium constant was $K_{cis/trans}$ 232 for cyclononene. When the double bond was substituted with a methyl group the equilibrium constant $K_{cis/trans}$ was $>5x10^3$.

Recently, the palladium(0)-catalysed reaction of bifunctional nitrogen-based nucleophiles with bifunctional allylic diacetates has been reported[107]. The number of methylene groups between the two nitrogens in the nucleophile was found to dictate the size of ring formed. When n=2 the smaller, six-membered ring only was formed, but when n=3 or n=4 the larger of the possible rings was obtained exclusively.



Kozikowski[108] has also examined the use of more closely-related electrophile-mediated cyclisations in the synthesis of medium rings. Although the alcohol (171, X= O) underwent cyclisation with N-(phenylseleno)phthalimide, the related carbamate derivative (171, X= NCO_2Et) failed to give a cyclic product (Scheme 109).

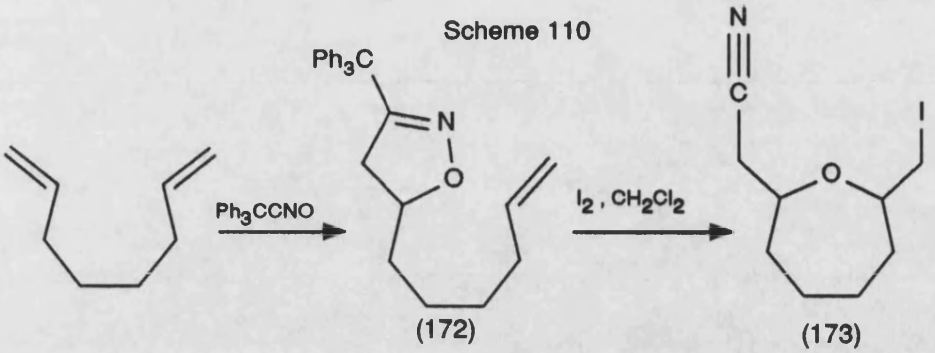
Scheme 109



(171)

Recently, an iodine-induced cyclisation procedure for the formation of oxepanes was reported by Kurth[109]. The isoxazoline (172) was readily prepared from triphenylacetonitrile oxide and a 1,7-diene. The treatment of this intermediate with iodine gave the disubstituted oxepane (173) in 80% yield. Smaller rings were also prepared, but attempts to extend the reaction to larger rings failed (Scheme 110).

Scheme 110



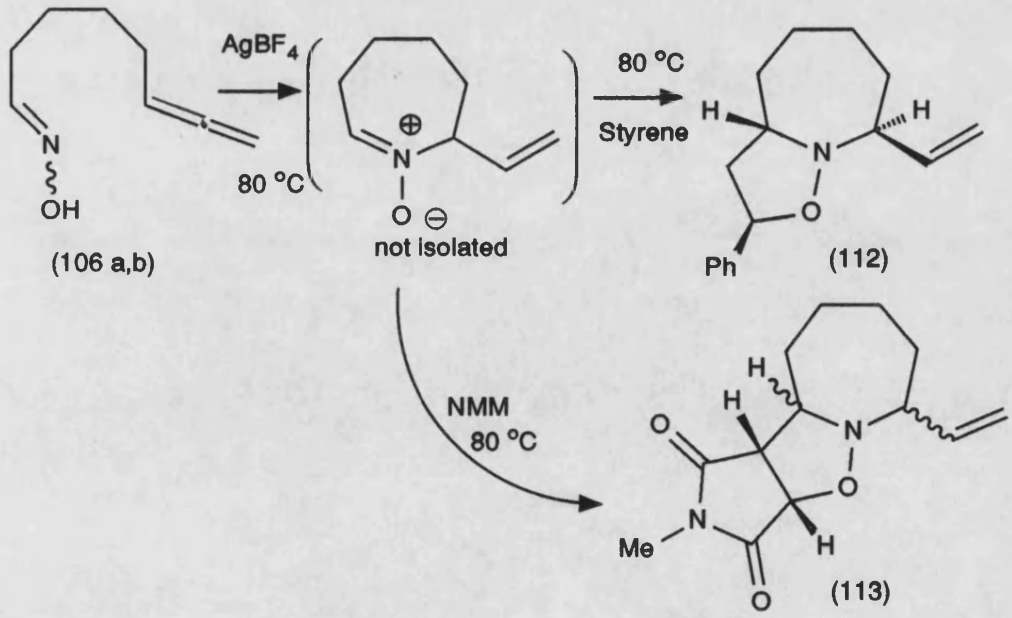
(172) (173)

Studies with Allenic Systems

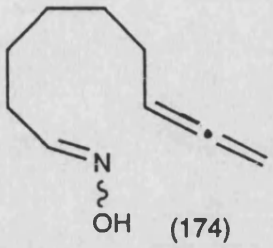
Silver(I)-Mediated Cyclisations

As previously described the Ag(I)-induced cyclisation of the oxime (106) gave the unstable seven-membered ring nitrone, which was trapped efficiently with N-methylmaleimide to give cycloadduct (113) or with styrene to give (112)(Scheme 80).

Scheme 80



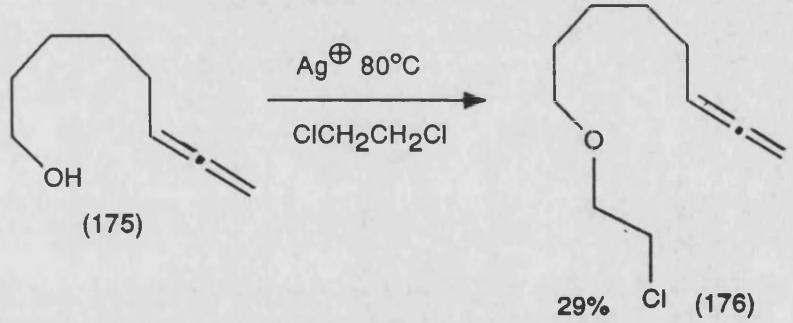
This process is nevertheless limited, and no cyclic products could be isolated from the analogous reaction involving (E) or (Z)-nona-7,8-dienal oxime (174).



(174)

Other approaches to the synthesis of medium/large rings based on Ag(I)-mediated cyclisations involving allenic substituents have also been investigated. The allenic alcohol (175) failed to react with Ag(I) at room temperature, but on heating at 80°C in 1,2-dichloroethane gave (176) as the only isolable product, resulting from O-alkylation by the solvent (Scheme 111).

Scheme 111



(175)

29% (176)

Barriers to the formation of medium/large N-containing rings have also been encountered. When N-tosyl deca-8,9-dienylamine (177) was stirred at room temperature with one equivalent of Ag(I), no reaction was observed (by tlc and ^{1}H NMR) after two weeks. In an effort to overcome the barrier to such medium ring cyclisation, we investigated the possible templating effect of side chains; this also allowed us to extend asymmetric synthesis to functionalised azepanes via a range of allenic chiral amines (178 a,b,c). These compounds failed to react with Ag(I) at room temperature after one week, but at 80°C small amounts of cyclic products (179 a,b) were produced (Table 8).

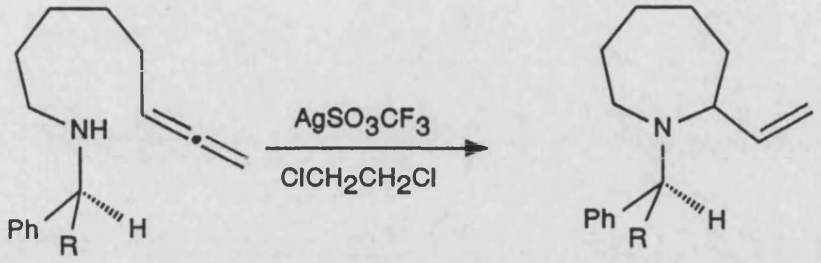


Table 8

(178) R	Temp/°C	Time/h	(179) Yield % *	Ratio **
a CONHMe	80	64	a 7	5:1
b CO_2Me	80	60	b 1	1:1
c CH_2NHMe	80	100	c 0	-

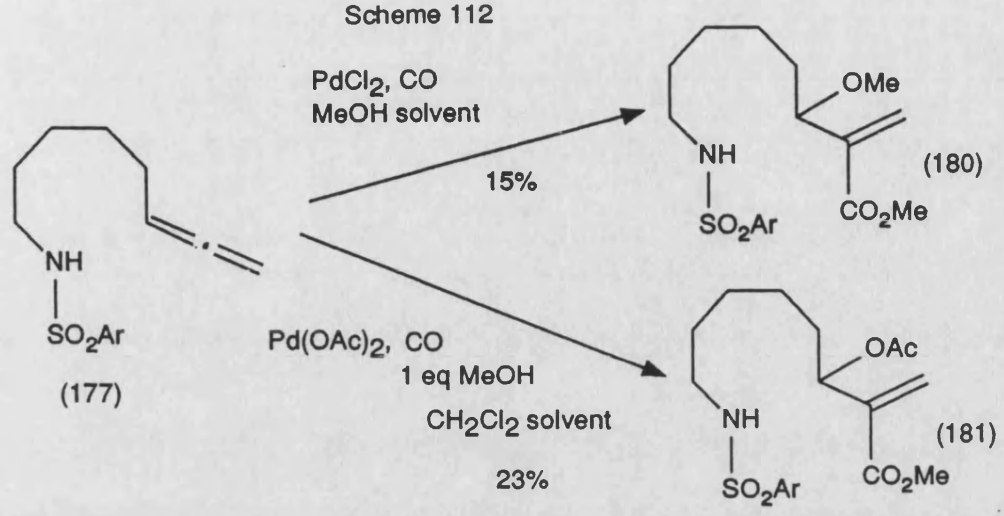
* isolated yields, after chromatography

** relative stereochemistry of the major product not determined

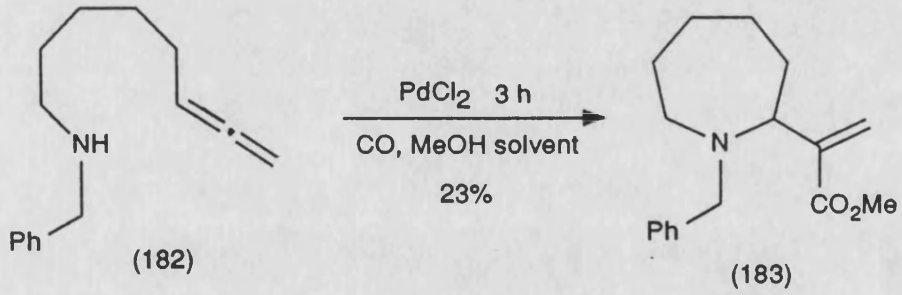
Palladium(II)-Mediated Cyclisations

We next briefly examined the Pd(II)-mediated medium ring cyclisations, but once again the initial results were disappointing. Attempted cyclisation of the sulphonamide (177) with palladium chloride under cabonylating conditions in the presence of an excess of methanol, resulted in carbonylation of the allenic residue and attack of the methanol leading to (180), instead of the anticipated intramolecular reaction. When palladium acetate was used together with only one equivalent of methanol, addition of palladium acetate across the π-bond of the allenic residue occurred, followed by carbonylation, and adduct (181) was isolated (Scheme 112).

Scheme 112



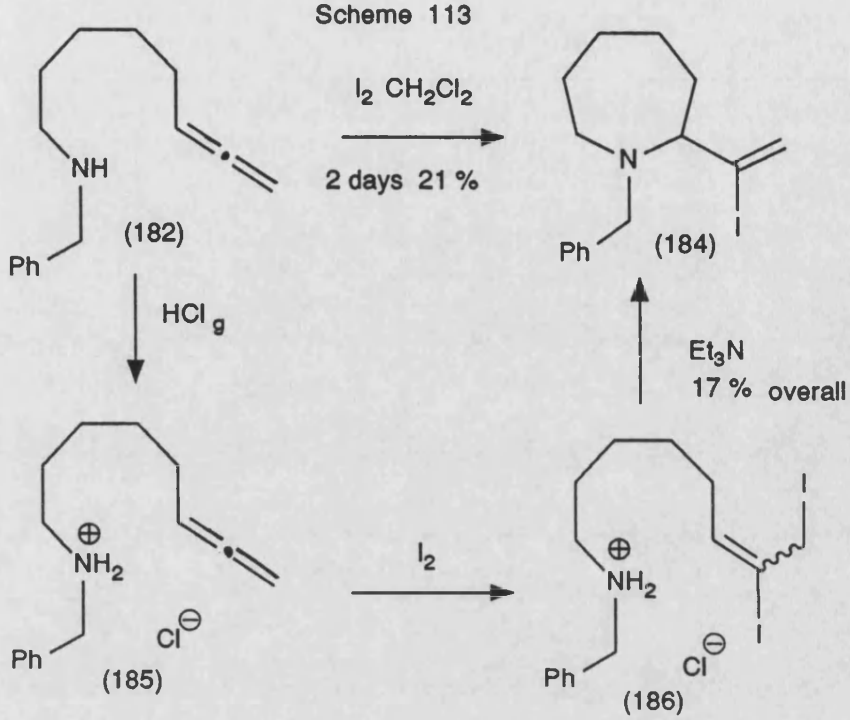
Sulphonamides clearly represent deactivated nucleophiles and we have also examined the role of more nucleophilic amines, in this context the N-benzyl allenic amine (182) was cyclised under carbonylating cyclisation conditions to give (183) in 23% isolated yield.



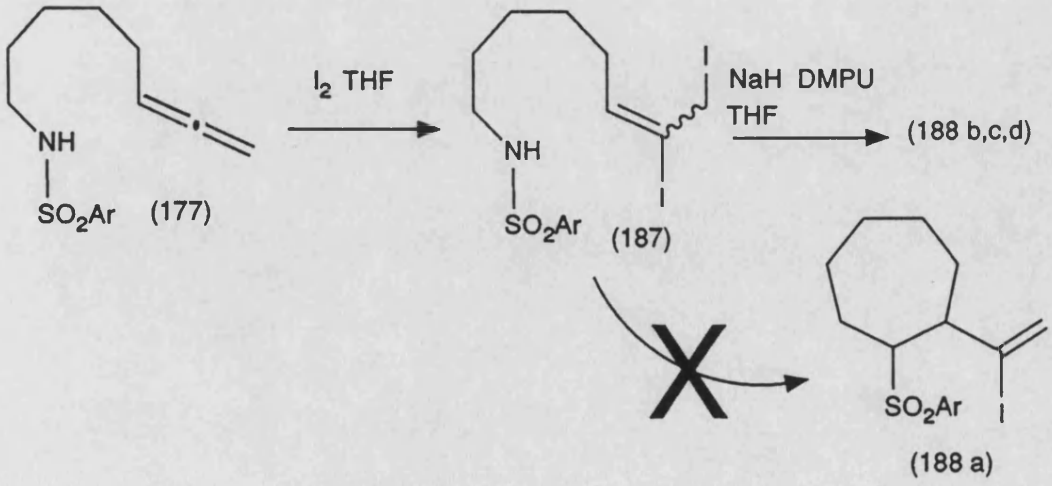
Iodine-Mediated Cyclisations

Other conditions for medium ring formation have also been examined. When the N-benzyl allenic amine (182) was treated with iodine, addition across the double bond rapidly occurred followed by slow cyclisation to give (184) in 21% yield (Scheme 113). In an effort to improve this yield, the nitrogen nucleophile was first protected as the hydrochloride salt (185) which was then treated with iodine to give (186). On treatment with triethylamine, however, the poor cyclisation step limited the overall yield to only 17% (Scheme 113).

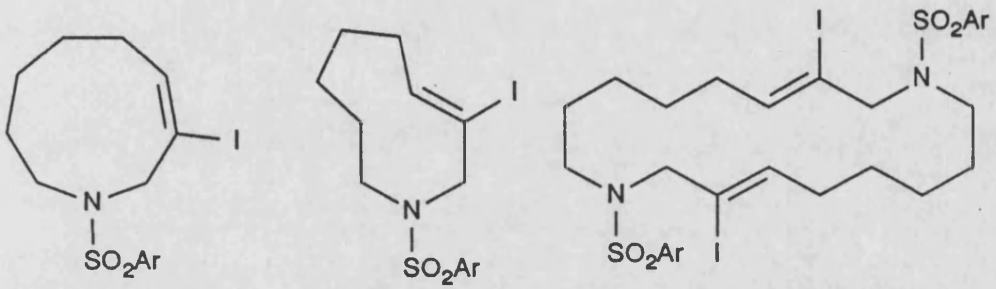
Scheme 113



The simple addition of iodine across the terminal double bond of N-tosyl allenic amine (177) occurred readily to give a mixture of (E)- and (Z)-isomers (187), but failed to induce direct cyclisation. When this N-tosyl amine (187) was deprotonated with sodium hydride, cyclisation occurred slowly to give three products in approximately equal amounts in 56% combined yield. Surprisingly, none of these products had the expected acyclic double bond as had been anticipated for the conventional mode of cyclisation leading to (188 a).



The three products from this reaction were identified as (188 b,c,d) (see later for evidence):



1 : 1 : 1 (188 b : c : d)

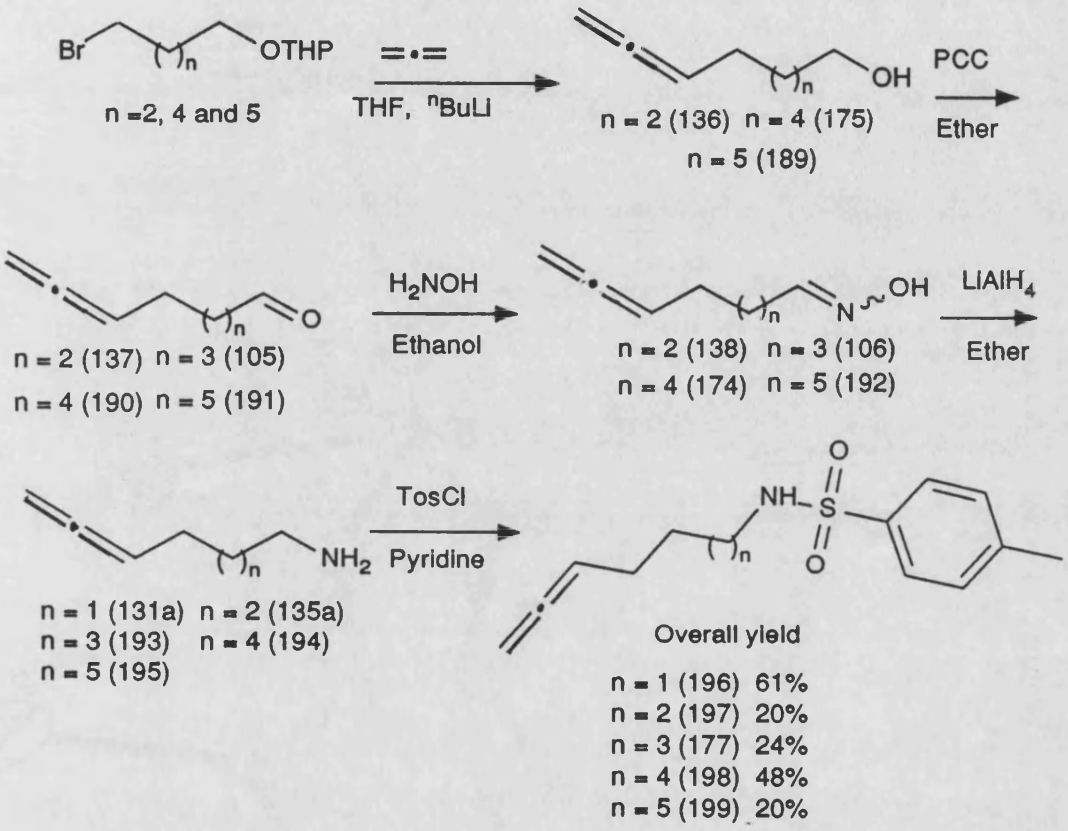
Even with the literature precedent for larger ring cyclisation selectivity (p.95), the above result is surprising, and warranted further investigation. The ratio of (E)- to (Z)-isomers is also surprising. In view of the steric bulk of the iodine in (188 b,c,d), the (Z)-isomer would be expected to be considerably less favourable than the (E)-isomer.

We have explored the scope of this macrocyclisation process and a range of N-tosyl allenic amines (177,196-199) were prepared. This involved either alkylation of lithioallene with protected ω-bromoalcohols ($Br(CH_2)_nOTHP$, n = 4, 6 and 7), followed by deprotection, oxidation (PCC), oxime formation and reduction ($LiAlH_4$) to give the allenic amines (135 a,194,195) or by simple homologation procedures, (131a,193) and were all converted to their corresponding sulphonamides (177,196-199) using TosCl/ pyridine (Scheme 114).

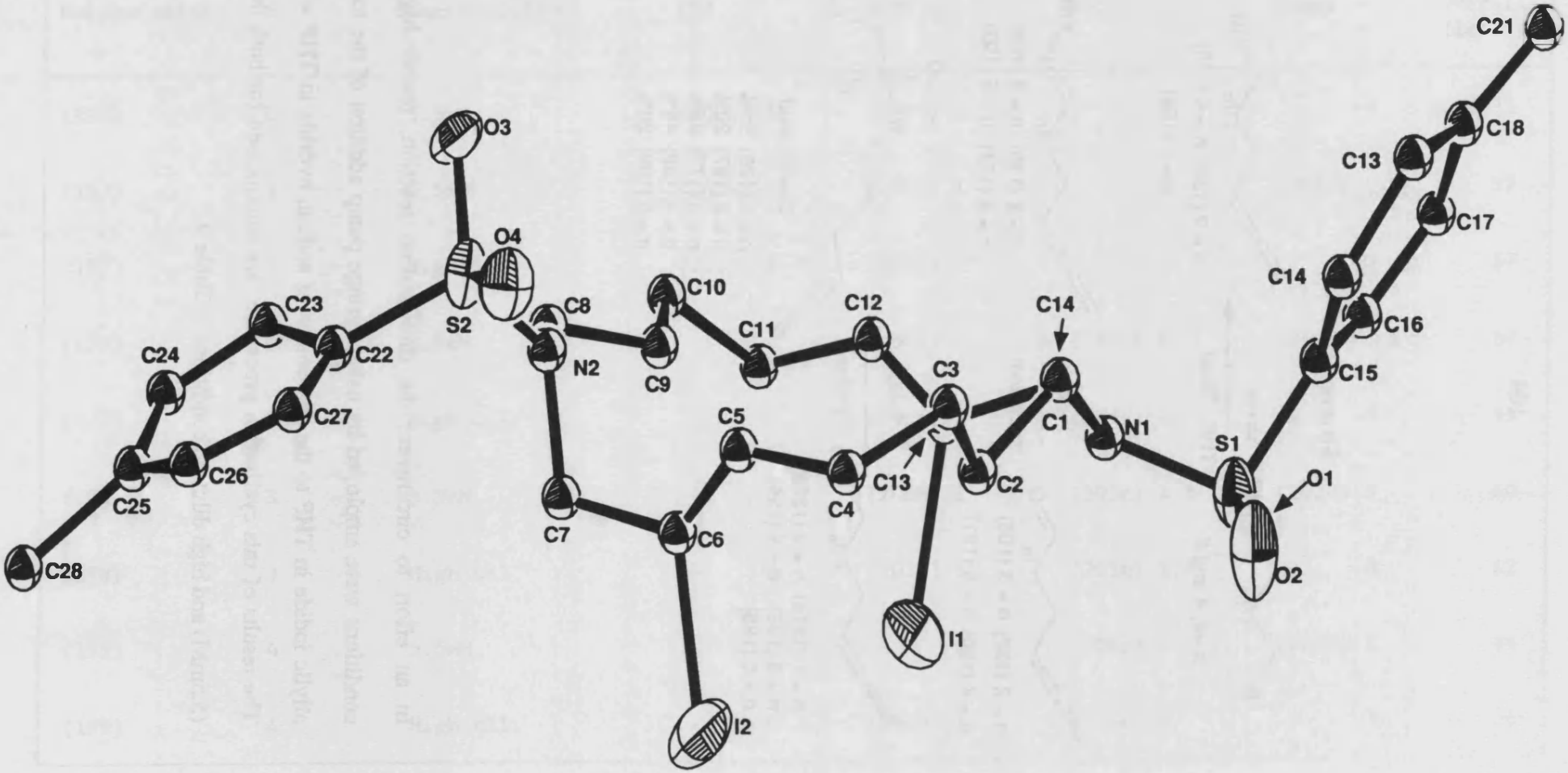
Table 9

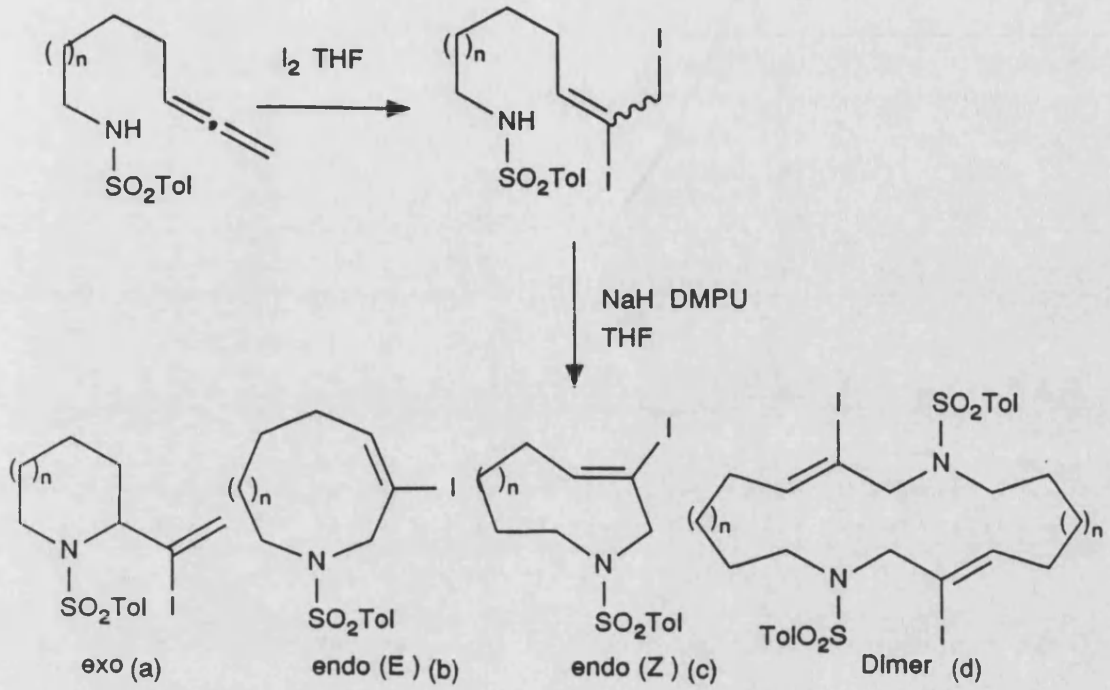
Sulphonamide	n	Concentration	RATIO EXO	Endo E	Endo Z	Dimer	Overall Yield (%)
(196)	0	5.5mM	(200a) 8	(200b) 1	- 0	- 0	93
(197)	1	5.5mM	(201a) 1	(201b) 1	- 0	(201d) 1.3	57
(197)	1	High dil.	(201a) 1	(201b) 1	- 0	- 0	57
(177)	2	5.5mM	- 0	(188b) 1	(188c) 1	(188d) 1.1	56
(177)	2	High dil.	- 0	(188b) 1	(188c) 1	- 0	55
(198)	3	5.5mM	- 0	(203b) 1	(203c) 1.5	(203d) 5	60
(198)	3	High dil.	- 0	(203b) 1	(203c) 1.4	- 0	62
(199)	4	5.5mM	- 0	- 0	(204c) 3	(204d) 1	39
(199)	4	High dil.	- 0	(204b) 1	(204c) 3	- 0	35

Scheme 114



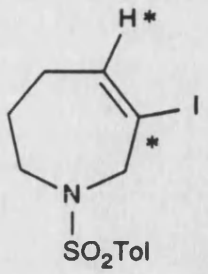
In an effort to circumvent the dimerisation reaction, psuedo-high dilution conditions were employed by using syringe pump addition of the intermediate allylic iodide in THF to the suspension of sodium hydride in THF and DMPU. The results of this cyclisation procedure are summarised for both the standard (5.5mM) and high dilution conditions in Table 9.


C21
C18
O3
C13
C17
O4
C14
C16
C23
S2
C8
C10
C12
C14
C11
C24
C22
N2
C9
C3
C15
C5
C1
N1
S1
C27
C26
C13
C2
O1
C25
C4
C7
C6
O2
C28
I1
I2

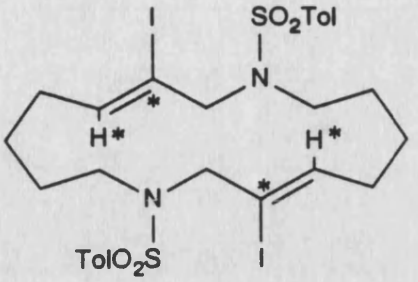


(E and Z)-Structural Assignment of the Cyclic Products (188,200-204)

From X-ray crystallographic analysis[110](Figure 1) the structure of 16-ring dimer (201 d) was unambiguously determined and the double bond was found to have a (Z)-geometry. By comparing both the chemical shifts of the olefinic proton and that of the alkenyl cabon atoms in the 7-membered ring (200 b), where the double bond can only exist in (E)-geometry (due to the severe strain involved in the (Z)-geometry) and the chemical shifts in the 16-ring dimer, we have tentatively assigned the configuration for the double bond in the other isomers. All the chemical shifts of the olefinic protons for the (E)-isomers were within the range δ_H(6.44-6.35) and the carbon shifts were within the range δ_C(96.6-87.4). Whereas most of the corresponding shifts for (Z)-isomers were within the range δ_H(5.92-5.74) and δ_C(102.0-99.8), the two exceptions were the proton signals for the compounds (203 c) and (204 c) which were outside the appropriate range, but were within the (Z)-isomer ^{13}C range .



200b endo (E)

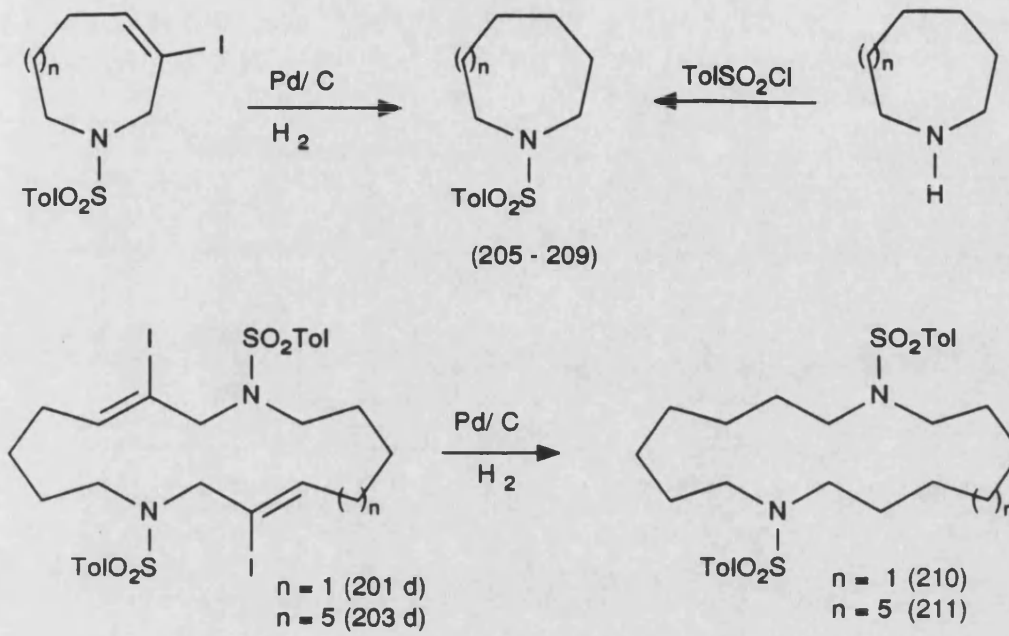


(201d) Dimer

	Ring Size	Chem.Shift δ_H*	δ_C*	Bond	Comments
(200 b)	7	6.35	-	E	Ring too small for Z-bond
(201 b)	8	6.44	96.6	E	NMR data
(188 b)	9	6.38	94.5	E	NMR data
(188 c)	9	5.87	99.8	Z	NMR data
(203 b)	10	6.42	94.8	E	NMR data
(203 c)	10	6.31	99.8	Z	^{13}C NMR data
(204 b)	11	6.35	87.4	E	NMR data
(204 c)	11	6.10	102.0	Z	^{13}C NMR data
Dimers					
(201 d)	16	5.90	104.6	Z	X-ray structure
(188 d)	18	5.74	-	Z	^{1}H NMR data
(203 d)	20	5.92	103.4	Z	^{1}H NMR data
(204 d)	22	5.80	-	Z	^{1}H NMR data

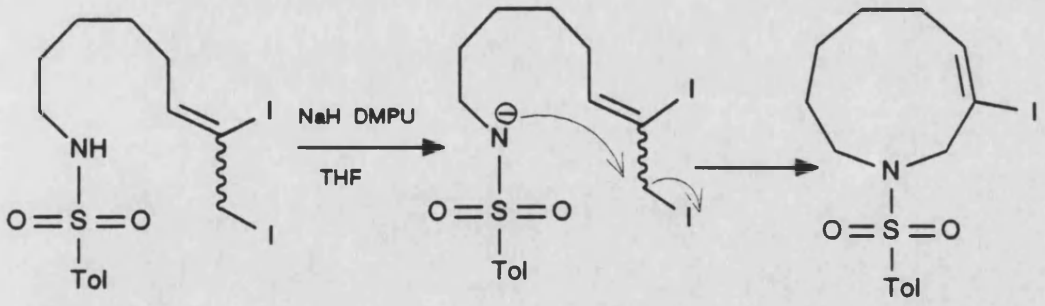
Cleavage of the iodo residue and reduction of the double bond was achieved (H_2, Pd/C) leading to the fully-reduced macrocycles (205-211), which proved to be identical with authentic samples prepared by a literature procedure[111,112] (mixed melting points, ^{1}H NMR, IR and mass spectra)(Scheme 115).

Scheme 115



Possible Mechanism of the Larger Ring Formation

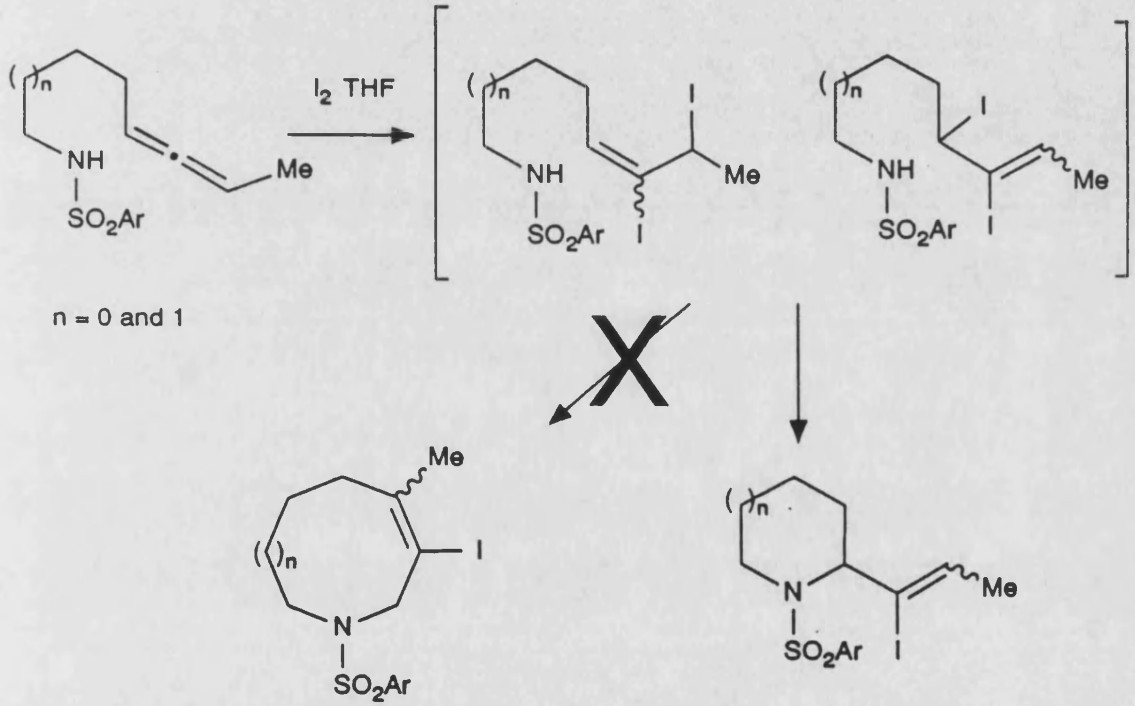
A possible mechanism for the unexpected larger ring formation could be via a straightforward displacement of the allylic iodide.



Due to time constraints, a more complete investigation of this direct displacement process was not undertaken, but a co worker[113] has probed this reaction in some detail. This mechanistic study was to see if the larger ring formation previously observed, was due the to the preferential attack of the nitrogen nucleophile at a primary centre, rather than at a secondary centre. By

investigating the iodine-induced cyclisation of 1,3-disubstituted allenic sulphonamides, where the nucleophilic displacement could only take place at a secondary centre, we hoped to see if the ring size would be effected. The cyclisation to form 5 vs 7 and 6 vs 8-membered rings was studied. The non-selective addition of iodine across the allenic residue, was followed by cyclisation to form exclusively the smaller of the two possible rings (Scheme 116).

Scheme 116



The rate of nucleophilic substitution (S_N2) using lithium azide at a primary allylic bromide (3-bromo-3-methyl-1-p-tolylsulphonyl-1-1butene) has been shown to be 2.9 times faster than the S_N2 reaction at the corresponding secondary allylic centre[114]. Although this rate difference is probably not large enough to fully compensate for the unfavourable entropy in the formation of the larger rings, it may be significant if other factors are taken in to account in the large ring formation. The unfavourable entropy for the larger ring formation is

shown by the relative rate constant at 40°C for the base-induced cyclisation reaction[115] where n = the ring size (Table 10)

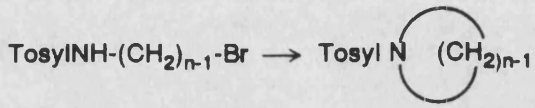
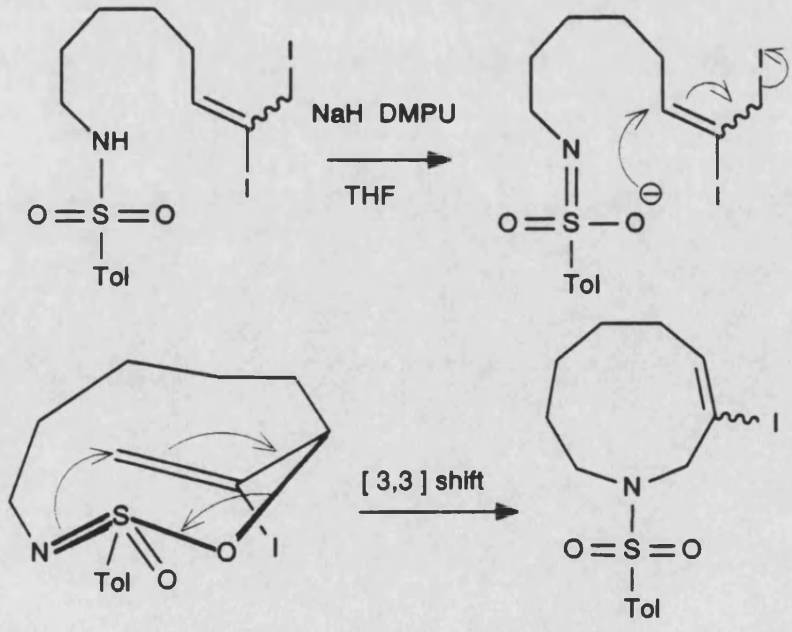


Table 10

Ring size n	relative rate
4	1
5	2.0×10^{4}
6	390
7	2.2
8	3.4×10^{-2}
9	1.5×10^{-3}
10	5.0×10^{-4}
11	2.1×10^{-3}

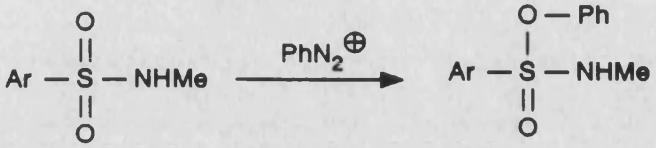
An intriguing alternative mechanism could involve initial O-alkylation (rather than N-alkylation) of the sulphonamide and a subsequent [3,3] rearrangement (Scheme 117).

Scheme 117



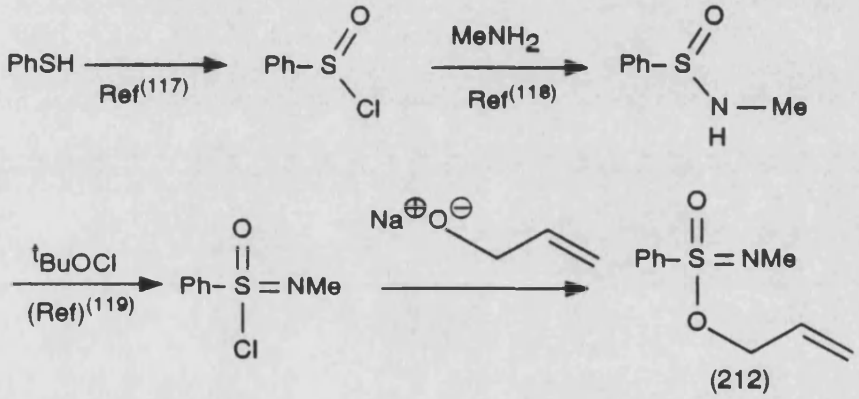
O-Arylation of a sulphonamide has been observed by Challis et al[116] (Scheme 118), though reports of O-alkylation of sulphonamides are very limited.

Scheme 118



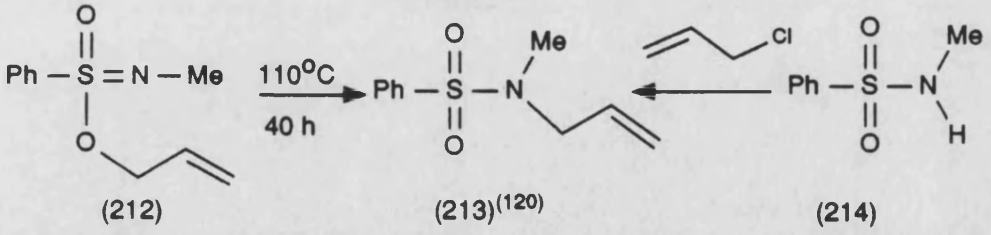
The feasibility of such a novel [3,3] rearrangement was examined with some simple related systems. The synthesis of the sulphonimidate (212) was accomplished via known chemistry from thiophenol (Scheme 119).

Scheme 119



On heating (212) at 110°C for 40 h it underwent rearrangement to give (213) in quantitative yield (Scheme 120).

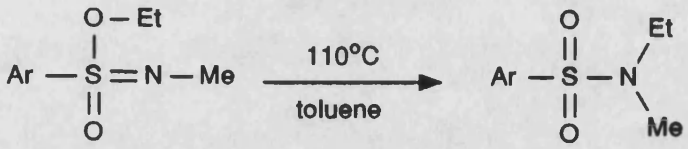
Scheme 120



An authentic sample of (213) was prepared via N-allylation of sulphonamide (214).

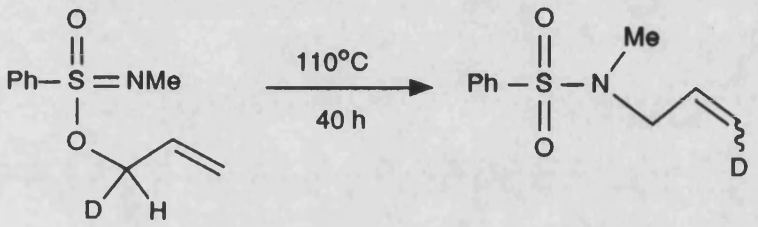
Challis[116] has previously demonstrated the migration of an ethyl group from oxygen to nitrogen in a related structure which had a $t_{\frac{1}{2}}$ of ca 20 days at 110°C (Scheme 121).

Scheme 121



Although our reaction proceeded considerably faster than this simple migration reaction, we could not rule out this migration mechanism. To confirm our model reaction was indeed a [3,3] rearrangement, the deuterated-propenyl derivative (215) was prepared and heated at 110°C for 40 h (Scheme 122).

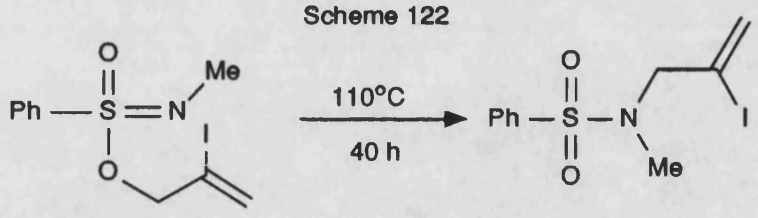
Scheme 122



(215) (216) 100 %

The quantitative formation of (216) proved this reaction was not a simple O-N migration, but a [3,3] rearrangemen. Similarly, the bulky vinyl iodide (217) was heated at 110°C for 40 h and after rearrangement gave (218)(Scheme 122).

Scheme 122



(217) (218) 10 %

The iodine did not greatly effect the rate of reaction but at 110°C a considerable amount of decomposition took place.

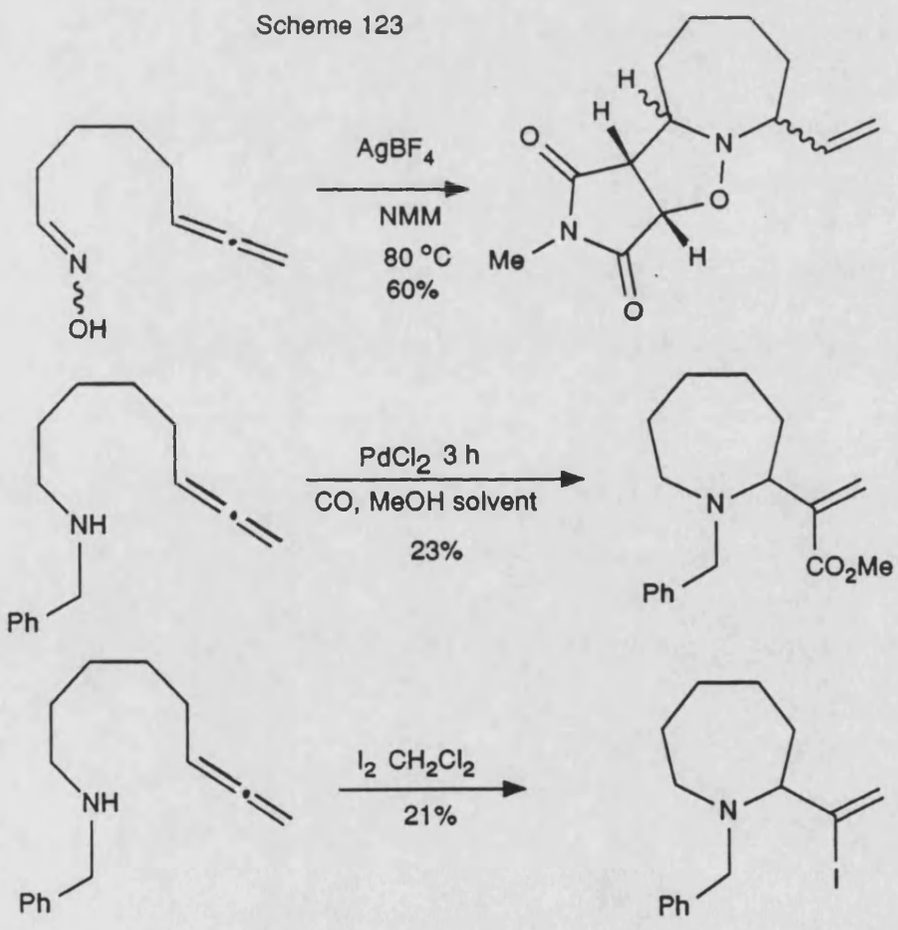
The obvious problem associated with our speculative mechanism, is the rate of cyclisation (25°C, 16 h) for the large ring in comparison with the model studies (110°C, 40 h). It can be envisaged that the adjacent ring could hold the atoms

involved in the [3,3] rearrangement in the correct position, therefore enhancing the rate considerably (Scheme 116), but we would need to establish the feasibility of this mechanism by an unambiguous synthesis of the O-alkylated intermediate shown in scheme 119. On balance, the reaction is more likely to be proceeding via a straightforward displacement of the allylic iodide, but the possibility of achieving O to N migration under mild conditions does offer a number of other synthetic opportunities.

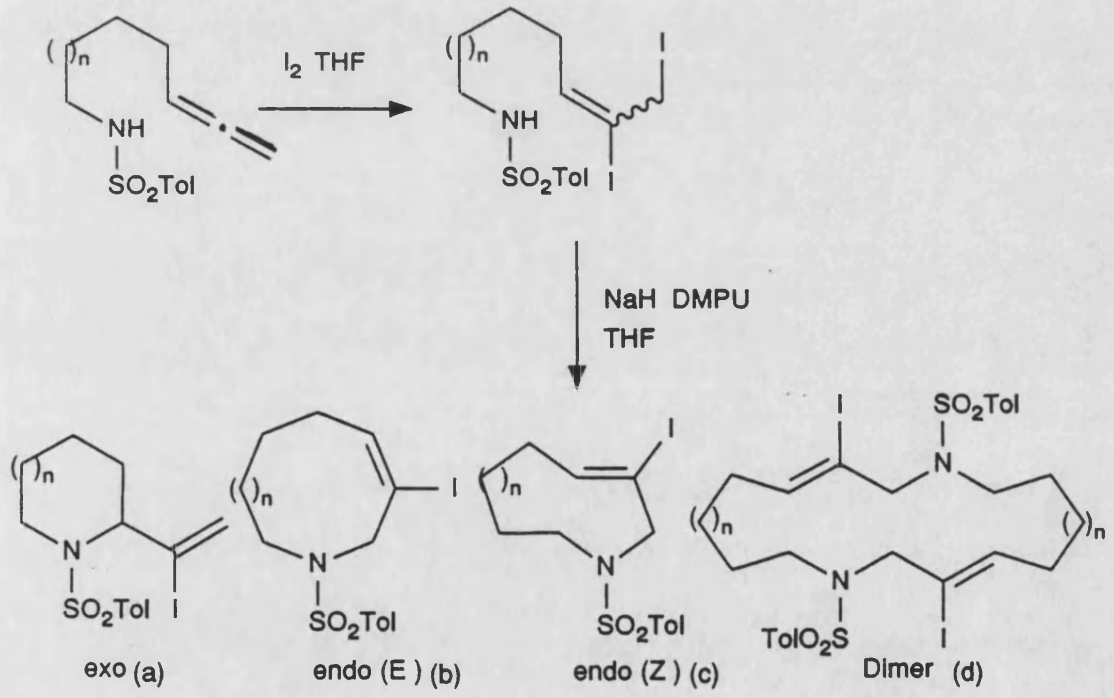
Conclusion

The formation of medium size rings via nucleophilic attack onto an activated allene moiety was successfully demonstrated using three different electrophiles ($Ag^{\oplus}$, $I^{\oplus}$, $Pd^{2\oplus}$), but only with specific nucleophiles (Scheme 123).

Scheme 123

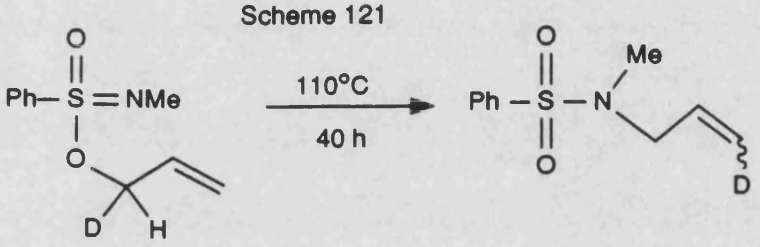


The main achievement of our investigations into routes for medium/large ring heterocyclisations, was the discovery of a two-step cyclisation of allenic sulphonamides. The addition of I_2 to N-sulphonyl allenic amines (177, 196-199) gave allylic iodides. Under pseudo-high dilution conditions deprotonation of these sulphonamides resulted in exclusive or predominant formation of the larger of the two possible ring sizes. The exception to this selectivity was (200a, n=0), where the smaller (five-membered) ring formation was preferred. This methodology has allowed us to gain access to 8-11-membered azacycles in reasonable yields. Under more concentrated conditions the 16, 18, 20 and 22 ring dimers were obtained along with the monomers.



The mechanism of such cyclisations was briefly explored and O-alkylation, followed by a novel [3,3] rearrangement cannot be ruled out. This rearrangement was demonstrated in simple cases to be very efficient (Scheme 121).

Scheme 121



(215) (216) 100 %

This large ring selectivity may be associated in some way with the nature of the sulphonamide group, since cyclisation of the N-benzyl compound (182) gave exclusively the smaller seven-membered ring (184) and none of the alternative nine-membered analogue.

EXPERIMENTAL

Instrumentation and Experimental Techniques

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1310 grating spectrophotometer and peaks are reported (υ_{max}) in wavenumbers (cm^{-1}). The abbreviation "br" is appended to a peak to indicate significant broadening. Spectra of liquid samples were taken as thin films on sodium chloride plates. Spectra of solid samples were taken as nujol mulls.

Routine mass spectra were obtained in the chemical ionisation mode (ci), with methane as reagent gas. Mass spectra were also obtained in the electron impact mode (ei) with an ionizing potential of 70eV and with low ionizing potential (Low eV ei) where appropriate (variable ionizing potential in the range 5-30 eV). These along with high resolution accurate mass determinations in the (ci) mode were recorded with a Finnigan MAT 90, Finnigan MAT 450 and an analytical 7070E instrument and a VG2000 data system.

Proton magnetic resonance (^1H nmr) spectra were routinely recorded at 300MHz, on a General Electric Company Nicolet QE300 or a Jeol GNM GX FT 270 spectrometer. Spectra were also obtained on a Bruker AM 360 MHz machine. Carbon 13 magnetic resonance (^{13}C nmr) spectra were recorded on the same machines.

Proton and ^{13}C nmr spectra were recorded, unless otherwise stated, in $CDCl_3$, and are expressed in parts per million (δ) downfield from internal tetramethylsilane.

Melting points (m.p.) were determined on commercially available apparatus (Gallenkamp) and are uncorrected. Elemental microanalyses were carried out using a Carlo Erba 1106 Elemental Analyser.

Thin layer chromatography (TLC) was used extensively as a qualitative guide

during reactions and for assessing the purity of compounds. Merck pre-coated TLC plates silica gel 60 F_{254} containing fluorescent indicator were used for this purpose. Visualisation of reaction components was achieved by illumination under short wavelength (254 nm) ultraviolet light (when possible) or using a reagent (typically a 7% (w/v) solution of dodeca-molybdophosphoric acid in methanol) that would give a colour change with the functional groups present, as described in "Dyeing Reagents for Thin Layer and Paper Chromatography", E. Merck, Darmstadt, 1980.

Medium pressure flash column chromatography was routinely employed using Kieselgel 60 (Merck 9385) (flash). Nitrogen gas was used to apply a pressure of up to 0.5 Kg/cm^2 and in all cases columns were prepared in the least polar solvent of the elutant mixture and chromatography was carried out with the least polar solvent as initial elutant, then eluting with solvent mixtures of steadily increasing polarity. Material to be chromatographed was preadsorbed onto the column support and applied as a thin layer to the top of the column. Preparative thin layer chromatography was performed using Merck 60 F_{254} silica gel, glass supported plates.

Unless otherwise stated petrol refers to that fraction of petroleum spirit boiling in the range 40-60°C.

Glassware used for water sensitive reactions was baked in an oven at 120°C for approximately 12h and allowed to cool in a desiccator over $CaCl_2$. In all experiments the excess solvent was removed with a Büchi rotary evaporator using a water aspirator at room temperature (unless otherwise stated) to avoid unnecessary decomposition. All yields quoted are of purified products and are uncorrected unless otherwise stated.

All other reagents and solvents were purified and dried, when required, according to accepted procedures.[121]

Methyl N-(1-cyanohepta-5,6-dienyl)glycinate (86)

Methyl glycinate. HCl (0.57 g, 4.5 mmol) in water (1.5 ml) was added to a solution of KCN (0.3 g, 4.5 mmol) in water (1.5 ml). Hepta-5,6-dienal (0.5 g, 4.5 mmol) in methanol (2 ml) was then added dropwise to this ice cold solution. The reaction mixture was stirred at room temperature for 16 h, and then diluted with ether (20 ml) and the resulting mixture extracted with ether (3 x 10 ml). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified to give, on elution with petrol-ether (3:2), (86) (0.36 g, 40%) as a colourless oil (Found: M^++H, 209.126. $C_{11}H_{16}N_2O_2$+H requires 209.129); υ_{max} (thin film) 2220, 1950, 1730 and 840 cm^{-1}; δ_H (300 MHz) 5.08 (1H, p, J7Hz), 4.68-4.75 (2H, m), 3.75 (3H, s), 3.67 (1H, m), 3.61 (1H, dd, J7.5, 17Hz), 3.51 (1H, dd, J7.5, 17Hz), 2.00-2.10 (2H, m), 1.78-1.88 (2H, m), 1.60-1.70 (3H, m); m/z (ci) 209 (M^++H).

Ethyl N-(1-cyanoheptyl)glycinate (73)

Using a similar procedure to that described for (86), heptanal was reacted with ethyl glycinate. HCl and KCN, to give (73) (2.7 g, 80%) as a colourless oil (Found: C, 63.4; H, 9.5; N, 12.3. $C_{12}H_{22}N_2O_2$ requires C, 63.7; H, 9.7; N, 12.4%); υ_{max} (thin film) 3300, 2210 and 1730 cm^{-1}; δ_H (300 MHz) 4.22 (2H, q, J7Hz), 3.63 (1H, m), 3.55 (2H, q, J15Hz), 1.82 (1H, m), 1.79 (2H, m), 1.42-1.57 (2H, m), 1.21-1.40 (9H, m), 0.83-0.92 (3H, m); m/z (ci) 227 (M^++H).

Ethyl N-methyl-N-(1-cyanoheptyl)glycinate (74)

Using a similar procedure to that described for (86), heptanal was reacted with ethyl N-methylglycinate. HCl and KCN, to give (74) (4.2 g, 35%) as a colourless oil (Found: C, 65.2; H, 10.2; N, 11.3. $C_{13}H_{24}N_2O_2$ requires C, 65.0; H, 10.0; N, 11.7%); υ_{max} (thin film) 2200 and 1740 cm^{-1}; δ_H (300 MHz) 4.18

(2H, q, J7Hz), 3.68 (1H, t, J7Hz), 3.33 (1H, d, J16Hz), 3.21 (1H, d, J16Hz), 2.39 (3H, s), 1.76 (2H, q, J7Hz), 1.40-1.53 (2H, m), 1.21-1.40 (9H, m), 0.32-0.40 (3H, m); m/z (ci) 241 (M+H).

Ethyl N-methyl-N-(1-cyano-2,2-dimethylethyl)glycinate (75)

Using a similar procedure to that described for (86), trimethyl acetaldehyde was reacted with ethyl N-methylglycinate. HCl and KCN, to give (75) (1.5 g, 50%) as a colourless oil (Found: C, 62.2; H, 9.5; N, 13.2. $C_{11}H_{20}N_2O_2$ requires C, 62.3; H, 9.4; N, 13.2%); υ_{max} (thin film) 2220 and 1720 cm^{-1}; δ_H (300 MHz) 4.19 (2H, q, J7Hz), 3.38 (1H, d, J16Hz), 3.35 (1H, s), 3.30 (1H, d, J16Hz), 2.51 (3H, s), 1.28 (3H, t, J7Hz), 1.05 (6H, s), 0.8-0.9 (3H, m); m/z (ci) 213 (M^++H).

Methyl N-(1-cyanohexa-5-ynyl)glycinate (76)

Using a similar procedure to that described for (86), hexa-5-ynal was reacted with KCN and methyl glycinate. HCl, to give (76) (0.70 g, 70%) as a colourless oil (Found: M^++H, 195.113. $C_{10}H_{14}N_2O_2$+H requires 195.113); υ_{max} (thin film) 3250, 2200, 2100 and 1720 cm^{-1}; δ_H (300 MHz) 3.77 (3H, s), 3.71 (1H, t, J7Hz), 3.63 (1H, d, J17Hz), 3.52 (1H, d, J17Hz), 2.28 (2H, dt, J3, 7Hz), 2.00 (1H, t, J3Hz), 1.85-1.98 (3H, m), 1.69-1.82 (2H, m); m/z (ci) 195 (M^++H).

Ethyl N-methyl-N-(1-cyanohexa-5-ynyl)glycinate (77)

Using a similar procedure to that described for (86), hexa-5-ynal was reacted with KCN and ethyl N-methylglycinate. HCl, to give (77) (2.20 g, 65%) a pale yellow oil (Found: C, 64.5; H, 8.1; N, 12.4. $C_{12}H_{18}N_2O_2$ requires C, 64.9; H, 8.1; N, 12.6%); υ_{max} (thin film) 3300, 2220, 2110, 1735 cm^{-1}; δ_H (300 MHz) 4.20 (2H, q, J7Hz), 3.77 (1H, t, J7Hz), 3.35 (1H, d, J7Hz), 3.25 (1H, d, J7Hz), 2.42 (3H, s), 2.28 (2H, dt, J2, 7Hz), 1.98 (1H, t, J2Hz), 1.88-1.95 (2H, m), 1.64-1.78 (2H, m), 1.28 (3H, t, J7Hz); m/z (ci) 223 (M^++H).

Ethyl N-(1-cyano-2,2-dimethylhexa-4,5-dienyl)glycinate (84)

Using a similar procedure to that described for (86), 2,2-dimethyl hexa-4,5-dienal was reacted with ethyl glycinate. HCl and KCN, to give (84) (3.67 g, 90%) as a pale yellow oil (Found: M^++H, 237.162. $C_{13}H_{20}N_2O_2$+H requires 237.160); υ_{max} (thin film) 3340, 3330, 1950, 1730 and 850 cm^{-1}; δ_H(300 MHz) 5.01 (1H, p, J6Hz), 4.65-4.70 (2H, m), 4.19 (2H, q, J6Hz), 3.60 (1H, d, J16Hz), 3.48 (1H, d, J16Hz), 3.35 (1H, s), 2.20-2.30 (2H, m), 1.70 (1H, m), 1.25 (3H, t, J6Hz), 1.05 (6H, s); m/z (ci) 237 (M^++H).

Methyl N-(1-cyanohexa-4,5-dienyl)glycinate (85)

Using a similar procedure to that described for (86), hexa-4,5-dienal was reacted with methyl glycinate. HCl and KCN, to give (85) (1.50 g, 72%) as a colourless oil (Found: M^++H, 195.112. $C_{10}H_{14}N_2O_2$+H requires 195.113); υ_{max} (thin film) 3320, 2220, 1950, 1735 and 840 cm^{-1}; δ_H (300 MHz) 5.12 (1H, p, J7Hz), 4.62-4.68 (2H, m), 3.75 (3H, s), 3.72(1H, d, J8Hz), 3.55 (2H, dq, J7, 15Hz), 2.15-2.30 (2H, m), 1.98 (2H, m), 1.81 (1H, m).

Ethyl octahydro-4,6-dioxo-3-(4-pentynyl)-2,5-dimethyl pyrrolo[3,4-c]pyrrole-1-carboxylate (81ab)

N-Methyl maleimide (1.25 g, 2.25 mmol) and ethyl N-methyl-N-(1-cyanohex-5-ynyl)glycinate (78) (0.10 g, 0.45 mmol) were heated in a sealed tube in toluene (10 ml) at 180°C for 50 h. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography to give, on elution with petrol-ether (2:1), the two isomers (81a) (45mg, 33%) and (81b) (45 mg, 40%) (the compound was characterised as a mixture but the nmr data refers to the separated isomers) (Found: M^++H, 307.165. $C_{16}H_{22}N_2O_4$+H requires 307.1265); υ_{max} (thin film) 1695 cm^{-1};

(81a) δ_H (300 MHz) 4.10-4.21 (2H, dq, J 1.5, 7.5Hz), 4.00 (1H, s), 3.30 (1H, t, J7.5Hz), 3.22 (1H, d, J7.5Hz), 3.15 (1H, dt, 3, 9Hz), 2.95 (3H, s), 2.30 (3H, s), 2.20-2.29 (2H, m), 1.97 (1H, t, J3Hz), 1.69-1.90 (4H, m), 1.25 (3H, t, J6.5Hz).
(81b) δ_H (300 MHz) 4.16 (2H, dq, J2, 8.5Hz), 3.90 (1H, d, J8.5Hz), 3.55 (1H, t, J8.5Hz), 3.32 (1H, m), 3.01 (1H, dd, J6, 10Hz), 2.95 (3H, s), 2.30 (3H, s), 2.20-2.29 (2H, m), 1.97 (1H, t, J2.5Hz), 1.60-1.90 (4H, m), 1.25 (3H, t, J6.5Hz).

Ethyl octahydro-4,6-dioxo-5-ethyl-3-hexyl pyrrolo[3,4-c]pyrrole-1-carboxylate (78abc)

Using a similar procedure to that described for (81), N-ethyl maleimide was reacted with (73) at 110°C for 4 days, to give (78abc) (100mg, 25%) as colourless oils (the compound was characterised as a mixture) (Found: C, 62.9; H, 8.65; N, 8.45. $C_{17}H_{28}N_2O_4$ requires C, 63.0; H, 8.6; N, 8.4%); υ_{max} (thin film) 3300 and 1700 cm^{-1};
δ_H (360 MHz) major isomer. 4.30 (2H, q, J7Hz), 3.92 (1H, d, J8Hz), 3.50 (2H, q, J7Hz), 3.50 (1H, t, J8Hz), 3.25 (1H, m), 3.21 (1H, q, J8Hz), 1.50 (1H, m, [underwent exchange with D_2O]) , 1.35 (3H, t, J7Hz), 1.20-1.30 (10H, m), 1.13 (3H, t, J7Hz), 0.89 (3H, m).
The two minor isomer were not separated but had similar spectra to the major isomer, the only real differences were that δ3.92 (major isomer) had shifted to δ4.00 (1H, d, J5Hz) and δ4.12 (1H, d, J8Hz); m/z (ci) 325 (M^++H).

Ethyl octahydro-4,6-dioxo-5-ethyl-3-hexyl-2-methyl pyrrolo[3,4-c]pyrrole-1-carboxylate (79ab)

Using a similar procedure to that described for (81), N-ethyl maleimide reacted with (74), to give (79a) (160 mg, 49%) and (79b) (70 mg, 21%) as colourless oils (the compound was characterised as a mixture but the nmr data refers to the separated isomers) (Found: M^++H, 339.227. $C_{18}H_{30}N_2O_4$+H requires 339.228);

υ_{max} (thin film) 1770 and 1700 cm^{-1};

(79a) δ_H (300 MHz) 4.14 (2H, q, J7Hz), 3.96 (1H, s), 3.48 (2H, q, J7Hz), 3.28 (1H, t, J7Hz), 3.20 (1H, d, J7Hz), 3.10 (1H, m), 2.24 (3H, s), 1.5 (1H, m), 1.15-1.35 (12H, m), 1.08 (3H, t, J7Hz), 0.80 (3H, m);

(79b) δ_H (300MHz) 4.12 (2H, q, J7Hz), 3.86 (1H, d, J9Hz), 3.48 (1H, t, J9Hz), 3.48 (3H, q, J7Hz), 3.30 (1H, m), 3.00 (1H, dd, J4, 9Hz), 2.28 (3H, s), 1.20-1.40 (12H, m), 1.10 (3H, t, J7Hz), 0.85 (3H, m);

(79a) δ_c 177.1, 176.2, 170.4, 67.65, 63.9, 60.5, 46.96, 46.94, 35.1, 33.8, 31.6, 29.5, 26.1, 22.5, 14.2, 13.9, 12.8; m/z (ei) 338 (M^+).

Methyl 1α,3α,3aα,6aα-octahydro-4,6-dioxo-5-methyl-3-(pent-4-ynyl) pyrrolo[3,4-c]pyrrole-1-carboxylate (80b)

Using a similar procedure to that described for (81), N-methyl maleimide was reacted with (76), to give one isomer (80b) (780 mg, 56%) as a colourless solid, m.p. 95.5-96°C (from Methanol) (Found: C, 60.0; H, 6.5; N, 10.0. $C_{14}H_{18}N_2O_4$ requires C, 60.4; H, 6.5; N, 10.0%); υ_{max} (thin film) 3600, 3300, 2900, 2100, 1720 and 1680 cm^{-1}; δ_H (270 MHz) 4.11 (1H, d, J8Hz), 3.81 (3H, s), 3.70 (1H, m), 3.55 (1H, t, J8Hz), 3.05 (1H, dd, J8, 2Hz), 2.95 (3H, s), 2.35 (1H, br.s [underwent exchange with D_2O]), 2.21-2.26 (2H, m), 1.97 (1H, t, J2.5Hz), 1.58-1.69 (4H, m); δ_c 177.5, 175.9, 170.8, 83.75, 68.8, 61.75, 61.4, 52.55, 49.5, 34.0, 25.3, 25.1, 18.0; m/z (ci) 279 (M^++H).

Ethyl 2-cyano-3,3-dimethyl-5-ethenyl-1-pyrrolidine-1-ethanoanate (87)

Silver tetrafluoroborate (250 mg, 1.3 mmol) was added to a stirred solution of ethyl N-(1-cyano-2,2-dimethylhexa-4,5-dienyl)glycinate (84) (300 mg, 1.3 mmol) in CH_2Cl_2 (30 ml) at -78°C. The reaction mixture was stirred at -30°C for 5 h and then washed with brine (10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to

give, on elution with petrol-ether (8:1), recovered starting material (10 mg) and the cyclised product (87) (80 mg, 40%) (1:1 mixture of isomers) as a colourless oil (Found: M^++H, 237.158. $C_{13}H_{20}N_2O_2$+H requires 237.162); υ_{max} (thin film) 2240, 1730 and 1640 cm^{-1}; δ_H (300 MHz) (1:1 mixture of isomers) 5.62 (1H, m), 5.07-5.18 (2H,), 4.13 (2H, q, J7Hz), 4.13 (0.5H, s), 3.95 (0.5H, s), 3.66 (1H, q, J7Hz), 3.52 (1H, d, J17Hz), 3.52 (1H, d, J17Hz), 1.91 (1H, dd, J7, 12Hz), 1.60 (1H, dd, J7, 12Hz), 1.29 (3H, s), 1.27 (3H, t, J7Hz), 1.20 (3H, s).

Methyl 2-cyano-5-ethenylpyrrolidine-1-ethanoate (88)

Using a similar procedure to that described for (87), methyl N-(1-cyano hexa-4,5-dienyl)glycinate (85) was cyclised with silver tetrafluoroborate, to give (88) (30 mg, 25%) (1:1 mixture of isomers). These isomers were separated by flash chromatography using petrol-ether (3:1) as elutant (Found: M^++H, 195.112. $C_{10}H_{14}N_2O_2$+H requires 195.113); υ_{max} (thin film) 2300, 1740, 1435 and 1420 cm^{-1}; δ_H (300 MHz) 5.62 (1H, m), 5.09-5.30 (2H, m), 4.48 (0.5H, d, J8Hz), 4.12 (0.5H, dd, J5, 8Hz), 3.70 (3H, s), 3.62 (0.5H, d, J18Hz), 3.65 (0.5H, d, J18Hz), 3.28 (0.5H, d, J18Hz), 3.52 (0.5H, d, J18Hz), 3.12 (0.5H, q, J8Hz), 3.50 (0.5H, m), 1.97-2.38 (3H, m), 1.65-1.88 (1H, m); m/z (ci) 195 (M^++H).

Ethyl 1α,3β,3aα,6β-3-methoxycarbonyl-4,4-dimethyl-6-ethenyloctahydro pyrrolizine-1-carboxylate (91)

A solution of (87) (0.10 g, 4.23 mmol) and methyl acylate (0.4 ml, 42.0 mmol) in toluene (20 ml) were heated at 110°C for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography to give, on elution with petrol-ether (1:1), (91) (10 mg, 10%) as a pale yellow oil (Found: M^++H, 296.185. $C_{16}H_{25}NO_4$+H requires 296.186); υ_{max} (thin film) 1725 cm^{-1}; δ_H (300 MHz) 6.00 (1H, ddd J6, 10, 16Hz), 5.15-5.23 (2H, dd, J10, 16Hz), 4.14 (2H, q, J7Hz), 3.85 (2H, m), 3.70 (3H, s),

3.60 (1H, d, J7Hz), 3.40 (1H, q, J8.5Hz), 2.41 (1H, dt, J13, 9Hz), 2.15 (1H, m), 1.60-175 (2H, m), 1.24 (3H, t, J7Hz), 1.11 (3H, s), 0.95 (3H, s); δ_c 173.1, 137.0, 118.9, 76.3, 61.4, 60.8, 58.8, 51.4, 46.7, 44.7, 40.0, 30.1, 30.1, 29.6, 24.6, 14.1; m/z (ci) 296 (M^++H).

Methyl 1β,1aα,4aα-hexahydro-2,4-dioxo-7-ethenyl-3-methyl-2H,4H-pyrrolo [3,4-a]pyrrolizine-1-carboxylate (92)

A solution of (88) (220mg, 1.13 mmol) and N-methyl maleimide (650 mg, 5.6 mmol) in toluene (50 ml) were heated in a sealed tube at 180°C for 16h. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography to give, on elution with petrol-ether (1:1), one isomer (92) (180 mg, 60%) as a colourless solid, m.p. 75-77°C (from hexane) (Found: C, 60.2; H, 6.6; N, 10.1. $C_{14}H_{18}N_2O_4$ requires C, 60.4; H, 6.5; 10.1%); υ_{max} (thin film) 1780, 1740, 1700 and 1640 cm^{-1}; δ_H (360 MHz) 5.62 (1H, ddd, J7, 10, 16.5Hz), 5.09 (1H, ddd, J1, 2, 17Hz), 5.03 (1H, ddd, J1, 2, 10Hz), 4.19 (1H, d, J1.6Hz), 4.06 (1H, ddd, J5, 8, 9Hz), 3.70 (3H, s), 3.66 (1H, dd, J2, 9Hz), 3.39 (1H, t, J9Hz), 2.93 (3H, s), 2.80 (1H, dt, J9, 7Hz), 2.00-2.20 (2H, m), 1.80-1.90 (1H, m), 1.60-1.80 (1H, m); m/z (ci) 279 (M^++H).

Methyl 2,2-dimethylhexa-5-ynoate

n-Butyl-lithium (3.96 ml, 9.0 mmol, 2.5 M in hexanes) was added to di-isopropylamine (1.37 ml, 9.0 mmol) in THF (30 ml) at -78°C. The reaction mixture was stirred at -78°C for 30 min. Methyl isobutyrate (1.03 ml, 8.0 mmol) in THF (10 ml) was added slowly to the solution of lithium di-isopropylamine at -78°C and stirred at -78°C for 30 min. 4-Bromobut-1-yn (1.2 g, 9.0 mmol) in THF (10 ml) was added slowly to the reaction mixture at -78°C, which was then allowed to warm to room temperature. The reaction mixture was diluted with ether (100 ml), acidified with 2N HCl and the organic layer was separated, dried

($MgSO_4$) and concentrated under reduced pressure. The residue was purified to give, on elution with petrol-ether (6:1), methyl 2,2-dimethylhexa-5-ynoate (0.88 g, 80%) as a colourless oil (Found: M^++H, 155.106. $C_9H_{14}O_2$+H requires 155.107); υ_{max} (thin film) 3300, 2100 and 1720 cm^{-1}; δ_H (300 MHz) 3.66 (3H, s), 2.12 (2H, dt, J2, 7Hz), 1.94 (1H, t, J2Hz), 1.30 (2H, t, J7Hz), 1.19 (6H, s); m/z (ci) 155 (M^++H).

Methyl 2,2-dimethylhexa-4,5-dienoate

Using a similar procedure to that described before, 4-bromobuta-1,2-diene was alkylated using methyl isobutyrate, to give methyl 2,2-dimethylhexa -4,5-dienoate (1.3 g, 56%) as a colourless oil, b.p. 75°C/4 mm Hg (Found: M^++H, 155.107. $C_9H_{14}O_2$+H requires 155.107); υ_{max} (thin film) 1955, 1725 and 850 cm^{-1}; δ_H (300 MHz) 5.00 (1H, m), 4.60-4.68 (2H, m), 3.66 (3H, s), 2.22 (2H, dt, J2, 7Hz), 1.19 (6H; s); m/z (ci) 155 (M^++H).

Methyl 2,2-dimethylhexa-1-enoate

Using a similar procedure to that described before, methyl isobutyrate was alkylated with 4-bromohexa-1-ene to give methyl 2,2-dimethylhexa-1-enoate (129.5 g, 85%) as a colourless oil (Found: C, 69.0; H, 10.15. $C_9H_{16}O_2$ requires C, 69.2; H, 10.25%); υ_{max} (thin film) 3800, 1725 and 1635 cm^{-1}; δ_H (300 MHz) 5.74 (1H, m), 4.89-5.04 (2H, dd, J10, 17Hz), 3.62 (3H, s), 1.95 (2H, m), 1.60 (2H, m), 1.15 (6H, m); m/z (ci) 157 (M^++H).

2,2-Dimethylhexa-5-yn-1-ol

Methyl 2,2-dimethylhexa-5-ynoate (6.2 g, 40.0 mmol) in ether (25 ml) was added to a stirred suspension of $LiAlH_4$ (1.5 g, 40.0 mmol) at -78°C and stirred at -78°C for 1 h and then quenched with aqueous NaOH. The mixture was filtered and the filtrate was dried ($MgSO_4$), concentrated under reduced

pressure, to give 2,2-dimethylhexa-5-yn-1-ol (4.2 g, 84%) as a colourless oil (Found: M^++H, 127.112. $C_8H_{14}O$+H requires 127.112); υ_{max} (thin film) 3000 and 2100 cm^{-1}; δ_H (300 MHz) 3.32 (2H, d, J5Hz), 2.18 (2H, dt, J2, 7Hz), 1.95 (1H, t, J2Hz), 1.60 (1H, m), 1.54 (2H, t, J7Hz), 0.86 (6H, s); m/z (ci) 127 (M^++H).

2,2-Dimethylhexa-4,5-dien-1-ol

Using a similar procedure to that described before, methyl 2,2-dimethyl hexa-4,5-dienoate was reduced with $LiAlH_4$, to give 2,2-dimethyl hexa-4,5-dien-1-ol (1.0 g, 94%) as a colourless oil (Found: C, 76.1; H, 11.4. $C_8H_{14}O$ requires C, 76.2; H, 11.1%); υ_{max} (thin film) 3300, 1950 and 840 cm^{-1}; δ_H (300 MHz) 5.05 (1H, p, J7Hz), 4.60-4.68 (2H, m), 3.35 (2H, s), 1.99 (1H, m), 1.94 (1H, m), 1.50 (1H, s), 0.90 (6H, s); m/z (ci) 127 (M^++H).

Methyl N-(2,2-dimethylhexa-1,5-dienyl)glycinate (94a)

2,2-Dimethylhexa-5-enal (6 g, 0.047 mol) in CH_2Cl_2 (20 ml) was added dropwise to a stirred suspension of methyl glycinate (4.23 g, 0.047 mol) and oven-dried $MgSO_4$ (1 g) in CH_2Cl_2 (30 ml) at 0°C. After 1 h at 0°C the solids were filtered off and the solvent removed under reduced pressure, to give (94a) (6.8 g, 73%) as a colourless oil, which was used without further purification (Found: C, 67.3; H, 9.3; N, 7.5. $C_{11}H_{19}NO_2$ requires C, 67.0; H, 9.6; N, 7.1%); υ_{max} (thin film) 1740, 1660 and 1640 cm^{-1}; δ_H (300 MHz) 7.50 (1H, s), 5.79 (1H, m), 4.94 (2H, dd, J10, 17Hz), 4.18 (2H, s), 3.70 (3H, s), 1.95-2.06 (2H, m), 1.48-1.55 (2H, m), 1.09 (6H, s); m/z (ci) 198 (M^++H).

Methyl N-(2,2-dimethylhexa-1,4,5-trienyl)glycinate (94b)

Using a similar procedure to that described for (94a), 2,2-dimethyl hexa-4,5-dienal was reacted with methyl glycinate, to give (94b) (0.99 g, 71%)

as a colourless oil (Found: C, 68.0; H, 8.7; N, 7.3. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.7; N, 7.2%); υ_{max} (thin film) 1950, 1740, 1660 and 845 cm^{-1}; δ_H (300 MHz) 7.52 (1H, s), 5.05 (1H, p, J7Hz), 4.60-4.65 (2H, m), 4.18 (2H, s), 3.72 (3H, s), 2.18 (1H, t, J2Hz), 2.15 (1H, t, J2Hz), 1.10 (6H, s); m/z (ci) 196 (M^++H).

Methyl N-(2,2-dimethylhexa-1-en-5-ynyl)glycinate (94c)

Using a similar procedure to that described for 94a), 2,2-dimethylhexa-5-ynal was reacted with methyl glycinate, to give (94c) (2.0 g, 70%) as a yellow oil (Found: M^++H, 196.134. $C_{11}H_{17}NO_2$+H requires 196.133); υ_{max} (thin film) 2100, 1730 and 1660 cm^{-1}; δ_H (300 MHz) 7.50 (1H, s), 4.16 (2H, s), 3.71 (3H, s), 2.10-2.20 (2H, m), 1.91 (1H, t, J2Hz), 1.72 (2H, t, J8Hz), 1.08 (6H, s); m/z (ci) 196 (M^++H).

Methyl 1α,3α,3aα,6aα-octahydro-4,6-dioxo-3-(1,1-dimethylpenta-4-enyl) -5-ethylpyrrolo[3,4-c]pyrrole-1-carboxylate (96a)

A stirred solution of N-ethyl maleimide (630 mg, 5 mmol) and methyl N-(2,2-dimethylhexa-1,5-dienyl)glycinate (94a) (1.0 g, 5 mmol) were heated at 110°C in toluene (20 ml) for 16 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography to give, on elution with petrol-ether (2:1), a single isomer (96a) (1.3 g, 82%) as a colourless solid, m.p. 75-77°C (from petrol) (Found: C, 63.0; H, 8.4; N, 8.6. $C_{17}H_{26}N_2O_4$ requires C, 63.4; H, 8.1; N, 8.7%); υ_{max} ($CHCl_3$) 1740 and 1690 cm^{-1}; δ_H (300 MHz) 5.80 (1H, m), 5.03 (1H, br.d, J17Hz), 4.89 (1H, br.d, J10Hz), 3.81 (3H,s), 3.80 (1H, m), 3.50 (2H, t, J8Hz), 3.45-3.57 (1H, m), 3.21 (1H, t, J8Hz), 3.02 (1H, dd, J8, 11Hz [the signal collapsed to a d, J8Hz with a D_2O shake]), 2.06 (2H, q, J8Hz), 2.00 (1H, br.d, J11Hz, [exchanges with D_2O]), 1.53-1.68 (2H, m), 1.12 (3H, t, J7Hz), 1.12 (3H, s), 1.04 (3H, s); m/z (ci) 323.198 (M^++H).

Methyl 1α,3α,3aα,6aα-octahydro-4,6-dioxo-3-(1,1-dimethylpenta-3,4-dienyl) -5-methylpyrrolo[3,4-c]pyrrole-1-carboxylate (96b)

Using a similar procedure to that described for (96a), methyl N-(2,2-dimethylhexa-1,4,5-trienyl)glycinate (94b) reacted with N-methyl maleimide to give one isomer (96b) (180 mg, 60%) as a colourless solid, m.p. 106-108°C (from methanol) (Found: M^++H, 307.165. $C_{16}H_{22}N_2O_4$+H requires 307.166); υ_{max} (thin film) 3300, 1950, 1740 and 1680 cm^{-1}; δ_H (300 MHz) 5.08 (1H, p, J7Hz), 4.60-4.68 (2H, m), 3.81 (3H, s), 3.80 (1H, m [the signal collapsed to a d J7Hz with D_2O shake]), 3.50 (1H, t, J7Hz), 3.23 (1H, t, J7Hz), 3.05 (1H, d, J7Hz), 2.95 (3H, s), 2.14-2.40 (3H, m, [1H exchanges with D_2O shake]), 1.09 (3H, s), 1.02 (3H, s).

Methyl 1α,3α,3aα,6aα-octahydro-4,6-dioxo-3-(1,1-dimethylpenta-4-yn)-5-ethyl pyrrolo[3,4-c]pyrrole-1-carboxylate (96c)

Using a similar procedure to that described for (96a), methyl (2,2-dimethyl hexa-1-en-5-ynyl)glycinate (94c) reacted with N-ethyl maleimide, to give two products which were separated by flash chromatography to give, on elution with petrol-ether (2:1), (96c) (110 mg, 13%) and (96d) (450 mg, 54%).

Minor isomer (96c) (Found: M^++H, 321.182. $C_{17}H_{24}N_2O_4$+H requires 321.1815); υ_{max} (thin film) 3300, 2100, 1740 and 1690 cm^{-1}; δ_H (300 MHz) 3.81 (3H, d), 3.58 (1H, obscured), 3.42-3.58 (3H, m), 3.21 (1H, t, J7.5Hz), 3.00 (1H, d, J7Hz), 2.15-2.25 (2H, m), 2.00 (1H, m), 1.91 (1H, t, J2Hz), 1.70-1.90 (2H, m), 1.09 (3H, t, J7.5Hz), 1.09 (3H, s), 1.00 (3H, s).

Methyl 3aα,4β,8aα,8bα-2-ethyl-1,3-dioxo-1,2,3,3a,4,7,8,9b-octahydro-5,8,8-trimethyl-9aH-pyrrolo[3,4-a]indolizine-4-carboxylate (96d)

Major isomer (96d) m.p. 95-97°C (from methanol) (Found: C, 63.6; H, 7.8; N, 8.4. $C_{17}H_{24}N_2O_4$ requires C, 63.75; H, 7.5; N, 8.75%); υ_{max} (thin film) 1725 and 1690 cm^{-1}; δ_H (300 MHz) 4.64 (1H, s), 4.27 (1H, m), 3.70 (3H, s), 3.48 (2H, q, J7Hz), 3.48 (1H, d, J8Hz), 3.35 (1H, d, J8Hz), 3.22 (1H, t, J8Hz), 1.97 (1H, m), 1.67 (3H, s), 1.52 (1H, m), 1.21 (3H, s), 1.10 (3H, t, J7Hz), 0.72 (3H, s); δ_c 176.9, 176.5, 171.3, 136.3, 98.1, 67.6, 61.3, 52.0, 48.4, 45.6, 41.2, 34.1, 31.0, 26.1, 19.8, 19.0, 12.45; m/z (ci) 321 (M^++H).

Methyl 2α,3aα.6aα-octahydro-6,6-dimethylcyclopenta[b]pyrrole-2-carboxylate (97)

A solution of methyl N-(2,2-dimethylhexa-1,5-dienyl)glycinate (94a) (2.5 g, 12.5 mmol) in toluene (400 ml) was heated at 110°C for 26 h. The solution was cooled and concentrated under reduced pressure and the residue was purified by flash chromatography to give, on elution with petrol-ether (3:2), (97) (0.75 g, 30%) as a pale yellow oil (Found: 198.150. $C_{11}H_{19}NO_2$+H requires 198.149); υ_{max} (thin film) 3350 and 1735 cm^{-1}; δ_H (300 MHz) 3.71 (3H, s), 3.58 (1H, dd, J6.5, 10.5Hz), 3.02 (1H, d, J7.5Hz), 2.63 (1H, dp, J1.5, 7.5Hz), 2.34 (1H, ddd, J7, 10, 12Hz), 1.75-1.98 (2H, m), 1.67 (1H, dt, J10, 12Hz), 1.43 (1H, ddd, J6, 7, 12Hz), 1.20-1.35 (2H, m), 1.06 (3H, s), 0.87 (3H, s); δ_c 174.11, 73.3, 61.2, 51.6, 41.9, 38.6, 36.7, 30.9, 26.95, 23.4.

Methyl 2α,6aα-1.2,3,5,6,6a-hexahydro-6,6-dimethylcyclopenta[b]pyrrole-2-carboxylate (98)

Using a similar procedure to that described for (97), methyl N-(2,2-dimethylhexa-1,4,5-trienyl)glycinate (94b) was heated, to give (98) (0.10 g, 53%) as a single isomer (Found: M^++H, 196.133. $C_{11}H_{17}NO_2$+H

requires 196.134); υ_{max} (thin film) 3300 and 1720 cm^{-1}; δ_H (270 MHz) 5.29 (1H, s), 4.14 (1H, dd, J6, 9Hz), 3.80 (1H, s), 3.74 (3H, s), 2.56-261 (2H, m), 2.42 (1H, m), 2.17-2.38 (2H, m), 1.21 (3H, s), 0.95 (3H, s); δ_c 174.2, 146.5, 118.25, 78.55, 63.9, 52.5, 51.9, 43.5, 29.8, 27.8, 22.3.

Methyl 1,2,4,5,6,6a-hexahydro-6,6-dimethylcyclopenta[b]pyrrole-2-carboxylate (99ab)

Using a similar procedure to that described for (97), methyl N-(2,2-dimethylhexa-1-en-5-ynyl)glycinate (94c) was heated, to give (99a, b) (0.17 g, 34%) as a 1:1 mixture (the compound was characterised as a mixture but the nmr data refers to the separated isomers) (Found: M^++H, 196.133. $C_{11}H_{17}NO_2$+H requires 196.134); υ_{max} (thin film) 3360, 1730 and 1690 cm^{-1}; δ_H (270 MHz) 5.28 (1H, s), 4.65 (1H, s), 4.15 (1H, s), 3.70 (3H, s), 2.35 (1H, br.s), 2.08-2.21 (2H, m), 1.60-1.82 (2H, m), 1.00 (3H, s), 0.71 (3H, s)
δ_H (270 MHz) 5.28 (1H, s), 4.82 (1H, s), 4.00 (1H, s), 3.72 (3H, s), 3.20 (1H, br.s), 2.08-2.22 (2H, m), 1.60-1.82 (2H, s), 1.02 (3H, s), 0.75 (3H, s); δ_c 152.7, 115.1, 80.6, 72.95, 51.95, 41.9, 38.3, 27.05, 20.15, 19.9; m/z (ei) 195 (M^+).

Methyl 2α,3aα,6aα-octahydro-6,6-dimethylcyclopenta[b]pyrrole-2-carboxylate (97)

Sodium acetate (0.168 g, 2.05 mmol) in water (1 ml) was added over 4 h to a stirred solution of the cyclic amino ester (98) (20 mg, 0.103 mmol) and p-toluene sulphonyl hydrazide (0.23 g, 1.03 mmol) in methanol (1 ml) at 65°C. The reaction mixture was then concentrated under reduced pressure and saturated aqueous ammonium chloride (5 ml) was added, the resulting mixture was extracted with CH_2Cl_2 (4 x 10 ml). The extracts were combined and washed with aqueous 2N sodium hydroxide (5 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash

chromatography to give, on elution with petrol-ether (3:2), (97) (90 mg, 45%) as a colourless oil δ_H (300 MHz) 3.71 (3H, s), 3.59 (1H, dd, J7, 10Hz), 3.05 (1H, d, J7.5Hz), 2.65 (1H, dp, J1.5, 7.5Hz), 2.35 (1H, ddd, J7, 10, 12Hz), 1.75-2.00 (2H, m), 1.65 (1H, dt, J10, 12Hz), 1.45 (1H, ddd, J6, 7, 12Hz), 1.20-1.35 (2H, m), 1.08 (3H, s), 0.88 (3H, s).

Methyl 2α,3aα,6aα-octahydro-6,6-dimethylcyclopenta[b]pyrrole-2-carboxylate (97)

Using a similar procedure to that described for (97), (99a) was reduced to give (97) (25 mg, 50%) δ_H (270 MHz) 3.73 (3H, s), 3.65 (1H, dd, J7, 9Hz), 3.09 (1H, d, J7Hz), 2.66 (1H, m), 2.00 (1H, br.s), 1.90 (1H, m), 1.68 (1H, m), 1.48 (1H, m), 1.20-1.35 (2H, m), 1.09 (3H, s), 0.89 (3H, s).

Methyl 2α,3aβ,6aβ-octahydro-6,6-dimethylcyclopenta[b]pyrrole-2-carboxylate (97b)

Using a similar procedure to that described for (97), (99b) was reduced to give (97b) (20 mg, 25%) δ_H (270 MHz) 3.85 (1H, dd, J5, 7Hz), 3.70 (3H, s), 3.25 (1H, d, J7Hz), 2.68 (1H, m), 2.31 (1H, br.s), 2.18 (1H, ddd, J5, 8.5, 13.5Hz), 1.75-1.98 (2H, m), 1.55 (1H, m), 1.20-1.37 (2H, m), 1.04 (3H, s), 0.86 (3H, s); m/z (ci) 198 (M^++H).

Methyl 2α,3aβ,6aβ-octahydro-6,6-dimethylcyclopenta[b]pyrrole-2-carboxylate (97b)

A solution of (97)(40 mg, 0.2 mmol) in methanol (3 ml) was added to a stirred solution of sodium methoxide (made by using ~1 mg of sodium) in methanol (15 ml). This solution was then heated at 60°C for 60 h. The reaction was quenched with water (1 drop), concentrated under reduced pressure and the residue was purified by flash chromatography, to give on elution with

petrol-ether (2:3), recovered starting material (25 mg) and (97b) (10 mg, 67%) δ_H (270 MHz) 3.82 (1H, dd, J5, 7Hz), 3.70 (3H, s), 3.24 (1H, d, J7Hz), 2.67 (1H, m), 2.10-2.25 (2H, m), 1.75-1.95 (2H, m), 1.55 (1H, m), 1.20-1.38 (2H, m), 1.03 (3H, s), 0.85 (3H, s).

(E)- and (Z)-hepta-5,6-dien-2-one oxime (102a,b)

n-Butyl-lithium (4.7 ml, 7.5 mmol, 1.6 M in hexanes) was added dropwise to an ice cold solution of acetone oxime (0.275 g, 3.75 mmol) in THF (10 ml). The resulting yellow solution was stirred at 0°C for 30 min after which time, 4-bromobuta-1,2-diene (0.5 g, 3.75 mmol) in THF (2 ml) was added slowly. The reaction mixture was stirred at room temperature for 1 h and then quenched with water (5 ml). The resulting mixture was extracted with ether (3 x 30 ml) the organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure, to give mainly the (Z)- isomer of oxime (120b). This isomer was dissolved in chloroform (20 ml), p-toluene sulphonic acid (1 crystal) was added and the solution was stirred for 2 h at room temperature and then concentrated under reduced pressure. The (E)- and (Z)- isomers were then separated by flash chromatography to give, on elution with petrol-ether (6:1), a 1:1 mixture of (E)- and (Z)- isomers (102a, b) (0.085 g, 19% and 0.085 g, 19%) as colourless oils (the compound was characterised as a mixture but the nmr data refers to the separated isomers) Found: M^++H, 126.092. $C_7H_{11}NO$+H, requires 126.092); υ_{max} (thin film) 3250, 1950, 1650 and 850 cm^{-1};

E-(120b) δ_H (270 MHz) 8.26 (1H, br.s), 5.14 (1H, p, J6.5Hz), 4.68-4.74 (2H, m), 2.44-2.54 (2H, m), 2.17-2.30 (2H, m), 1.90 (3H, s);

Z-(120a) δ_H (270 MHz) 8.38 (1H, br.s), 5.14 (1H, p, J6.5Hz), 4.76-4.67 (2H, m), 2.44-2.54 (2H, m), 2.17-2.30 (2H, m), 1.88 (3H, s); m/z (ci) 126 (M^++H).

(E)- and (Z)- Octa-6,7-dien-2-one oxime (104a,b)

Using a similar procedure to that described for (102), alkylation of acetone oxime with 5-iodopenta-1,2-diene gave an (E)- and (Z)- mixture which was separated by flash chromatography to give, on elution with petrol-ether (8:1), (E)- and (Z)-oximes (140a, b) (1.5 g, 75%) as pale yellow oils (the compound was characterised as a mixture but the nmr data refers to the separated isomers) (Found: C, 69.0; H, 9.4; N, 10.4. $C_8H_{13}NO$ requires C, 69.1, H, 9.35; N, 10.1%); υ_{max} (thin film) 3250, 1950, 1625 and 840 cm^{-1};

E-(140b) δ_H (270 MHz) isomer 8.25 (1H, br.s), 5.10 (1H, p, J6.5Hz), 4.65-4.70 (2H, m), 2.20-2.25 (2H, m), 1.97-2.07 (2H, m), 1.88 (3H, s), 1.58-1.73 (2H, m);

(Z)-(140a) δ_H (270 MHz) isomer 8.38 (1H, br.s), 5.13 (1H, p, J6.5Hz), 4.66-4.71 (2H, m), 2.38-2.44 (2H, m), 2.00-2.10 (2H, m), 1.87 (3H, s), 1.58-1.73 (2H, m); m/z (ei) 139 (M^+).

(E)- and (Z)-Hex-5-yn-2-one oxime (117)

Using a similar procedure to that described for the oxime (102a, b), alkylation of acetone oxime with 3-bromoprop-1-yne, gave a mixture of the (E)- and (Z)-isomers (117) (6.5 g, 67%) as a colourless solid, m.p. 42.8-43.5°C (Found: C, 64.8, H, 8.4; N, 12.8. C_6H_9NO requires C, 64.9; H, 8.1; N, 12.6%); υ_{max} (thin film) 3250, 2120 and 1650 cm^{-1};

E-(117) isomer δ_H (270 MHz) 8.50 (1H, br.s), 2.44-2.42 (4H, m), 1.99 (1H, t, J2.5Hz) 1.92 (3H, s);

Z-(117) isomer δ_H (270 MHz) 7.00 (1H, br.s), 2.57-2.64 (2H, m), 2.42-2.49 (2H, m), 1.99 (1H, t, J2.5Hz), 1.95 (3H, s); m/z (ei) 111 (M^+).

(E)- and (Z)-Pent-4-ynal oxime (118ab)

Using a similar procedure to that described for (102), alkylation of acetaldehyde oxime with 3-bromoprop-1-yne gave (118) (0.5 g, 23%) as a pale

pale yellow solid, m.p. 46.5-47°C (Found: C, 61.4; H, 7.3; N, 14.0. C_5H_7NO requires C, 61.5; H, 7.2; N, 14.4%); υ_{max} (thin film) 3025, 2105 and 1650 cm^{-1}; (E)-(118) isomer δ_H (300 MHz) 8.90 (1H, br.s), 7.51 (1H, t, J4.5Hz) 2.58-2.68 (2H, m), 2.35-2.45 (2H, m), 2.01 (1H, t, J2.5Hz);
(Z)-(118) δ_H (300 MHz) 9.10 (1H, br.s), 6.85 (1H, t, J4.5Hz), 2.58-2.68 (2H, m), 2.35-2.45 (2H, m), 2.01 (1H, t, J2.5 Hz); m/z (ci) 98 (M^++H).

(E)- and (Z)-Deca-8,9-dienal oxime (192)

A solution of deca-8,9-dien-1-ol (189) (14 g, 90 mmol) in CH_2Cl_2 (120 ml) was added in a single portion, to a rapidly stirred suspension of pyridinium chlorochromate (39 g, 180 mmol), anhydrous sodium acetate (7.4 g) and crushed 4Å molecular sieves (6.0 g) in CH_2Cl_2 (300 ml) at 0°C. The reaction mixture was allowed to warm to room temperature and then stirred for 3 h. Ether (500 ml) was then added and the mixture was filtered through a florisil column, the filtrate was carefully concentrated under reduced pressure to give deca-8,9-dienal (191) which was used without further purification.

The crude aldehyde (191) was dissolved in methanol (60 ml) and treated with a solution of sodium acetate (18.4 g) and hydroxylamine hydrochloride (6.3 g, 90 mmol) in water (30 ml). The mixture was heated at 60°C for 1 h and then cooled and water (150 ml) added. The product was extracted with CH_2Cl_2 (3 x 100 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, an elution with CH_2Cl_2, a 1:1 mixture of (E)- and (Z)- deca-8,9-dienal oxime (192a, b) (8.3 g, 55%) as a yellow oil (Found: M^++H, 168.140. $C_{10}H_{17}NO$+H requires 168.138); υ_{max} (thin film) 3300, 1955, 1650, 1450 and 1430 cm^{-1}; δ_H (300 MHz) 7.90 (1H, br.s), 7.41 and 6.72 (1H, 2xt, J7Hz), 5.06 (1H, p, J7Hz), 4.60-4.65 (2H, m), 2.32-2.42 and 2.13-2.25 (2H, 2xm), 1.90-2.05 (2H, m), 1.22-1.60 (8H, m); m/z (ci) 168 (M^++H).

(E)- and (Z)- Octa-6,7-dienal oxime (106a, b)

Using a procedure similar to that described for (192), octa-6,7-dienal was prepared by reduction of octa-6,7-dienenitrile, which was then reacted with hydroxylamine to give a 1:1 mixture of (E)- and (Z)- oximes (106a, b) (0.33 g, 58%) as a yellow oil (Found: M^++H, 140.107. $C_8H_{13}NO$+H requires 140.1075); υ_{max} (thin film) 3300, 1955 and 850 cm^{-1}; δ_H (300 MHz) 7.81 (1H, br.s), 7.41 and 6.70 (1H, 2xt, J7.5Hz), 5.08 (1H, p, J7Hz), 4.60-4.70 (2H, m), 2.30 and 2.20 (2H, 2xq, J7Hz), 1.95-2.09 (2H, m), 1.40-1.62 (4H, m); m/z (ci) 140 (M^++H).

(E)- and (Z)-nona-7,8-dienal oxime (174)

Using a similar procedure to that described for (192), nona-7,8-dien-1-ol(175) was oxidised and then reacted with hydroxylamine, to give a 1:1 mixture of the (E)- and (Z)- oximes (174) (130 mg, 93%) as a pale yellow oil (Found: M^++H, 154.123. $C_9H_{15}NO$+H requires 154.123); υ_{max} (thin film) 3300, 1950, 1700, 1650 and 840 cm^{-1}; δ_H (300 MHz) 8.30 (1H, br.s), 7.40 and 6.71 (1H, 2xt, J7Hz), 5.08 (1H, p, J7Hz), 4.40-4.49 (2H, m), 2.38 and 2.10 (2H, 2xq, J7Hz), 1.92-2.06 (2H, m), 1.30-1.60 (6H, m); m/z (ci) 154 (M^++H).

2-Ethenyl-3,4-dihydro-5-methyl-2H-pyrrole-1-oxide (107)

Silver tetrafluoroborate (64 mg, 0.328 mmol) was added to a solution of (E)-hepta-5,6-dien-2-one oxime (102b) (41 mg, 0.328 mmol) in CH_2Cl_2 (1 ml). The reaction was stirred in the dark (covered with foil) for 1 h and then, ethyl acetate (5 ml) was added and the reaction washed with brine (5 ml). The organic phase was dried ($MgSO_4$), concentrated under reduced pressure and the residue was purified by flash chromatography to give, on elution with chloroform-methanol (5:1), (107) (30 mg, 74%) (Found: M^+, 125.0840. $C_7H_{11}NO$ requires 125.0840); υ_{max} (thin film) 1700 and 1620 cm^{-1}; δ_H (270 MHz) 6.00 (1H, ddd,

J7, 10, 17Hz), 5.33-5.43 (2H, ddt, J10, 17, 1Hz), 4.55 (1H, m), 2.60-2.80 (2H, m), 2.35 (1H, m), 2.07 (3H, d, J2Hz), 1.95 (1H, m); m/z (ei) 125 (M^+).

2-Ethenyl-2,3,5,5-tetrahydro-6-methyl-2H-pyridine-1-oxide (108)

Using a similar procedure to that described for (107), (E)- octa-6,7-dien-2-one oxime (104b) was treated with silver tetrafluoroborate, to give (108) (19 mg, 66%) (Found: M^+, 139.098. $C_8H_{13}NO$ requires 139.099); υ_{max} (thin film) 1630 and 1610 cm^{-1}; δ_H (270 MHz) 5.98 (1H, ddd, J6, 10, 17Hz), 5.30-5.25 (2H, ddt, J10, 17, J1.5Hz), 4.40 (1H, m), 2.43-2.48 (2H, m), 2.11 (3H, d, J1.5 Hz), 1.99-2.08 (2H, m), 1.62-1.86 (2H, m); δ_c (67.8 MHz) 167.6, 133.2, 119.6, 67.75, 31.9, 27.7, 20.0, 14.2; m/z (ei) 139 (M^+).

6-Ethenyl-5,6-dihydro-3-methyl-4H-1,2-oxazine (109)

Silver tetrafluoroborate (230 mg, 1.2 mmol) was added to a solution of (Z)-oxime (102a) (150 mg, 1.2 mmol) in CH_2Cl_2 (5 ml). The solution was protected from light and stirred for 16 h and then diluted with ethyl acetate (10 ml) and washed with 2N NaOH (5 ml). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure and the residue purified by flash chromatography to give, on elution with petrol-ether (2:1), (109) (50 mg, 34%) as a colourless oil (Found: M^+, 125.085. $C_7H_{11}NO$ requires 125.084); υ_{max} (thin film) 1630 and 1620 cm^{-1}; δ_H (270 MHz) 5.88 (1H, ddd, J5, 10, 17Hz), 5.35 (1H, br.d, J17Hz), 5.25 (1H, br.d, J10Hz), 4.16 (1H, m), 2.04-2.30 (2H, m), 1.91 (3H, s), 1.70-2.30 (2H, m): δ_c 155.0, 136.2, 117.1, 74.3, 24.1, 24,0, 21.6; m/z (ei) 125 (M^+).

5-Ethenyl-2-methyl-1,3-dioxodecahydropyrrolo[3,4-b]isoxazolo[2,3-a]azepine (113 a,b,c)

Silver tetrafluoroborate (58 mg, 0.30 mmol) was added to a stirred solution of (E)- and (Z)-octa-6,7-dienal oxime (106a, b) (100 mg, 0.30 mmol) and N-methylmaleimide (100 mg, 0.90 mmol) in 1,2-dichloroethane (50 ml). The reaction mixture was heated for 9 h at 80°C and the solvent was then removed under reduced pressure. The residue was purified by flash chromatography to give, on elution with methanol-CH_2Cl_2 (1:100) the cycloadduct (113a, b, c) (46 mg, 60%) as an inseparable mixture (2:2:1) of three isomers (Found: M^++H, 251.139. $C_{13}H_{18}N_2O_3$+H requires 251.1395); υ_{max} (thin film) 1780 and 1700 cm^{-1};

(113a) δ_H (300 MHz) major isomer, 6.02 (1H, ddd, J8, 11, 17Hz), 5.26, (2H, dd, J11, 17Hz), 4.70 (1H, d, J7Hz), 4.05 (1H, m), 3.38 (1H, q, J7Hz), 3.35 (1H, m), 3.02 (3H, s), 1.36-2.10 (8H, m);

(113b) δ_H (300 MHz) major isomer, 5.76 (1H, ddd, J6, 10, 17Hz), 5.08 (1H, d, J16Hz), 4.96 (1H, d, J10Hz), 4.70 (1H, d, J7Hz), 3.74 (1H, d, J10Hz), 3.40 (1H, m), 3.22 (1H, d, J7Hz), 3.02 (3H, s), 1.36-2.10 (8H, m);

(113c) δ_H (300 MHz) minor isomer, 5.85 (1H, ddd J7, 10, 18Hz), 5.21 (1H, d, J17Hz), 5.02 (1H, d, J10Hz), 4.76 (1H, d, J7Hz), 3.28-3.38 (2H, m), 3.15 (1H, m), 2.98 (3H, s), 1.36-2.10 (8H, m); m/z (ci) 251 (M^++H).

8-Ethenyloctahydro-2-phenylisoxazolo[2,3-a]azepine (112)

Using a similar procedure to that described for (113), but (E)- and (Z)-octa-6,7-dienal oxime (106a, b) reacted with silver tetrafluoroborate and then trapped with styrene, to give the cycloadduct (112) (18 mg, 20%) as a (5:1) mixture of two isomers (Found: M^++H, 244.171. $C_{16}H_{21}NO$+H requires, 244.170); υ_{max} (thin film) 3070, 3040, 1640 and 1605 cm^{-1};

Major isomer δ_H (300 MHz) 7.20-7.40 (5H, m), 6.12 (1H, ddd, J8, 10, 17Hz,),

5.16 (1H, d, J17Hz), 5.09 (1H, d, J10Hz), 5.01 (1H, t, J5Hz), 3.84 (1H, m), 3.67 (1H, m), 2.26-2.46 (2 H, m) 1.45-1.92 (8H, m);

Minor isomer δ_H (300 MHz) 7.20-7.40 (5H, m), 6.03 (1H, ddd, J8, 10, 17Hz), 5.18 (1H, d, J17Hz), 5.04 (1H, d, J10Hz), 5.01 (1H, t, J5Hz), 3.35 (1H, m), 3.15 (1H, m), 2.26-2.46 (2H, m), 1.45-1.92 (8H, m); m/z (ci) 244 (M^++H).

2-(4,4-Dimethylpent-1-yn-5-ylideneaminoyl)-3,4-dihydro-3,3,5-trimethyl-2H-pyrrole-1-oxide (120)

Silver tetrafluoroborate (0.54 g, 2.8 mmol) was added in a single portion to a stirred solution of 2,2-dimethylpent-4-ynal oxime (119)[69] (0.35 g, 2.8 mmol) in CH_2Cl_2 (50 ml) at -78°C. The reaction mixture was gradually allowed to warm to room temperature over 3 h. Brine (20 ml) was added and the mixture was stirred for 30 min. The organic layer was separated with CH_2Cl_2 (3 x 50 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified to give, on elution with CH_2Cl_2-methanol (25:1), (120) (0.28 g, 80%) as a yellow solid (Found: M^++H, 251.176. $C_{14}H_{22}N_2O_2$+H requires 251.176); υ_{max} (thin film) 3300, 2100, 1700 and 1600 cm^{-1}; δ_H (300 MHz) 7.55 (1H, s), 5.12 (1H, s), 2.65 (1H, d, J17Hz), 2.34 (1H, d, J17Hz), 2.29 (2H, d, J2.5Hz), 2.08 (3H, d, J1.5Hz), 2.00 (1H, t, J2.5Hz), 1.21 (3H, s), 1.18 (6H, s), 1.15 (3H, s); δ_c 156.5, 148.7, 106.95, 80.6, 70.7, 46.4, 36.45, 36.0, 29.9, 28.1, 22.5, 24.7, 21.7, 12.8; m/z (ci) 251 (M^++H).

2α,3aβ-4,4-Dimethyl-6-methyl-2-phenyl-2,3-tetrahydropyrrolo[1,2-b]isoxazole (121)

A stirred solution of (120) (0.27 g, 1.08 mmol) and styrene (2.5 ml, 21.6 mmol) in toluene (20 ml) was heated for 2 h at 110°C. The solvent was removed by distillation and the residue purified by flash chromatography to give, on elution with petrol-ether (8:1), 2,2-dimethylhex-4-ynal oxime (119) (80 mg, 60%)

(identified by ^1H nmr) and the cycloadduct (121) (10 mg, 4%) (Found: M^++H, 230.154. $C_{15}H_{19}NO$+H requires 230.1544); υ_{max} (thin film) 1650 and 1600 cm^{-1}; δ_H (300 MHz) 7.20-7.40 (5H, m), 4.79 (1H, s), 4.71 (1H, t, J7Hz), 3.79 (1H, dd, J5, 10Hz), 2.57 (1H, m), 2.08 (1H, m), 1.80 (3H, s), 1.20 (3H, s), 1.10 (3H, s); m/z (ei) 299 (M^+).

2-Cyano-3,4-dihydro-3,3-dimethyl-5-methyl-2H-pyrrole-1-oxide (122)

2,2-Dimethylpent-4-ynal oxime (119)[69] (0.25 g, 2.0 mmol) in CH_2Cl_2 (100 ml) was added slowly over 3 h to a stirred suspension of silver tetrafluoroborate (0.385 g, 2.0 mmol) in CH_2Cl_2 (2.00 ml) at -40°C. The reaction was then quenched with trimethylsilyl cyanide (0.266 ml, 4.0 mmol) and stirred at room temperature for 30 min. Brine (50 ml) was added and the product extracted with CH_2Cl_2 (2 x 50 ml), dried ($MgSO_4$) and concentrated under reduced pressure and purified by flash chromatography to give, on elution with methanol-CH_2Cl_2 (1:20), (122) (36 mg, 12%) (Found: M^++H, 153.103. $C_8H_{12}N_2O$+H requires 153.103); υ_{max} (thin film) 2460 and 1610 cm^{-1}; δ_H (300 MHz) 4.59 (1H, set, J1.5Hz) 2.68 (1H, dp, J17, 1.5Hz), 2.59 (1H, dp, J17, 1.5Hz), 2.08 (3H, q, J1.5Hz), 1.40 (3H, s), 1.32 (3H,); δ_c 145.5, 113.3, 73.5, 46.8, 36.5, 27.3, 25.3, 12.9; m/z (ci) 153 (M^++H).

1-[6-(4,4-Dimethylpent-1-yn-5-ylideneaminoxyl)-3a,5,5-trimethylhexahydro pyrrolo[1,2-b]isoazol-3-yl]ethanone (123)

A solution (120) (3.3 g, 26.4 mmol) and methyl vinyl ketone (10 ml, mmol) in toluene (100 ml) were stirred at 110°C for 30 min. The solution was concentrated under reduced pressure and the residue purified by flash chromatography to give on elution with petrol-ether (3:2), (123) (2.1 g, 6.5 mmol 25%) as a colourless oil (Found: M^++H, 321.218. $C_{18}H_{28}N_2O_3$+H requires 321.218); υ_{max} (thin film) 3300, 2100 and 1700 cm^{-1}; δ_H (300 MHz)

7.41 (1H, s), 4.83 (1H, s), 4.19 (1H, t, J10Hz), 3.99 (1H, dd, J7, 10Hz), 3.13 (1H, dd, J7, 10Hz), 2.23 (2H, d, J2Hz), 2.01 (3H, s), 1.95 (1H, t, J2Hz), 1.59 (3H, s), 1.64 (1H, d, J12Hz), 1.55 (1H, d, J12Hz), 1.11 (3H, s), 1.10 (3H, s), 1.05 (3H, s), 1.00 (3H, s); m/z (ci) 321 (M^++H).

3,3-Dimethyl-5-methyl-2-hydroxy-3,4-dihydro-2H-pyrrole-1-oxide (124)

2,2-Dimethylpent-4-ynal oxime (119)[69] (0.80 g, 6.4 mmol) in CH_2Cl_2 (50 ml) was added over 24 h using a syringe pump to a stirred solution of silver tetrafluoroborate (1.24 g, 6.4 mmol) in CH_2Cl_2 (250 ml) at -78°C . The reaction mixture was then stirred at -78°C for 2 days and was then quenched with brine. The organic layer was separated using CH_2Cl_2 (200 ml) and the solvent removed under reduced pressure. The residue was purified by flash chromatography to give, on elution with CH_2Cl_2-methanol (25:1), (124) (0.20 g, 25%) (Found: C, 58.6; H, 9.3; N, 9.65. $C_7H_{13}NO_2$ requires, C, 58.7; H, 9.1; N, 9.8%); υ_{max} (Nujol) 3000 and 1600 cm^{-1}; δ_H (300 MHz) 9.20 (1H, br.s), 5.04 (1H, br.s), 2.30-2.50 (2H, m), 2.00 (3H, br.s), 1.02-1.25 (6H, m); m/z (ci) 144 (M^++H).

2-(Benzylideneaminoxy)-3,4-dihydro-3,3,5-trimethyl-2H-pyrrole-1-oxide

Silver tetrafluoroborate (0.8 g, 4.1 mmol) was added to a stirred solution of benzaldehyde oxime (1 g, 8.2 mmol) and 2,2-dimethylpent-4-ynal oxime (119)[69] (0.5 g, 4.1 mmol) in CH_2Cl_2 (150 ml) at -78°C in the dark. The mixture was allowed to gradually warm to room temperature over 6 h. The reaction was quenched with brine (50 ml) and stirred for 30 min at room temperature. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (50 x 2 ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with CH_2Cl_2 and methanol-CH_2Cl_2 (1:20),

the cycloadduct (0.4 g, 40%) as a colourless oil (Found: M^++H, 247.144. $C_{14}H_{18}N_2O_2$+H requires 247.145); υ_{max} (thin film) 1610 cm^{-1}; δ_H (300 MHz) 8.22 (1H, s), 7.54-7.60 (2H, m), 7.31-7.41 (3H, m), 5.30 (1H, s), 2.70 (1H, d, J17Hz), 2.41 (1H, d, J17Hz), 2.10 (3H, s), 1.28 (3H, s), 1.18 (3H, s); m/z (ci) 247 (M^++H).

2-(2-Naphthylideneaminoxy)-3,4-dihydro-3,3,5-trimethyl-2H-pyrrole-1-oxide

Naphthaldehyde oxime was reacted with 2,2-dimethylpent-4-ynal oxime (119)[69] and silver tetrafluoroborate using a similar procedure to that described for the benzyaldehyde oxime, to give (0.90 g, 50%) as a colourless oil (Found: C, 73.1; H, 6.8; N, 9.7. $C_{18}H_{20}N_2O_2$ requires C, 73.0; H, 6.75; N, 9.5%); υ_{max} (thin film) 1600 cm^{-1}; δ_H (300 MHz) 8.37 (1H, s), 6.75-7.90 (5H, m), 7.45-7.53 (2H, m), 5.36 (1H, s), 2.72 (1H, d, J17Hz), 2.42 (1H, d, J17Hz), 2.10 (3H, s), 1.28 (3H, s), 1.20 (3H, s); m/z (ci) 297 (M^++H).

2-(9-Anthrylideneaminoxy)-3,4-dihydro-3,3,5-trimethyl-2H-pyrrole-1-oxide

9-Anthraldehyde oxime, reacted with 2,2-dimethylpent-4-ynal oxime (119)[69] and silver tetrafluoroborate, using similar procedure to that described for the benzyaldehyde oxime, to give (0.16 g, 10%), (10:1 mixture) as a yellow solid, m.p. 145.7-146.4 (ethanol) (Found: C, 76.4; H, 6.5; N, 8.2. $C_{22}H_{22}N_2O_2$ requires C, 76.3; H, 6.35; N, 8.09%); υ_{max} (Nujol) 1610 cm^{-1}; δ_H (300 MHz) major isomer 9.36 (1H, s), 8.50 (1H, s), 8.44 (2H, d, J8Hz), 8.00 (3H, d, J8Hz), 7.43-7.60 (4H, m), 6.96 (1H, s), 2.78 (1H, d, J14Hz), 2.21 (1H, d, J14Hz), 1.90 (3H, s), 1.26 (3H, s), 1.16 (3H, s);

δ_H(300 MHz) minor isomer 9.36 (1H, s), 8.50 (1H, s), 8.44 (2H, d, J8Hz), 8.00 (2H, d, J8Hz), 7.43-7.60 (4H, m), 5.50 (1H, s), 2.79 (1H, d, J17Hz), 2.42 (1H, d, J17Hz), 2.20 (3H, s), 1.32 (3H, s), 1.28 (3H, s); m/z (ci) 347 (M^++H).

Ethyl nona-3,4-dienoate (128b)

A mixture of 1-heptyn-3-ol (25 g, 0.223 mol), 2-methylbutyric acid (2 ml) and triethylorthoacetate (170 ml, 0.926 mol) were heated at 110-115°C for 16 h with the constant removal of ethanol by distillation. The solvent was then removed under reduced pressure. The mixture was diluted with ether (200 ml), washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was then distilled to give ethyl nona-3,4-dienoate (128b) (29.5 g, 75%) as a colourless liquid, b.p. 107°C/10 mm Hg (Found : C, 72.4; H, 9.9. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.9%); υ_{max} (thin film) 1960 and 1740 cm^{-1}; δ_H (300 MHz) 5.11-5.26 (2H, m), 4.13 (2H, q, J7Hz), 3.00 (2H, dd, J2, 7Hz), 1.93-2.05 (2H, m), 1.30-1.40 (4H, m), 1.24 (3H, t, J7Hz), 0.89 (3H, t, J7Hz); m/z (ci) 183 (M^++H).

Nona-3,4-dien-1-o1 (129b)

Ethyl nona-3,4-dieneoate (128b) (29.0 g, 0.159 mol) in ether (50 ml) was added to a stirred suspension of $LiAlH_4$ (4.0 g, 0.106 mol) in ether (150 ml) at -78°C. The mixture was stirred at room temperature for 1 h and then quenched with aqueous NaOH. The suspension was filtered and the filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by distillation to give nona-3,4-diene-1-o1 (129b) (19 g, 85%) as a colourless oil, b.p. 89-90°C/5 mm Hg (Found: C, 76.9; H, 11.2. $C_9H_{16}O$ requires C, 77.1; H, 11.4%); υ_{max} (thin film) 3310 and 1960 cm^{-1}; δ_H (300 MHz) 5.10-5.20 (2H, m), 4.69 (2H, q, J7Hz), 2.20-2.30 (2H, m), 1.93-2.05 (2H, m), 1.28-1.46 (5H, m), 0.90 (3H, t, J7Hz); m/z (ci) 141 (M^++H).

Deca-4,5-dienenitrile (130b)

Tosyl chloride (9.3 g, 48 mmol) and DMAP (10 mg) were added to a stirred solution of nona-3,4-dien-1-ol (129b) (5 g, 32 mmol) in pyridine (30 ml) at 0°C

and the reaction mixture was then stored at +4°C for 16 h. The mixture was neutralised with aqueous 2N HCl and then diluted with ether (150 ml). The ether layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure to give the crude tosylate which was used without further purification.

The crude tosylate prepared above and NaCN (4g, 80 mmol) were added to DMSO (150 ml) and heated at 80°C for 3 h. The reaction mixture was cooled and then poured onto water (300 ml) and the product extracted with ether (3 x 100 ml). The combined extracts were washed with brine (50 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with petrol-ether (19:1), deca-4,5-dienenitrile (130b) (4.0 g, 56%) as a yellow oil, b.p. 78-82°C/2 mm Hg (Found: C, 80.9; H, 10.4; N, 9.4. $C_{10}H_{15}N$ requires C, 80.5; H, 10.1; N, 9.4%); υ_{max} (thin film) 2240 and 1950 cm^{-1}; δ_H (300 MHz) 5.25 (1H, m), 5.15 (1H, m), 2.40 (2H, t, J7Hz), 2.25-2.35 (2H, m), 1.96-2.05 (2H, m), 1.30-1.40 (4H, m), 0.88 (3H, t, J7.5Hz); m/z (ci) 150 (M^++H).

Undeca-5,6-dienenitrile (134)

Using a similar procedure to that described for (103b), deca-4,5-dien-1-ol (133) was reacted with tosyl chloride and displacement with cyanide to give undeca-5,6-dienenitrile (134) (3.5 g, 62%) as a colourless oil (Found: C, 81.2; H, 10.3; N, 8.5. $C_{11}H_{17}N$ requires C, 81.0; H, 10.4; N, 8.6%); υ_{max} (thin film) 2250 and 1960 cm^{-1}; δ_H(300 MHz) 5.15 (1H, m), 5.05 (1H, m), 2.38 (2H, t, J7.5Hz), 2.06-2.18 (2H, m), 1.95-2.05 (2H, m), 1.71-1.85 (2H, m), 1.25-1.45 (4H, m), 0.89 (3H, t, J7.5Hz); m/z (ci) 164 (M^++H).

Undeca-5,6-dienylamine (135b)

Undeca-5,6-dienenitrile (134) (2.5 g, 15 mmol) in ether (5 ml) was added to a stirred suspension of $LiAlH_4$ (0.6 g, 15 mmol) in ether (10 ml) at -78°C. The

reaction mixture was stirred at room temperature for 1 h and then quenched with aqueous NaOH. Following filtration, the filtrate was dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by distillation, to give (135b) (1.92 g, 77%) as a pale yellow oil, b.p. 74-75°C/0.7 mm Hg (Found: C, 79.5; H, 12.6; N, 8.8. $C_{11}H_{21}N$ requires C, 79.0; H, 12.6; N, 8.4%); υ_{max} (thin film) 3300 and 1960 cm^{-1}; δ_H (300 MHz) 5.00-5.12 (2H, m), 2.68 (2H, t, J7Hz), 1.90-2.05 (4H, m), 1.07-1.57 (10H, m), 0.89 (3H, t, J7Hz); m/z (ci) 168 (M^++H).

Deca-4,5-dienylamine (131b)

Using a similar procedure to that for (135b), reduction of (130b) gave deca-4,5-dienylamine (131b) (7.0 g, 70%) as a yellow oil,
b.p. 65-68°C/1 mm Hg (Found: C, 78.6; H, 12.5; N; 9.2. $C_{10}H_{19}N$ requires C, 78.4; H, 12.4; N, 9.15%); υ_{max} (thin film) 3300 and 1950 cm^{-1}; δ_H (300 MHz) 5.00-5.10 (2H, m), 2.70 (2H, t, J7Hz), 1.90-2.06 (4H, m), 1.53 (2H, p, J7Hz), 1.23-1.43 (6H, m), 0.88 (3H, t, J7Hz); m/z (ci) 154 (M^++H).

Deca-4,5-dien-1-ol (133)

Di-isobutylaluminium hydride (27 ml, 0.04 mol, 1.5 M in toluene) was added to a stirred solution of deca-4,5-dienenitrile (130b) (6.0 g, 0.04 mol) in ether (50 ml). The reaction mixture was stirred at room temperature for 30 min and then aqueous 2N HCl (30 ml) was added. The resulting mixture was extracted with ether (3 x 100 ml) and the combined extracts were dried ($MgSO_4$) and concentrated carefully, to about 10 ml. This ethereal solution was added to ethanol (60 ml) and $NaBH_4$ (1.5 g, 0.04 mol) was added. After 30 min at room temperature the reaction mixture was quenched with water, diluted with ether (100 ml) and the ether layer separated using ether (3 x 50 ml). The organic extracts were combined, dried ($MgSO_4$), concentrated under reduced pressure

and purified by flash chromatography to give, on elution with petrol-ether (5:1), deca-4,5-dien-1-ol (133) (6.0 g, 95%) (Found: C, 77.8; H, 11.2. $C_{10}H_{18}O$ requires C, 77.9; H, 11.7%); υ_{max} (thin film) 3300 and 1950 cm^{-1}; δ_H (300 MHz) 5.10-5.20 (2H, m), 3.66 (2H, t, J6Hz), 1.90-2.10 (4H, m), 1.68 (2H, p, J6Hz), 1.26-1.45 (5H, m), 0.89 (3H, t, J5Hz); m/z (ci) 155 (M^++H).

Octan-6,7-dienenitrile

Methanesulphonyl chloride (2.5 ml, 32 mmol) in CH_2Cl_2 (10 ml) was added slowly to hepta-5,6-dien-1-ol (136) (3.30 g, 29 mmol) and triethylamine (5.8 ml, 40 mmol) in CH_2Cl_2 (200 ml) at -30°C. The reaction mixture was stirred at -10°C for 1 hour and then poured onto aqueous sodium bicarbonate (100 ml). The resulting mixture was extracted with CH_2Cl_2 (3 x 50 ml) and the extracts were then combined, washed with brine (50 ml) and dried ($MgSO_4$). The solution was concentrated under reduced pressure to give the crude mesylate which was used without further purification.

A stirred solution of the crude mesylate (prepared above) and KCN (7.5 g, 116 mmol) in DMSO (100 ml) was heated at 75°C for 2 h. The reaction mixture was cooled and then poured onto water (100 ml) and the product extracted with ether (3 x 50 ml). The combined extracts were washed with water (50 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with CH_2Cl_2, octa-6,7-dienenitrile (3.30 g, 94%) as a colourless oil (Found: M^+ 121.089. $C_8H_{11}N$ requires 121.089); υ_{max} (thin film) 2200, 1950, 850 cm^{-1}; δ_H (300 MHz) 5.05 (1H, p, J7Hz), 4.60-4.70 (2H, m), 2.34 (2H, t, J7.5Hz), 1.96-2.07 (2H, m), 1.61-1.76 (2H, m), 1.50-1.61 (2H, m); m/z (ci) 122 (M^++H).

N-(Benzyloxycarbonyl)hexa-4,5-dienylamine (140a)

Benzyl chloroformate (1.1 ml, 7.7 mmol) was added to hexa 4,5-dienylamine (131a) (0.72 g, 7.7 mmol) and triethylamine (1 ml, 7.7 mmol) in ether (10 ml) at 0°C. The reaction mixture was stirred for 1 h at room temperature, washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with petrol-ether (3:2), (140a) (0.94 g, 52%) as a pale yellow oil (Found: M^++H, 232.136. $C_{14}H_{17}NO_2$+H requires 232.134); υ_{max} (thin film) 3300, 1950, 1705 and 840 cm^{-1}; δ_H (300 MHz) 7.35 (5H, s), 5.09 (1H, m), 5.09 (2H, s), 4.75 (1H, br.s), 4.63-4.72 (2H, m), 3.22 (2H, q, J7Hz) 1.98-2.08 (2H, m), 1.58-1.68 (2H, m); m/z (ci) 232 (M^++H).

N-(Benzyloxycarbonyl)deca-4,5-dienylamine (140b)

Using a similar procedure to that described for (140a), benzyl chloroformate reacted with deca-4,5-dienylamine (131b), to give (140b) (2.1 g, 60%) as a straw coloured oil (Found: C, 75.4; H, 9.0; N, 5.1. $C_{18}H_{25}NO_2$ requires C, 75.3; H, 8.7; N, 4.9%); υ_{max} (thin film) 3300, 1950 and 1700 cm^{-1}; δ_H (300 MHz) 7.34 (5H, br.s), 5.09 (4H, br.s), 4.75 (1H, br.s), 3.22 (2H, q, J7.5Hz), 1.90-2.05 (4H, m), 1.55-1.58 (2H, m), 1.32-1.40 (4H, m), 0.89 (3H, t, J7Hz).

N-(Benzyloxycarbonyl)hepta-5,6-dienylamine (141a)

Using a similar procedure to that for (140a), benzyl chloroformate was reacted with hepta-5,6-dienylamine (135a) to give (141a) (0.195 g, 56%) as a straw coloured oil (Found: C, 73.5; H, 8.1; N, 5.9. $C_{15}H_{19}NO_2$ requires C, 73.5; H, 7.75; N, 5.7%); υ_{max} (thin film) 3300, 1950 and 1700cm^{-1}; δ_H (300 MHz) 7.40 (5H, br.s), 5.06-5.09 (1H, m), 5.09 (2H, s), 4.74 (1H, br.s), 4.61-4.70 (2H, m), 3.20 (2H, q, J7Hz), 1.95-2.05 (2H, m), 1.38-1.62 (4H, m); m/z (ci) 246 (M^++H).

N-(Benzyloxycarbonyl)undeca-5,6-dienylamine (141b)

Using a similar procedure to that described for (140a), benzyl chloroformate was reacted with undeca-5,6-dienylamine (135b) to give (141b) (1.0 g, 63%) (Found: C, 75.8; H, 8.8; N, 4.8. $C_{19}H_{27}NO_2$ requires C, 75.75; H, 9.0; N, 4.65%); υ_{max} (thin film) 3300, 1950 and 1700 cm^{-1}; δ_H (300 MHz) 7.36 (5H, br.s), 5.08 (2H, s), 5.00-5.20 (2H, m), 4.72 (1H, br.s), 3.19 (2H, q, J7Hz) 1.98 (4H, m), 1.26-1.70 (8H, m), 0.90 (3H, t J7Hz); m/z (ci) 302 (M^++H).

Ethyl N-(hexa-4,5-dienyl)acetimidate (142a)

Hexa-4,5-dienylamine (131a) (2 g, 0.02 mol) in CH_2Cl_2 (10 ml) was added dropwise to an ice cold solution of ethyl acetimidate. HCl (2.55 g 0.02 mol) in CH_2Cl_2 (90 ml). The reaction mixture was stirred at 0°C for 6 h, diluted with CH_2Cl_2 (100 ml) and washed with water (50 ml). The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (basic alumina) to give, on elution with CH_2Cl_2, (142a) (2.0 g, 60%) as a colourless oil (Found: C, 71.8; H, 10.4; N, 8.28. $C_{10}H_{17}NO$ requires C, 71.85; H, 10.2, N, 8.4%); υ_{max} (thin film) 1950, 1680 and 840 cm^{-1}; δ_H (300 MHz) 5.12 (1H, p, J7Hz), 4.60-4.70 (2H, m), 4.00 (2H, q, J7Hz), 3.20 (2H, t, J7Hz), 2.00-2.09 (2H, m), 1.87 (3H, s), 1.65 (2H, p, J7Hz), 1.22 (3H, t, J7Hz); m/z (ci) 168 (M^++H).

Ethyl N-(deca-4,5-dienyl)acetimidate (142b)

Using a similar procedure to that described for (142a), deca-4,5-dienylamine (131b) was reacted with ethyl acetimidate. HCl, to give a ethyl N-(deca-4,5-dienyl)acetimidate (142b) (2.2 g, 81%) as a colourless oil (Found: C, 74.9; H, 11.4; N, 6.2. $C_{14}H_{25}NO$ requires C, 75.3; H, 11.2; N, 6.3%); υ_{max} (thin film) 1960 and 1680 cm^{-1}; δ_H (300 MHz) 5.01-5.09 (2H, m), 4.00 (2H, q, J7Hz), 3.02 (2H, t, J7Hz), 1.90-2.10 (4H, m), 1.83 (3H, s), 1.61 (2H, p, J7Hz),

1.30-1.40 (4H, m), 1.21 (3H, t, J7Hz), 0.88 (3H, t, J7Hz); m/z (ci) 224 (M^++H).

Ethyl N-(hepta-5,6-dienyl)acetimidate (143a)

Using a similar procedure to that described for (142a), hepta-5,6-dienylamine (135a) was reacted with ethyl acetimidate. HCl, to give (143a) (80 mg, 27%) as a colourless oil (Found: M^++H, 182.1515. $C_{11}H_{19}NO$+H requires 182.154); υ_{max} (thin film) 1960, 1680 and 840 cm^{-1}; δ_H (300 MHz) 5.10 (1H, p, J7Hz), 4.11-4.20 (2H, m), 4.01 (2H, q, J7Hz), 3.18 (2H, t, J7Hz), 1.95-2.10 (2H, m), 1.84 (3H, s), 1.40-1.60 (4H, m), 1.22 (3H, t, J7Hz); m/z (ci) 182 (M^++H).

Ethyl N-(undeca-5,6-dienyl)acetimidate (143b)

Using a similar procedure to that described for (142a), undeca-5,6-dienylamine (135b) reacted with ethyl acetimidate. HCl, to give (143b) (0.45 g, 41%) as a colourless oil (Found: M^++H, 238.205. $C_{15}H_{27}NO$+H requires 238.207); υ_{max} (thin film) 1960 and 1660 cm^{-1}; δ_H (300 MHz) 5.07 (2H, p, J5Hz), 4.01 (2H, q, J7Hz), 3.18 (2H, t, J7Hz), 1.92-2.06 (4H, m), 1.84 (3H, s), 1.26-1.81 (8H, m), 1.22 (3H, t, J7Hz), 0.89 (3H, t, J5Hz); m/z (ci) 238 (M^++H).

N-(Benzyloxycarbonyl)-2-ethenylpyrrolidine (144a)

Silver tetrafluoroborate (0.17 g, 0.84 mmol) was added in a single portion to a stirred solution of N-(benzyloxycarbonyl)hexa-4,5-dienylamine (140a) (0.20 g, 0.86 mmol) in CH_2Cl_2 (15 ml) at room temperature. The reaction mixture was stirred for 3 h in the dark, then diluted with CH_2Cl_2 (50 ml) and washed with brine. The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with CH_2Cl_2, (144a) (0.17 g, 85%) as a colourless oil (Found: C, 72.9; H, 7.3; N, 6.3. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%); υ_{max} (thin film) 1700 cm^{-1}; δ_H (360 MHz) [$(CD_3)_2SO$, spectrum run at 353 K] 7.28-7.40 (5H,

m), 3.38 (2H, t, J6Hz), 4.33 (1H, m), 4.96-5.10 (2H, m) 5.08 (2H, s), 5.82 (1H, m), 1.65-2.90 (4H, m); m/z (ci) 232 (M^++H).

N-(Benzyloxycarbonyl)-2-hex-1-enylpyrrolidine (144b)

Using a similar procedure to that described for (144a), N-(benzyloxycarbonyl) deca-4,5-dienylamine (140b) reacted with silver tetrafluoroborate to give (144b) (100 mg, 50%) (Found: C, 75.8; H, 8.6; N, 4.6. $C_{18}H_{25}NO_2$ requires C, 75.3; H, 8.7; N, 4.9%); υ_{max} (thin film) 1700 cm^{-1}; δ_H (360 MHz) [$(CD_3)_2SO$, spectrum run at 353 k] 7.32 (5H, s), 5.32-5.48 (2H, m), 5.10 (1H, d, J12Hz) 5.01 (1H, d, J12Hz), 4.30 (1H, m), 3.32-3.42 (2H, m), 1.60-2.05 (6H, m), 1.20-1.35 (4 H, m), 0.86 (3H, m); m/z (ci) 288.196 (M^++H).

N-(Benzyloxycarbonyl)-2-ethenylpiperidine (146a)

Using a similar procedure to that described for (144a), N-(benzyloxycarbonyl) hepta-5,6-dienylamine (141a) was treated with silver tetrafluoroborate. After 5 days the reaction had gone to approximately 50% completion, to give (146a) (20 mg 70% based on recovered starting material, 21 mg) (Found: M^++H, 246.143. $C_{15}H_{19}NO_2$+H requires 246.149); υ_{max} (thin film) 1700 cm^{-1}; δ_H (300 MHz) 7.32 (5H, br.s), 5.78 (1H, ddd, J5, 10 and 15Hz), 5.19 (1H, br.d, J10Hz), 5.15 (2H, s), 5.06 (1H, d, J15Hz), 4.89 (1H, br.s), 4.05 (1H, br.d, J12Hz), 2.91 (1H, br.t, J12Hz), 1.33-1.82 (6H, m); m/z (ci) 246 (M^++H).

N-(Benzyloxycarbonyl)-2-hex-1-enylpiperidine (146b)

Using a similar procedure to that described for (144a), N-(benzyloxycarbonyl) undeca-5,6-dienylamine (141b) was treated with silver tetrafluoroborate after 11 days to give (146b) (0.113 g, 80% based on recovered starting material, 30 mg) (Found: C, 76.0; H, 9.3; N, 5.0. $C_{19}H_{27}NO_2$ requires C, 75.75; H, 9.0; N, 4.65%); υ_{max} (thin film) 1700 cm^{-1}; δ_H (300 MHz) 7.27-7.40 (5H, m), 5.40-5.50

(2H, m), 5.17 (1H, d, J12Hz), 5.10 (1H, d, J12Hz), 4.84 (1H, br.s), 4.00 (1H, br.d, J12Hz), 2.90 (1H, br.t, J12Hz), 1.96-2.01 (2H, m), 1.21-1.75 (10H, m), 0.89 (3H, t, J7Hz); m/z (ci) 302 (M^++H).

1-Acetyl-2-ethenylpyrrolidine (147)

Silver tetrafluoroborate (203 mg, 1.04 mmol) was added to a solution of ethyl N-(hexa-4,5-dienyl)acetimidate (142a) (175 mg, 1.04 mmol) in CH_2Cl_2 (30 ml). The reaction mixture was stirred at room temperature for 5 h, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with ethyl acetate, (147) (20 mg, 14%) as a colourless oil (Found: M^+, 139.099. $C_8H_{13}NO$ requires 139.100); υ_{max} (thin film) 1640 and 1410 cm^{-1}; δ_H (300 MHz) 5.72 (1H, m), 4.94-5.15 (2H, m), 4.61 and 4.29 (1H, m), 3.42-3.51 (2H, m), 1.70-2.10 (7H, m); m/z (ci) 140 (M^++H).

N-(Benzyloxycarbonyl)-2-(1-bromoethenyl)pyrrolidine (148a)

N-Bromosuccinimide (77 mg, 0.438 mmol) was added in a single portion to a stirred solution of N-(benzyloxycarbonyl)hexa-4,5-dienylamine (140a) (100 mg, 0.438 mmol) in CH_2Cl_2 (20 ml) at room temperature. The reaction mixture was stirred at room temperature for 14 days in the dark and then diluted with CH_2Cl_2 (100 ml) and washed with water (20 ml). The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with petrol-ether (3:2), (148a) (74 mg, 55%) (Found: C, 54.0; H, 5.2; N, 4.6. $C_{14}H_{16}BrNO_2$ requires C, 54.2; H, 5.2; N, 4.5%); υ_{max} (thin film) 1700 and 1630 cm^{-1}; δ_H (360 MHz) [$(CD_3)_2SO$ spectrum run at 353 K] 7.36 (5H, m), 5.76 (1H, d, J2Hz), 5.50 (1H, d, J2Hz), 5.10 (2H, s), 4.49 (1H, m), 3.42-3.52 (2H, m), 2.05-2.16 (2H, m), 1.80-1.92 (2H, m); m/z (ci) 310 and 312 (M^++H).

N-(Benzyloxycarbonyl)-2-(1-bromohex-1-enyl)pyrrolidine (148b)

Using a similar procedure to that described for (148a), N-(benzyloxycarbonyl) deca-4,5-dienylamine (140b) was reacted with N-bromosuccinimide and after 6 days gave N-(benzyloxycarbonyl)-2-(1-bromohex-1-enyl)pyrrolidine (148b) (100 mg, 50%) (Found: M^+, 365.097. $C_{18}H_{24}BrNO_2$ requires 365.099); υ_{max} (thin film) 1710 cm^{-1}; δ_H (360 MHz) [$(C_3D)_2SO$ spectrum run at 353 K] 7.25-7.45 (5H, m), 5.80 (1H, t, J6Hz), 5.00-5.12 (2H, m), 4.48 (1H, br.d), 3.40-3.58 (2H, m), 2.03-2.18 (3H, m), 1.75-1.93 (3H, m), 1.22-1.38 (4H, m), 0.89 (3H, t, J6Hz); m/z (ci) 366 and 368 (M^++H).

N-(Benzyloxycarbonyl)-4-chloro-5-(phenylseleno)hex-5-enylamine (149a), (E)-and (Z)-N-(Benzyloxycarbonyl)-6-chloro-5-(phenylseleno) hex-4-enylamine (149b) (149c).

Benzeneselenenyl chloride (0.17 g, 0.86 mmol) was added to a stirred solution of N-(benzyloxycarbonyl)hexa-4,5-dienylamine (140a) (0.20 g, 0.86 mmol) in CH_2Cl_2 (20 ml). After 10 min the reaction mixture was diluted with ether (50 ml), washed with aqueous sodium carbonate (20 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The three isomers were separated by prep tlc elution with petrol- ether (3:2), (149a) (149b) and (149c) in the ratio (1:1:1) (0.28 g, 78%) (the compound was characterised as a mixture but the nmr data refers to the separated isomers) (Found: C, 56.85; H, 5.2; N, 3.5. $C_{20}H_{22}ClNO_2Se$ requires C, 56.8; H, 5.2; N, 3.3%); υ_{max} (thin film) 3300, 1700, 740 and 690 cm^{-1};

Top compound δ_H (300 MHz) 7.20-7.60 (10 H, m), 5.90 (1H, s), 5.28 (1H, s), 5.11 (2H, s), 4.72 (1H, br.s), 4.50 (1H, t, J7Hz), 3.20 (2H, q, J7.5Hz), 1.95-2.04 (2H, m), 1.52-1.70 (2H, m).

Middle compound δ_H (300 MHz) 7.25-7.60 (10H, m), 6.29 (1H, J7.5Hz), 5.10 (2H, s), 4.85 (1H, br.s), 4.10 (2H, s), 3.20 (2H, q, J7Hz), 2.39 (2H, q, J7Hz),

1.56-1.70 (2H, m).

Bottom compound δ_H (300 MHz) 7.25-7.60 (10H, m), 6.11 (1H, t, J7Hz), 5.10 (2H, s), 4.85 (1H, br.s), 4.16 (2H, s), 3.20 (2H, q, J7Hz), 2.24 (2H, q, J7Hz), 1.60-1.70 (2H, m).

N-(Benzyloxycarbonyl)-2-(1-phenylselenoethenyl)pyrrolidine (150)

Sodium hydride (3 mg, 0.12 mmol, 60% dispersion in oil) was added to a stirred solution of N-(benzyloxycarbonyl)-4-chloro-5-phenylselenohexa-5-en ylamine (149a) (47 mg, 0.10 mmol) in THF (10 ml) at room temperature. The reaction mixture was stirred at room temperature for 1 h, quenched with wet ether (10 ml), washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with ether-petrol (2:3), (150) (10 mg, 21%) as a yellow oil (Found: M^+, 387.074. $C_{20}H_{21}NO_2Se$, requires 387.074); υ_{max} (thin film) 1700 cm^{-1}; δ_H (250 MHz) [$(CD_3)_2SO$ spectrum run at 353 K] 7.20-7.56 (10 H, m), 5.61 (1H, s), 5.20 (1H, s), 5.03-5.10 (2H, m), 4.48 (1H, br.d, J7Hz), 3.48 (2H, br.t, J7Hz) 1.21-1.70 (4H, m); m/z (ci) 388 (M^++H).

1-Acetyl-2-(1-phenylselenoethenyl)pyrrolidine (151a)

Benzeneselenenyl bromide (0.26 g, 1.07 mmol) was added in a single portion to a stirred solution of ethyl N-(hexa-4,5-dienyl)acetimidate (142a) (0.18 g, 1.07 mmol) in $CHCl_3$ (25 ml) at room temperature. The reaction was stirred for 4 h, then concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with ethyl acetate, (151a) (0.13 g, 42%) as a yellow oil (Found: M^++H, 295.050. $C_{14}H_{17}NOSe$+H requires 295.0475); υ_{max} (thin film) 1650 and 1570 cm^{-1}; δ_H (250 MHz) [$(CD_3)_2SO$ spectrum run as 363 K] 7.2-7.7 (5H, m), 5.60 (1H, br.s), 5.18 (1H, br.s), 4.58 (1H, m), 3.29-3.59 (2H, m), 1.70-2.10 (7H, m); m/z (ci) 295 (M^++H).

1-Acetyl-2-(1-phenylselenohex-1-enyl)pyrrolidine (151b)

Using a similar procedure to that described before, ethyl N-(deca-4,5-dienyl) acetimidiate (142b) was reacted with benzeneselenenyl bromide, to give (151b) (0.17 g, 50%) as a yellow oil (Found: M^++H, 352.1145. $C_{18}H_{25}NOSe$+H requires 352.1179); υ_{max} (thin film) 1650 cm^{-1}; δ_H (300 MHz) 7.10-7.57 (5H, m), 5.55 and 5.72 and 5.94 and 6.06 (1H, 4xt J7.5 Hz), 4.20 and 4.73 (1H, 2xm), 3.31-3.60 (2H, m), 2.20-2.48 (6H, m) 1.62 and 1.75 1.91 and 1.95 (3H, 4xs), 1.20-1.40 (4H, m), 0.89 (3H, m); m/z (ci) 352 (M^++H).

1-Ethyl-2-(1-phenylselenohex-1-enyl)pyrrolidine (152)

1-Acetyl-2-(1-phenylselenohex-1-enyl) (151b) (75 mg, 0.214 mmol) in ether (5 ml) was added to a suspension of $LiAlH_4$ (16 mg, 0.41 mmol) in ether (10 ml) at 0°C. The mixture was stirred at room temperature for 2 h diluted with ether (50 ml) and quenched with aqueous NaOH. The resulting mixture was filtered, and the filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with CH_2Cl_2-methanol (20:1), (152) (30 mg, 44%) as a yellow oil (Found: M^+, 337.131. $C_{18}H_{27}NSe$ requires 337.131); υ_{max} (thin film) 1575 cm^{-1}; δ_H (300 MHz) 7.10-7.41 (5H, m), 6.17 (1H, br.s), 3.24 (1H, m), 2.70-2.95 (2H, m), 1.59-2.38 (8H, m), 1.18-1.38 (4H, m), 1.04 (3H, t, J6Hz), 0.83 (3H, t, J6Hz) m/z (ei) 337 (M^+).

2-Hydroxyundeca-5,6-dienenitrile (158)

Sulphuric acid (0.8 ml,8 M) was added dropwise to an ice cold solution of NaCN (0.49 g, 10.0 mmol) and deca-4,5-dienal (132) (0.42 g 2.7 mmol) in water (0.5 ml). The reaction mixture was warmed to room temperature and then the resulting mixture extracted with ether (3 x 5 ml) and the combined extracts

were, dried ($MgSO_4$) and concentrated under reduced pressure to give (158) (0.40 g, 83%) as a pale yellow oil (Found: C, 73.5; H, 9.5; N, 7.8. $C_{11}H_{17}NO$ requires C, 73.7; H, 9.5; N, 7.8%); υ_{max} (thin film) 3400, 2200 and 1960 cm^{-1}; δ_H (300 MHz) 5.05-5.21 (2H, m), 4.56 (1H, m), 2.47 (1H, m), 2.15-2.25 (2H, m), 1.92-2.05 (4H, m), 1.30-1.45 (4H, m), 0.89 (3H, t, J6Hz); m/z (ci) 180.138 (M^++H).

2-Hydroxyocta-6,7-dienenitrile (159)

Using a similar procedure to that described for (158), hepta-5,6-dienal (137) was reacted with NaCN to give (159) (0.360 g, 56%) as a colourless oil (Found: C, 69.7, H, 8.2; N, 10.5. $C_8H_{11}NO$ requires C, 70.1; H, 8.0; N 10.2%); υ_{max} (thin film) 3420, 2240 weak and 1955 cm^{-1}; δ_H (300 MHz) 5.10 (1H, p, J7Hz), 4.63-4.75 (2H, m), 4.50 (1H, t, J7Hz), 2.70 (1H, m), 2.00-2.10 (2H, m), 1.84-1.93 (2H, m), 1.60-1.68 (2H, m); m/z (ci) (M^+-HCN) 111.

(E)-2-Cyano-5-(hex-1-enyl)tetrahydrofuran (160)

Silver tetrafluoroborate (0.194 g, 0.83 mmol) was added to a stirred solution of 2-hydroxyundeca-5,6-dienenitrile (158) (0.15 g, 0.83 mmol) in CH_2Cl_2 (10 ml) at room temperature and the reaction mixture was stirred for 2 days in the dark. The reaction mixture was diluted with CH_2Cl_2 (50 ml), washed with brine (10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with petrol-ether (6:1), (160) (0.85 g, 57%) as a 1:1 mixture of diastereomers (Found: M^+, 179.134. $C_{11}H_{17}NO$ requires 179.131); υ_{max} (thin film) 2230 and 1670 cm^{-1};δ_H (300 MHz) 5.72 (1H, dt, J15, 7Hz), 5.50 (1H, dd, J15, 7Hz), 4.75 (1H, dd, J7, 2Hz), 4.51 (1H, q, J7Hz), 2.15-2.42 (3H, m), 1.95-2.08 (2H, m), 1.69 (1H, m), 1.21-1.44 (4H, m), 0.87 (3H, t, J7Hz);

δ_H (300 MHz) 5.72 (1H, dt, J15, 7Hz), 5.49 (1H, dd, J15, 7Hz), 4.65 (1H, dd, J7,

2Hz), 4.40 (1H, q, J7Hz), 2.10-2.40 (3H, m), 1.90-2.00 (2H, m), 1.89 (1H, m), 1.21-1.44 (4H, m), 0.87 (3H, t, J7Hz); m/z (ci) 180 (M^++H).

2-(1-Bromoethenyl)tetrahydropyran (161)

A solution of hepta-5,6-dien-1-ol (136) (180 mg, 0.60 mmol) and N-bromosuccinimide (280 mg, 0.60 mmol) in 1,2-dichloroethane (30 ml) was stirred at room temperature for 3 h. The reaction was concentrated under reduced pressure and the residue was purified by flash chromatography to give, on elution with $CHCl_3$, (161) (0.16 g, 52%) as a colourless oil (Found: M^+-H, 188.991. $C_7H_{11}BrO$-H requires 188.9915); υ_{max} (thin film) 1630 and 1090 cm^{-1}; δ_H (300 MHz) 5.90 (1H, s), 5.51 (1H, s), 4.07 (1H, br.d, J10Hz), 3.81 (1H, br.d, J10Hz), 3.50 (1H, t, J10Hz), 1.84-1.96 (2H, m), 1.40-1.62 (4H, m); m/z (ci) 189 (M^+-H).

Methyl 2-(6-methoxytetrahydropyran-1-yl)prop-2-enoate (163)

Methanol (0.04 ml, 1.0 mmol) was added to a solution of hepta-5,6-dienal (137) (110 mg, 1.0 mmol) in $CDCl_3$ (1 ml) in a nmr tube. After 30 min all the aldehyde had reacted, and the crude hemiacetal (162) was added to a suspension of palladium chloride (17 mg, 0.1 mmol), $CuCl_2$ (530 mg, 3.9 mmol) and triethylamine (0.14 ml, 1.0 mmol) in methanol (5 ml) and the reaction mixture was stirred for 5 h under an atmosphere of carbon monoxide. The mixture was then diluted with ether (150 ml) and washed with 10% aqueous ethanolamine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by flash chromatography to give, on elution with petrol-ether (4:1), (163) (30 mg, 15%) as a colourless oil as a 2:1 mixture of inseparable isomers (Found: C, 60.3; H, 7.9. $C_{10}H_{16}O_4$ requires 60.0; H, 8.0%); υ_{max} (thin film) 2170 and 1610 cm^{-1};

δ_H (270 MHz) major isomer 6.28 (1H, m), 5.91 (1H, t, J2Hz), 4.81 (1H, s), 4.65

(1H, d, J11Hz), 3.77 (3H, s), 3.49 (3H, s), 1.59-2.08 (6H, m);

δ_H (270 MHz) minor isomer 6.28 (1H, m), 6.00 (1H, t, J2Hz), 4.42 (1H, dd, J2, 9Hz), 4.30 (1H, d, J11Hz), 3.77 (3H, s), 3.49 (3H, s), 1.59-2.08 (6H, m); m/z (ci) (M^+-MeOH) 169.

2,3-Di(tetrahydropyran-2-yl)buta-1,3-diene (164)

A suspension of palladium chloride (0.03 g, 0.178 mmol), $CuCl_2$ (0.71 g, 5.3 mmol) and hepta-5,6-dien-1-ol (136) (0.20 g, 1.78 mmol) in methanol (10 ml) was heated at 65°C for 30 min. The reaction mixture was diluted with ether (50 ml) washed with 10% aqueous ethanolamine and extracted with ether (3 x 20 ml). The extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with petrol-ether (6:1), the dimer (164) (0.060 g, 30%) (Found: M^++H, 223.171. $C_{14}H_{22}O_2$ +H requires 223.170); υ_{max} (thin film) 1590 cm^{-1}; δ_H (300 MHz) 5.19 (2H, d, J7Hz), 5.06 (2H, d, J7Hz) 4.05 (2H, br.d, J12Hz), 3.95 (2H, br.t, J9Hz), 3.49 (2H, br.t, J10Hz), 1.69-1.91 (4H, m), 1.40-1.68 (4H, m), 1.20-1.40 (4H, m); δ_c 149.2, 148.8, 111.7, 110.9, 78.1, 77.7, (2 x 68.8), 31.6, 31.5, (2 x 25.9), 23.8, 23.7; m/z (ci) 223 (M^++H).

2,4-Di(tetrahydropyran-2-yl)penta-2,4-diene-3-one (165)

A suspension of hepta-5,6-dien-1-ol (136) (0.50 g, 4.46 mmol), palladium chloride (0.08 g, 0.44 mmol) and $CuCl_2$ (1.8 g, 13.4 mmol) in THF (30 ml) was stirred under an atmosphere of carbon monoxide for 4 h. The mixture was diluted with ether (30 ml) and washed with 10% aqueous ethanolamine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with petrol-ether (5:1), (165) (300 mg, 27%) as a 1:1 mixture of isomers (Found: M^+, 250.159. $C_{15}H_{22}O_3$ requires 250.157); υ_{max} (thin film) 1650 cm^{-1};

δ_H (300 MHz) 5.92 (2H, t, J1.5Hz), 5.75 (2H, t, J1.5Hz), 4.25 (2H, br.d, J10Hz), 4.05 (2H, m), 3.48-3.59 (2H, m), 1.78-1.88 (4H, m), 1.50-1.63 (6H, m), 1.22-1.36 (2H, m); δ_c 197.4, 149.4, 123.4, 75.5, 68.8, 31.7, 25.8, 23.5;

δ_H (300 MHz) 5.93 (2H, t, J1.5Hz), 5.73 (2H, t, J1.5Hz), 4.28 (2H, br.d, J10Hz), 4.05 (2H, m), 3.48-3.59 (2H, m), 1.78-1.88 (4H, m), 1.50-1.63 (6H, m), 1.22-1.34 (2H, m); δ_c 197.1, 149.6, 123.3, 75.4, 68.8, 31.5, 25.8, 23.5; m/z (ei) 250 (M^+).

Methyl 4-(tetrahydropyran-2-yl)penta-2,4-dienoate (166)

A suspension of palladium chloride (0.47 g, 2.6 mmol), triethylamine (0.56 ml, 3.9 mmol), methyl acrylate (1 ml, 13 mmol) and hepta-5,6-dien-1-ol (136) (0.30 g, 2.6 mmol) in CH_2Cl_2 (10 ml) were stirred at room temperature for 24 h. The reaction was diluted with CH_2Cl_2 (30 ml), washed with 10% aqueous ethanolamine and extracted with CH_2Cl_2 (3 x 50 ml). The extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with petrol-ether (2:1), (166) (80 mg, 15%) (Found: M^++H, 197.117. $C_{11}H_{16}O_3$+H requires 197.118); υ_{max} (thin film) 1730, 1625 and 1080 cm^{-1}; δ_H (300 MHz) 7.25 (1H, d, J15Hz), 6.00 (1H, d, J15Hz), 5.55 (1H, s), 5.42 (1H, s), 4.10-3.95 (2H, m), 3.71 (3H, s), 3.50 (1H, m), 1.50-1.92 (2H, m), 1.37-1.65 (4H, m); δ_c 167.3, 145.8, 144.3, 121.5, 118.1 76.8, 63.8, 51.4, 31.5, 25.7, 23.6; m/z (ci) 197 (M^++H).

Methyl 5-(tetrahydropyran-2-yl)-2,2-3,3-tetracyanocyclohexa-5-enoate (167)

Tetracyanoethylene (0.07 g, 0.56 mmol) and methyl 4-(tetrahydropyran-2-yl) penta-2,4-dienoate (166) (0.11 g, 0.56 mmol) in benzene (20 ml) were heated at 80°C for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography to give, on elution with CH_2Cl_2-methanol (50:1), (167) (40 mg, 30%) as a colourless oil (Found: M^++H,

325.128. $C_{17}H_{16}N_4O_3$+H requires 325.130); υ_{max} (thin film) 2260, 2180, 2120, 1749 and 1660 cm^{-1}; δ_H (300 MHz) 5.87 (1H, d, J15Hz), 4.61 (1H, br.d, J5Hz), 3.90-4.10 (2H, m), 3.98 (3H, s), 3.40-3.55 (3H, m), 2.18 (1H, m), 1.90 (1H, m), 1.79 (1H, m), 1.40-1.63 (3H, m); m/z (ci) 325 (M^++H).

Octa-6,7-dienylamine (193)

Octa-6,7-dienenitrile (2.0 g, 16.0 mmol) in ether (10 ml) was added to a stirred suspension of $LiAlH_4$ (0.63 g, 16.0 mmol) in ether (40 ml) at -20°C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 2 h. The reaction was quenched with aqueous NaOH and then filtered and the filtrate was carefully concentrated under reduced pressure to give (193) (1.60 g, 84%) as a pale yellow oil (Found: M^++H, 126.128. $C_8H_{15}N$+H requires 126.128); υ_{max}(thin film) 3300 (broad), 1950 and 840 cm^{-1}; δ_H (300 MHz) 5.08 (1H, p, J7Hz), 4.60-4.69 (2H, m), 2.68 (2H, t, J7Hz), 1.92-2.05 (2H, m), 1.24-1.50 (8H, m); m/z (ci) 126 (M+H).

Nona-7,8-dienylamine (194)

(E)- and (Z)-Nona-7,8-dienal oxime (174) (100 mg, 0.66 mmol) in ether (2 ml) was added to a stirred suspension of $LiAlH_4$ (50 mg, 1.32 mmol) in ether (5 ml) at -78°C and the mixture was then allowed to warm to room temperature. The reaction was quenched with aqueous NaOH and then filtered, and the filtrate concentrated under reduced pressure to give (194) (80 mg, 88%) as a colourless oil (Found: 140.144. $C_9H_{17}N$+H requires 140.144); υ_{max} (thin film) 3300 broad, 1950 and 840 cm^{-1}; δ_H (300 MHz) 5.00 (1H, p, J7Hz), 4.51-4.59 (2H, m), 2.60 (2H, t, J7Hz), 1.85-1.96 (2H, m), 1.55-1.70 (2H, br.s), 1.20-1.40 (8H, m); m/z (ci) 140 (M+H).

Hepta-5,6-dienylamine (135a)

Using a similar procedure to that described for (194), (E)- and (Z)-hepta-5,6-dienal oxime (138) was reduced with $LiAlH_4$, to give (135a) (0.53 g, 50%) as a colourless oil b.p. 130°C (water pump) (Found: M+H, 112.108. $C_7H_{13}N$+H requires 112.112); υ_{max} (thin film) 3300 and 1950 cm^{-1}; δ_H (300 MHz) 5.09 (1H, p, J7Hz), 4.60-4.68 (2H, m), 2.66 (2H, t, J6Hz), 1.31-2.10 (8H, m); m/z (ci) 112 (M^++H).

Deca-8,9-dienylamine (195)

Using a similar procedure to that described for (194), (E)- and (Z)-deca-8,9-dienal oxime (192) was reduced with $LiAlH_4$, to give (195) (4.0 g, 87%) as a yellow oil (Found: M^++H, 154.159. $C_{10}H_{19}N$+H requires 154.1595); υ_{max} (thin film) 3300, 1950 and 850 cm^{-1}; δ_H (270 MHz) 5.05 (1H, p, J7Hz), 4.81-4.85 (2H, m), 2.68 (2H, t, J7Hz), 1.95-2.00 (2H, m), 1.62-1.75 (2H, m), 1.20-1.60 (10H, m); m/z (ci) 154 (M^++H).

N-(octa-6,7-dienyl)-4-methylbenzenesulphonamide (177)

Tosyl chloride (3 g, 16 mmol) was added to octa-6,7-dienylamine (193) (2g, 16 mmol) in pyridine (60 ml) at 0°C and the solution was stored at +4°C for 40 h. The pyridine was neutralised by 2N hydrochloric acid and the mixture was extracted with ether (3 x 100 ml). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with petrol-ether (3:2), (177) (3.37 g, 76%) as a yellow oil (Found: M^++H, 280.137. $C_{15}H_{21}NO_2S$+H requires 280.137); υ_{max} (thin film) 3300, 1950, 1595, 1330 and 1150 cm^{-1}; δ_H (300 MHz) 7.74 (2H, d, J8Hz), 7.28 (2H, d, J8Hz), 5.10 (1H, m), 5.00 (1H, p, J7Hz), 4.55-4.65 (2H, m), 2.88 (2H, q, J7Hz), 2.39 (3H, s), 1.85-1.95 (2H, m), 1.36-1.49 (2H, m), 1.20-1.36 (4H, m); m/z (ci) 280 (M^++H); m/z (ci) 280 (M^++H).

N-(hexa-4,5-dienyl)-4-methylbenzenesulphonamide (196)

Using a similar procedure to that described for (177), tosyl chloride was reacted with hexa-4,5-dienylamine (131a), to give (196) (3.8 g, 62%) as a yellow oil (Found: C, 62.2; H, 7.0; N, 5.6. $C_{13}H_{17}NO_2S$ requires C, 62.15; H, 6.8; N, 5.6%); υ_{max} (thin film) 3300, 1950, 1600, 1310 and 1160 cm^{-1}; δ_H (300 MHz) 7.73 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 5.00 (1H, p, J7Hz), 4.60-4.68 (2H, m); 4.50 (1H, m), 2.95 (2H, q, J7Hz), 2.42 (3H, s), 1.94-2.03 (2H, m), 1.59 (2H, q, J7Hz); m/z (ci) 252 (M^++H).

N-(hepta-5,6-dienyl)-4-methylbenzenesulphonamide (197)

Using a similar procedure to that described for (177), tosyl chloride was reacted with hepta-5,6-dienylamine (135a), to give (197) (2.2 g, 62%) as a yellow oil (Found: M^++H, 266.121. $C_{14}H_{19}NO_2S$+H requires 266.1215); υ_{max} (thin film) 3300, 1950, 1600, 1320 and 1150 cm^{-1}; δ_H (300 MHz) 7.73 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 5.00 (1H, p, J7Hz), 4.59-4.67 (3H, m), 2.92 (2H, q, J7Hz), 2.41 (3H, s), 1.88-1.98 (2H, m), 1.30-1.55 (4H, m); m/z (ci) 266 (M^++H).

N-(nona-7,8-dienyl)-4-methylbenzenesulphonamide (198)

Using a similar procedure to that described for (177), tosyl chloride was reacted with nona-7,8-dienylamine (194), to give (198) (3.0 g, 65%) as a yellow oil (Found: M^++H, 294.153. $C_{16}H_{23}NO_2S$+H requires 294.153); υ_{max} (thin film) 3280, 1950, 1600, 1320 and 1150 cm^{-1}; δ_H (300 MHz) 7.75 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 5.04 (1H, q, J7Hz), 4.60-4.68 (2H, m), 4.45 (1H, m), 2.90 (2H, q, J7Hz), 2.41 (3H, s), 1.88-1.98 (2H, m), 1.38-1.48 (2H, m), 1.20-1.30 (6H, m); m/z (ci) 294 (M^++H).

N-(deca-8,9-dienyl)-4-methylbenzenesulphonamide (199)

Using a similar procedure to that described for (177), tosyl chloride was reacted with deca-8,9-dienylamine (195), to give (199) (0.38 g, 48%) as a pale yellow oil (Found: C, 66.0; H, 8.4; N, 4.7. $C_{17}H_{25}NO_2S$ requires C, 66.4; H, 8.1; N, 4.6%); υ_{max} (thin film) 3300, 1950, 1595, 1320 and 1150 cm^{-1}; δ_H (300 MHz) 7.75 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 5.06 (1H, p, J7Hz), 4.26-4.69 (2H, m), 4.40 (1H, m), 2.88-2.96 (2H, m), 2.43 (3H, s), 1.90-2.02 (2H, m), 1.51-1.10 (10H, m); m/z (ci) 308 (M^++H).

2-(Chloroethyl)hepta-6,7-dienyl ether (176)

Silver triflate (100 mg, 4.0 mmol) was added to a stirred solution of octa-6,7-dien-1-ol (175) (50 mg, 40 mmol) in 1,2-dichloroethane (30 ml). The reaction mixture was stirred at 80°C in the dark for 3 days. Brine (10 ml) was added to the cooled solution and the mixture was then stirred for 30 min. The product was extracted with CH_2Cl_2 (150 ml), the extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with petrol-ether (3:1), (176) (13 mg, 29%) as a yellow oil (Found: M^++H, 189.104. $C_{10}H_{17}ClO$+H requires 189.104); υ_{max} (thin film) 1955 and 840 cm^{-1}; δ_H (300 MHz) 5.09 (1H, p, J7Hz), 4.61-4.78 (2H, m), 3.67 (2H, d, J5Hz), 3.62 (2H, d, J7Hz), 3.48 (2H, t, J7Hz), 1.92-2.08 (2H, m), 1.54-1.66 (2H, m), 1.20-1.48 (4H, m); m/z (ci) 189 (M^++H).

(R)-α-(6,7-octadienylamino)-N-methylbenzeneacetamide (178a)

Di-isobutylaluminium hydride (4.13 ml, 4.13 mmol, 1M solution in toluene) was added to a stirred solution of octa-6,7-dienenitrile (0.50 g, 4.13 mmol) in ether (30 ml). The reaction mixture was stirred at room temperature for 30 min, cooled to 0°C and then 2N HCl (5 ml) was added. The mixture was extracted with ether (3 x 20 ml) and the extracts combined, washed with brine (20 ml) and

dried ($MgSO_4$). The solution was concentrated under reduced pressure, to give the crude aldehyde, which was used without further purification. (R)-N-Methyl-2-phenyl acetamide (0.74 g, 4.4 mmol) in CH_2Cl_2 (10 ml) was added to a stirred suspension of the crude aldehyde (prepared above) and oven-dried $MgSO_4$ (1 g) in CH_2Cl_2 (30 ml). The reaction was stirred at room temperature for 2 h and then the suspension was filtered and most of the solvent removed under reduced pressure. The residue was diluted with methanol (30 ml) and $NaBH_4$ (0.16 g, 4.2 mmol) was added to this ice cold solution. The reaction mixture was stirred at room temperature for 2 h and quenched with water (10 ml). The mixture was extracted with ether (3 x 30 ml), the combined extracts were washed with brine (10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with CH_2Cl_2-methanol (100:3), (178a) (0.59 g, 53%) as a yellow oil (Found: M^++H, 273.198. $C_{17}H_{24}N_2O$+H requires 273.198); υ_{max} (thin film) 3300, 1955 and 1650 cm^{-1}; δ_H (300 MHz) 7.27-7.40 (5H, m), 7.18 (1H, br.s), 5.06 (1H, p, J7.5Hz), 4.60-4.70 (2H, m), 4.14 (1H, s), 2.83 (3H, d, J5Hz), 2.50-2.70 (2H, m), 1.93-2.05 (2H, m), 1.6 (1H, br.s), 1.30-1.55 (6H, m); m/z (ci) 273 (M^++H).

(R)-α-Methyl (6,7-octadienylamino)benzeneacetate (178b)

Using a similar procedure to that described for (178a), octa-6,7-dienal was reacted with (R)-2-phenyl methyl glycinate, to give (178b) (0.34 g, 21%) as a yellow oil (Found: M^++H, 274.182. $C_{17}H_{23}NO_2$+H requires 274.181); υ_{max} (thin film) 3340, 1950 and 1730 cm^{-1}; δ_H (300 MHz) 7.29-7.39 (5H, m), 5.06 (1H, p, J7Hz), 4.62-4.67 (2H, m), 4.35 (1H, s), 3.69 (3H, s), 2.40-2.64 (2H, m), 1.92-2.04 (2H, m), 1.76 (1H, br.s), 1.30-1.56 (6H, m); m/z (ci) 274 (M^++H).

(R)-N^1-6,7-Octadienyl-N^2-methyl-1-phenyl-1,2-ethanediamine (178c)

Di-isobutylaluminium hydride (11 ml, 11 mmol, 1 M in toluene) was added to a stirred solution of (R)-α-methyl (6,7-octadienylamino)benzeneacetate (178b) (1.5 g, 5.5 mmol) in ether (10 ml). The reaction was stirred at room temperature for 2 h, quenched with 2N HCl, diluted with CH_2Cl_2 (50 ml) and neutralised with aqueous sodium bicarbonate. The product was extracted with CH_2Cl_2 (5 x 50 ml). The extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by flash chromatography to give, on elution with methanol-CH_2Cl_2 (1:10), (178c) (0.14 g, 10%) as a yellow oil (Found: M+H, 259.221. $C_{17}H_{26}N_2$+H requires 259.2175); υ_{max} (thin film) 3300 and 1955 cm^{-1}; δ_H (300 MHz) 7.20-7.38 (5H, m), 5.03 (1H, p, J7Hz), 4.50-4.67 (2H, m), 3.76 (1H, t, J7Hz), 2.78 (2H, d, J7Hz), 2.45 (3H, s), 2.40-2.50 (2H, m), 2.06-2.20 (3H, m), 1.90-2.00 (2H, m), 1.24-1.52 (5H, m); m/z (ci) 259 (M+H).

2-Ethenyl-N-methyl-α-phenyl-1-hexahydro-1H-azepineacetamide (179a)

Silver triflate (120 mg, 0.33 mmol) was added in one portion to a stirred suspension of silica gel (100 mg) and (R)-α-(6,7-octadienylamino)-N-methylbenzeneacetamide (178a) (90 mg, 0.33 mmol) in 1,2-dichloroethane (60 ml). The reaction mixture was heated at 80°C for 63 h, allowed to cool and brine (10 ml) added and stirred for 30 min. The resulting mixture was extracted with CH_2Cl_2 (3 x 50 ml), the extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with ether, (179a) (60 mg, 7%) as a 5:1 mixture of diastereoisomers (Found: M^++H, 273.198. $C_{17}H_{24}N_2O$+H requires 273.197); υ_{max} (thin film), 3300 cm^{-1}; δ_H (300 MHz) 7.40-7.20 (6H, m), 5.87 (1H, m), 5.00-5.12 (2H, d,d, J4, 7Hz), 4.50 major isomer and 4.37 minor isomer (1H, s), 3.30-3.38 (1H, m), 2.86 (3H, d, J5Hz), 2.70-2.80 (2H, m), 2.48 (2H, m),

1.39-1.75 (6H, m); m/z (ci) 273 (M+H).

Methyl 2-ethenyl-α-phenyl-1-hexahydro-1H-azepineacetate (179b)

Using a similar procedure to that described for (179a), the cyclised product (179b) was obtained as a 1:1 mixture (5 mg, 1%) (Found: M^++H, 274.182. $C_{17}H_{23}NO_2$+H requires 274.186); υ_{max}(thin film) 1730 cm^{-1}; δ_H (300 MHz) 7.29-7.39 (5H, m), 5.80 (1H, m), 4.85-5.20 (2H, m), 4.78 and 4.52 (1H, s), 3.62 and 3.73 (3H, s), 3.20-3.30 (1H, m), 2.65-2.80 (2H, m), 1.40-1.80 (8H, m); m/z (ci) 274 (M+H).

Methyl 3-methoxy-2-methylene-8-[(4-methylphenyl)sulphonyl]aminooctanoate (180)

A solution of (177) (25 mg, 0.089 mmol) and palladium (II) chloride (16 mg, 0.089 mmol) in methanol (15 ml) under an atmosphere of carbon monoxide was heated at 70°C for 2 days. 10% Aqueous ethanolamine (3 ml) was added to the reaction mixture and diluted with ether (20 ml). The organic layer was extracted, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with petrol-ether (3:2), (180) (4 mg, 13%) as a colourless oil (Found: M^++H, 370.168. $C_{18}H_{27}NO_5S$+H requires 370.164); υ_{max} (thin film) 3300, 1710, 1430 and 1160 cm^{-1}; δ_H (300 MHz) 7.72 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 6.30 (1H, s), 5.80 (1H, s), 4.35 (1H, br.s), 4.02 (1H, m), 3.76 (3H, s), 3.24 (3H, s), 2.91 (2H, q, J7Hz), 2.92 (3H, s), 1.20-1.50 (8H, m); m/z (ci) 370 (M^++H).

Methyl 3-acetoxy-2-methylene-8-[(4-methylphenyl)sulphonyl]aminooctanoate (181)

Palladium (II) acetate (102 mg, 0.45 mmol) was added to a stirred solution of N-tosyl octa-6,7-dienylamine (177) (127 mg, 0.45 mmol), triethylamine

(0.063 ml, 0.45 mmol), and methanol (0.081 ml, 0.45 mmol) in CH_2Cl_2 (25 ml) at room temperature and the reaction mixture was stirred for 18 h under an atmosphere of carbon monoxide. The solution was filtered through celite, the solvent removed under reduced pressure and the residue was purified by flash chromatography to give, on elution with petrol-ether (3:2), (181) (30 mg, 17%) as a colourless oil (Found: M^++H, 398.163. $C_{19}H_{27}NO_6S$+H requires 398.164); υ_{max} (thin film) 3300, 1720, 1625, 1595, 1230 and 1160 cm^{-1}; δ_H (300 MHz) 7.60 (2H, d, J8Hz), 7.29 (2H, d, J8Hz), 6.25 (1H, s), 5.71 (1H, s), 5.55 (1H, dd, J5, 7Hz), 4.5 (1H, m), 3.74 (3H, s), 2.89 (2H, q, J7Hz), 2.40 (3H, s), 2.06 (3H, s), 1.75-1.20 (8H; m); m/z (ci) 398 (M^++H).

N-6,7-octadienylbenzenemethanamine (182)

A solution of octa-6,7-dienylamine (193) (0.90 g, 7.2 mmol) and benzaldehyde (0.73 ml, 7.2 mmol) in ethanol (20 ml) was stirred at room temperature for 16 h. Sodium borohydride (0.27 g, 7.2 mmol) was added and this solution was stirred for 1 h. Ether (100 ml) was then added and the reaction mixture was washed with water (10 ml), brine (10 ml), dried ($MgSO_4$) and then concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with CH_2Cl_2 and then CH_2Cl_2 - methanol (10:1), (182) (0.91 g, 61%) as a yellow oil (Found: M^++H, 216.716. $C_{15}H_{21}N$+H requires 216.175); υ_{max} (thin film) 3300 and 1950 cm^{-1}; δ_H (300 MHz) 7.20-7.35 (5H, m), 5.08 (1H, p, J7Hz), 4.61-4.68 (2H, m), 3.79 (2H, s), 2.62 (2H, t, J7Hz), 1.95-2.05 (2H, m), 1.65 (1H, s), 1.30-1.58 (6H, m); m/z (ci) 216 (M^++H).

Methyl hexahydro-α-methylene-1-(phenylmethyl)-2-1H-azepineacetate (183)

Palladium (II) bis(benzonitrile) dichloride (50 mg, 0.13 mmol) was added to a stirred solution of N-6,7-octadienylbenzenemethanamine (182) (28 mg, 0.13 mmol) and triethylamine (0.017 ml, 0.13 mmol) in methanol (30 ml). The

mixture was stirred at room temperature for 3 h under an atmosphere of carbon monoxide. The reaction mixture was diluted with ether (100 ml) and washed with 10% aqueous ethanolamine (20 ml). The organic layer was extracted with ether (3 x 20 ml) and the extracts combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with petrol-ether (4:1), (183) (8 mg, 23%) (Found: M^++H, 274.182. $C_{17}H_{23}NO_2$+H requires 274.180); υ_{max} (thin film) 1720 and 1625 cm^{-1}; δ_H (300 MHz) 7.18-7.32 (5H, m), 6.25 (1H, s), 6.12 (1H, s), 3.77 (3H, s), 3.76 (1H, m), 3.70 (1H, d, J14Hz), 3.50 (1H, d, J14Hz), 2.62-2.82 (2H, m), 1.40-1.94 (8H, m); m/z (ci) 274 (M^++H).

Hexahydro-2-(1-iodoethenyl)-1-(phenylmethyl)-1H-azepine (184)

A solution of iodine (236 mg, 9.3 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of N-6,7-octadienylbenzenemethanamine (182) (20 mg, 8.3 mmol) in CH_2Cl_2 (40 ml). The reaction was stirred at room temperature for 4 days, concentrated under reduced pressure and purified by flash chromatography to give, on elution with hexane, (184) (70 mg, 22%) as a yellow oil (Found: M^++H, 342.073. $C_{15}H_{20}IN$+H requires 342.072); υ_{max} (thin film) 1610 cm^{-1}; δ_H (300 MHz) 7.20-7.4 (5H, m), 6.39 (1H, s), 5.80 (1H, s), 3.81 (1H, d, J15Hz), 3.62 (1H, d, J15Hz), 2.95-3.05 (2H, m), 2.70 (1H, m), 1.78-1.90 (2H, m), 1.40-1.70 (6H, m); m/z (ci) 342 (M^++H).

Hexahydro-2-(1-iodoethenyl)-1-(phenylmethyl)-1H-azepine (184)

Dry HCl gas was bubbled into an ice cold solution of N-octadienyl benzenemethanamine (182) (71 mg, 0.33 mmol) in ether (10 ml). The resulting hydrochloride salt (185) (data given below) was filtered off and dissolved in CH_2Cl_2 (20 ml). A solution of iodine (84 mg, 0.33 mmol) in CH_2Cl_2 (5 ml) was added and the reaction mixture stirred at room temperature for 1 h to give (186)

(data given below). Triethylamine (0.1 ml, 0.66 mmol) in CH_2Cl_2 (5 ml) was added slowly to the reaction mixture and stirred at room temperature for 24 h. The reaction mixture was washed with brine (10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified to give, on elution with petrol-ether (10:1), (184) (20 mg, 17%) (data as before).

N-6,7-Octadienylbenzenemethanamine. hydrochloride (185)

(Found: C, 71.8; H, 9.0; N, 5.2. $C_{15}H_{22}Cl\,N$ requires C, 71.6; H, 8.75; N, 5.6%); υ_{max} (Nujol) 2920, 1950 and 850 cm^{-1}; δ (300 MHz) 9.71-9.95 (2H, br.s), 7.25-7.60 (5H, m), 4.99 (1H, p, J7Hz), 4.5-4.60 (2H, m), 3.91-4.00 (2H, br.s), 2.61-2.89 (2H, m), 1.70-1.95 (4H, m), 1.20-1.45 (4H, m).

(E)- and (Z)-N-(7,8-diiodoocta-6-enyl)benzenemethanamine. hydrochloride (186)

(3:1, ratio) δ_H (300 MHz) 9.30-10.0 (2H, br.s), 7.54-7.61 (2H, m), 7.34-7.45 (3H, m), minor isomer 6.15 (1H, t, J7Hz), major isomer 5.88 (1H, t, J7Hz), major isomer 4.38 (2H, s), minor isomer 4.26 (2H, s), 4.00 (2H, s), 2.70-2.81 (2H, m), 1.94-2.09 (2H, m), 1.78-1.93 (2H, m), 1.28-1.48 (4H, m).

(E)- and (Z)-3-Iodo-1-[(4-methylphenyl)sulphonyl]azacycloundec-3-ene (204b,c)

A solution of iodine (0.107 g, 0.42 mmol) in THF (5 ml) was added dropwise to a stirred solution of N-(deca-8,9-dienyl)-4-methylbenzenesulphonamide (199) (0.13 g, 0.42 mmol) in THF (20 ml). The reaction mixture was stirred at room temperature in the dark for 1 h (or until all the allenic sulphonamide had reacted, as monitored by tlc ether-petrol (2:3)). The reaction mixture was diluted with THF (25 ml) and added, at a rate of 2 ml/h (syringe pump), to a stirred suspension of sodium hydride (0.17 g, 0.42 mmol 60%, dispersion in oil)

in THF (20 ml) and DMPU (5 ml) over 25 h in the dark.

The reaction was quenched with wet ether (10 ml) and then concentrated under reduced pressure. The bulk of the DMPU was removed by bulb to bulb distillation (approximately 100°C/0.1 mm Hg) and the residue was purified by flash chromatography to give, on elution with CH_2Cl_2, (204b, c) as a inseparable 3:1 mixture of E and Z isomers respectively (0.062 g, 35%) as a colourless oil (Found: C, 47.4; H, 5.6; N, 3.4. $C_{17}H_{24}INO_2S$ requires C, 47.1; H, 5.5; N, 3.2%); υ_{max} ($CHCl_3$) 1630, 1590, 1330 and 1150 cm^{-1};

δ_H (270 MHz) major isomer 7.76 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 6.10 (1H, t, J7.5Hz), 3.95 (2H, s), 3.00 (2H, t, J6Hz), 2.40 (3H, s), 2.20-2.30 (2H, m), 1.42-1.78 (4H, m), 1.15-1.40 (6H, m);

minor isomer 7.76 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 6.35 (1H, t, J7.5Hz), 4.06 (2H, s), 3.11 (2H,t, J6Hz), 2.40 (3H,s), 2.20-2.30 (2H, m), 1.42-1.78 (4H, m), 1.15-1.40 (6H, m); δ_c 147.6, 143.3, 140.3, 135.8, 129.7, 127.4, 127.2, 102.0, 87.4, 63.2, 54.2, 49.3, 47.3, 40.9, 36.2, 29.6, 28.8, 27.7, 26.8, 26.4, 25.9, 25.6, 23.8, 22.5, 21.8, 21.5; m/z (ci) 434 (M^++H).

<u>(Z,Z)-3,14-Diiodo-1,12-bis[(4-methylphenyl)sulphonyl]</u>

<u>-1,12-diazacyclodocosa-3,14-diene (204d) and</u>

<u>(Z)-3-Iodo-1-[(4-methylphenyl)sulphonyl]azacycloundec-3-ene (204c)</u>

A solution of iodine (0.22 g, 0.88 mmol) in THF (10 ml) was added dropwise, to a stirred solution of (199) (0.27 g, 0.88 mmol) in THF (140 ml). The reaction mixture was stirred at room temperature in the dark for 1 h (or until all the allenic sulphonamide had reacted, as monitored by tlc ether-petrol (2:3)). DMPU (10 ml) and sodium hydride (0.036 g, 0.88 ml, 60% dispersion in oil) were added and the mixture stirred for 16 h at room temperature in the dark. The reaction was quenched with wet ether (20 ml) and concentrated under reduced pressure. The bulk of the DMPU was removed by distillation

(approximately 100°C/0.1 mm Hg) and the residue was purified by flash chromatography to give, on elution with CH_2Cl_2-petrol (1:1), the (Z)-isomer (204c) (0.11 g, 29%) (data as before) followed by dimer (204d) (0.04 g, 10%) as a colourless solid, m.p. 199-201°C (from toluene-petrol)

(204d) (Found: C, 47.0; H, 5.5; N, 3.0. $C_{34}H_{48}I_2N_2O_4S_2$ requires C, 47.1; H, 5.5; N, 3.2%); υ_{max} (Nujol) 1590, and 1330 cm^{-1}; δ_H (270 MHz) 7.72 (4H, d, J8Hz), 7.30 (4H, d, J8Hz), 5.80 (2H, t, J7Hz), 4.01 (4H, br.s), 2.95-3.04 (4H, m), 2.42 (6H, s), 2.06-2.18 (4H, m), 1.05-1.60 (20 H, m); δ_c 143.3, 139.9, 136.8, 129.6, 127.4, 102.8, 59.6, 46.8, 35.9, 31.6, 29.6, 29.2, 28.25, 28.0, 26.95, 21.5; m/z (thermospray) 867.130 (M^++H).

(E)- and (Z)-N-(9,10-diiodo-8-decenyl)-4-methylbenzenesulphonamide

Only ^1H nmr data was obtained for the diiodo-intermediate

δ_H (300 MHz) 7.75 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 6.20 minor, 5.88 major (1H, t, J7Hz), 4.40 major, 4.22 minor (2H, s), 4.20 (1H, m), 2.90 (2H, t, J7Hz), 2.40 (3H s), 1.95-2.05 (2H, m), 1.16-1.60 (10 H, m).

(E)- and (Z)-2,3,4,5,6,9-hexahydro-8-Iodo-1-[(4-methylphenyl)sulphonyl] -1H-azonine (188b,c) and

(Z,Z)-3-12-Diiodo-1,10-bis[(4-methylphenyl)sulphonyl] -1,10-diazacyclooctadeca-3,12-diene (188d)

Using a similar procedure to that described before, (177) reacted with iodine to give (187) (data see below) and then sodium hydride was added. The three products (ratio 188b:188c:188d, 1:1:1) were separated by flash chromatography to give, on elution with CH_2Cl_2, (188b, c, d).

(Z)-isomer (188c) (18 mg, 18%) as a colourless solid, m.p. 140-141°C (from cyclohexane) (Found: C, 44.6, H, 5.0; N, 3.5. $C_{15}H_{20}INO_2S$ requires C, 44.4; H, 4.9; N, 3.5%); υ_{max} (thin film) 1600, 1340 and 1160 cm^{-1}; δ_H (270 MHz) 7.69

(2H, d, J8Hz), 7.31 (2H, d, J8Hz), 5.87 (1H, dd, J5, 11Hz), 4.33 (1H, d, J13Hz), 3.80 (1H, d, J13Hz), 3.28 (1H, dt, J15, 5Hz), 2.86 (1H, ddd, J2, 9, 15Hz), 2.40 (3H, s), 2.20-2.35 (2H, m), 1.90-2.00 (2H, m), 1.20-1.65 (4H, m); δ_c 143.2, 143.1, 136.1, 129.7, 127.2, 99.8, 63.5, 47.3, 34.8, 33.0, 27.9, 23.3, 21.5; m/z (ci) 406 (M^++H).

(E)-isomer (188b) (20 mg, 20%) as a colourless solid, m.p. 103-104°C (from cyclohexane) (Found: C, 44.7; H, 5.4; N, 3.5. $C_{15}H_{20}INO_2S$ requires C, 44.4; H, 4.9; N, 3.5%); υ_{max} (thin film) 1340 and 1160 cm^{-1}; δ_H (270 MHz) 7.69 (2H, d, J8Hz), 7.31 (2H, d, J8Hz), 6.38 (1H, t, J9.5Hz), 5.68 (2H, s), 3.00-3.10 (2H, m), 2.57-2.69 (2H, m), 2.43 (3H, s), 1.74-1.84 (2H, m), 1.58-1.73 (2H, m), 1.45-1.57 (2H, m); δ_c 144.3, 143.5, 135.2, 129.7, 127.2, 94.5, 61.6, 53.1, 30.2, 29.2, 26.9, 25.4, 21.5; m/z (ci) 406 (M^++H).

dimer (188d) (20 mg, 20%) as a colourless solid, m.p. 239-240°C (from benzene) (Found: C, 44.7; H, 5.0; N, 3.45. $C_{30}H_{40}I_2N_2O_4S_2$ requires C, 44.4; H, 4.9; N, 3.5%); υ_{max} ($CHCl_3$) 1600, 1320 and 1160 cm^{-1}; δ_H (270 MHz) 7.73 (4H, d, J8Hz), 7.30 (4H, d, J8Hz), 5.74 (2H, t, J7Hz), 4.04 (4H, s), 2.92-3.03 (4H, m), 2.42 (6H, s), 2.12-2.36 (4H, m), 1.42-1.58 (4H, m), 1.27-1.41 (4H, m), 1.02-1.25 (4H, m); m/z (thermospray) 811 (M^++H).

<u>(E)- and (Z)-2,3,4,5,6,9-hexahydro-8-Iodo-1-[(4-methylphenyl)sulphonyl -1H-azonine (188b, c)</u>

Using a similar procedure to that described for (188b,c), (177) was reacted with iodine to give (187) (data see below) and this solution was added via a syringe pump to sodium hydride to give two isomers 188b and 188c as a 1:1 mixture (40 mg, 55%) (data as before).

(E)- and (Z)-N-(7,8-diiodo-6-octenyl)-4-methylbezenesulphonamide (187)

Only ^1H nmr data was obtained for the diiodo-intermediate

δ_H (300 MHz) 7.75 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 6.15 minor, 5.85 major (1H, t, J7Hz), 4.50 (1H, br.s), 4.38 major, 4.26 minor (2H, s), 2.92 (2H, q, J7Hz), 2.41 (3H, s), 2.00 (2H, q, J8Hz) 1.22-1.50 (6H, m); N.O.e experiments involved irradiation at;

(a) δ5.85 (t) which resulted in enhancement of δ4.38 (s) and δ2.00 (q);

(b) δ4.38 (s) which resulted in enhancement of δ5.85 (t);

(c) δ6.15 (t) which resulted in enhancement of δ2.00 (q);

(d) δ4.26 (t) which resulted in enhancement of δ2.00 (q).

2-(1-Iodoethenyl)-1-[(4-methylphenyl)sulphonyl]pyrrolidine (200a) and (E)-2,3,4,7-tetrahydro-6-Iodo-1-[(4-methylphenyl)sulphonyl]-1H-azepine (200b)

Using a similar procedure to that described for (188), iodine was reacted with N-tosyl-hexa-4,5-dienylamine (196) and then sodium hydride in THF and DMPU was added. The two products were separated by flash chromatography to give, on elution with CH_2Cl_2-petrol (1:1),(200a) (2.32g, 83%) and (200b) (0.28g, 10%).

2-(1-Iodoethenyl)-1-[(4-methylphenyl)sulphonyl]pyrrolidine (200a)

(200a) as a colourless solid, m.p. 103-104°C (from cyclohexane) (Found: C, 41.5; H, 4.3; N, 3.7. $C_{13}H_{16}INO_2S$ requires C, 41.4; H, 4.2; N, 3.7%); υ_{max} (Nujol) 1710, 1610, 1590, 1340 and 1150 cm^{-1}; δ_H (300 MHz) 7.72 (2H, d, J8Hz), 7.31 (2H, d, J8Hz), 5.95 (1H, t, J1.5Hz), 5.85 (1H, dd, J1, 2Hz), 4.15 (1H, m), 3.49 (1H, m), 3.30 (1H, m), 2.42 (3H, s), 1.55-2.00 (4H, m); m/z (ci) 378 (M^++H).

(E)-2,3,4,7-tetrahydro-6-Iodo-1-[(4-methylphenyl)sulphonyl]-1H-azepine (200b)

(200b) as a colourless oil (Found: M^+, 376.993. $C_{13}H_{16}INO_2S$ requires 376.994); υ_{max} (thin film) 1710, 1330 and 1160 cm^{-1}; δ_H (300 MHz) 7.70 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 6.35 (1H, t, J6Hz), 4.18 (2H, s), 3.40 (2H, t, J7Hz), 2.41 (3H, s), 2.02-2.11 (2H, m), 1.78-189 (2H, m); m/z (ci) 378 (M^++H).

(E)-,(Z)-N-(5,6-diiodo-4-hexenyl)-4-methylbenzenesulponamide

Only ^1H nmr data was obtained for the diiodo-intermediate

δ_H (300 MHz) 7.75 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 6.09 minor, 5.81 major (1H, t, J7Hz), 4.70 (1H, br.t), 4.35 major 4.22 minor (2H, s) 2.90-3.00 (2H, m), 2.42 (3H, s), 1.95-2.10 (2H, m), 1.52-1.65 (2H, m).

2-(1-Iodoethenyl)-1-[(4-methylphenyl)sulphonyl]piperidine (201a)
(E)-1,2,3,4,5,8-hexahydro-7-Iodo-1-[(4-methylphenyl)sulphonyl]
-1H-azocine (201b) and (Z,Z)-3,11-Diiodo-1,9-bis[(4-methylphenyl)sulphonyl]-1,9-diazacyclohexadeca-3,11-diene (201d)

Using a similar procedure to that described for (188b,c,d), N-tosyl hepta-5,6-dienylamine (197) reacted with iodine and then sodium hydride in THF and DMPU was added. The three products (201a), (201b) and (201d) were obtained as a 1:1:1.3 mixture respectively (470 mg, 57%) and were separated by flash chromatography to give, on elution with CH_2Cl_2-petrol (1:1 to 1:0) the three colourless solids (201a) (201b) and (201d).

(201a) (104 mg, 13%) m.p. 60.5-61.5°C (from benzene-petrol) (Found: M^++H, 392.020. $C_{14}H_{18}INO_2S$+H requires 392.018); υ_{max} (thin film) 1620, 1600, 1340 and 1160 cm^{-1}; δ_H (270 MHz) 7.65 (2H, d, J8Hz), 7.31 (2H, d, J8Hz), 6.29 (1H, t, J2.2Hz), 6.02 (1H, t, J2.2Hz), 4.74 (1H, s), 3.71 (1H, dd, J4, 14Hz), 3.06 (1H, dt, J3, 12Hz), 2.42 (3H, s), 2.30 (1H, m), 1.20-1.60 (5H, m); δ_c 143.2, 137.9,

129.6, 128.4, 127.05, 110.7, 60.33, 41.7, 27.9, 23.8, 21.5, 18.5; m/z (ci) 392 (M^++H).

(201b) (100 mg, 13%) m.p. 112.5-113°C (from benzene-petrol) (Found: M^++H, 392.020. $C_{14}H_{18}INO_2S$+H, requires 392.018); υ_{max} (thin film) 1620, 1600, 1340, 1160 cm^{-1}; δ_H (300 MHz) 7.65 (2H, d, J8Hz), 7.31 (2H, d, J8Hz), 6.44 (1H, t, J8.7Hz), 4.02 (2H, s), 3.28 (2H, dd, J5, 6Hz), 2.58 (2H, dt, J7.5, 6.2Hz), 2.43 (3H, s), 1.58-1.78 (4H, m); δ_c 143.4, 140.6, 135.4, 129.7, 126.9, 96.6, 57.9, 49.0, 28.0, 25.8, 24.2, 21.4; m/z (ci) 392 (M^++H).

(201d) (190 mg, 23%), m.p. 212-213°C (from benzene) (Found: C, 42.9; H, 4.6; N, 3.5. $C_{28}H_{36}I_2N_2O_4S_2$ requires C, 43.0, H, 4.6; N, 3.6%); υ_{max} (Nujol) 1595, 1330 and 1130 cm^{-1}; δ_H (270 MHz) 7.69 (4H, d, J8Hz), 7.30 (4H, d, J8Hz), 5.90 (2H, t, J7Hz), 3.95 (4H, s), 2.96-3.05 (4H, m), 2.43 (6H, s), 2.38-2.58 (4H, m), 1.38-1.63 (8H, m); δ_c 143.5, 136.9, 136.0, 129.8, 127.2, 104.6, 61.2, 50.2, 34.9, 28.5, 25.7, 21.5; m/z (thermospray) 783 (M^++H).

2-(1-Iodoethenyl)-1-[(4-methylphenyl)sulphonyl]piperidine (201a) and (E)-1,2,3,4,5,8-hexahydro-7-Iodo-1-[(4-methylphenyl)sulphonyl]-1H-azocine (201b)

Using a similar procedure to that described for (188), iodine was reacted with N-tosyl hepta-5,6-dienylamine (197) in THF and this was added using a syringe pump to sodium hydride in THF and DMPU. The two products (201a) and (201b) (50 mg, 57%) were obtained as a 1:1.6 mixture respectively and were separated by flash chromatography to (201a) and (201b) (data as before).

(E)- and (Z)-1,2,3,4,5,6,7,10-octahydro-9-Iodo-1-[(4-methylphenyl)sulphonyl] azecine (203b, c)

Using a similar procedure, to that described for (188), iodine was added to N-tosyl nona-7,8-dienylamine (198) in THF and this was added using a syringe

pump to sodium hydride in THF and DMPU. The two isomers (203b) and (203c) were obtained as a 1:1.4 mixture respectively (80 mg, 62%) and were separated by flash chromatography to give, on elution with CH_2Cl_2-petrol (1:1), (203b, c) as colourless solids.

(Z)-isomer (203c) (47 mg, 36%) m.p. 90-91°C (from petrol-benzene) (Found: M^++H, 420.052. $C_{16}H_{22}INO_2S$+H requires 420.049); υ_{max} (thin film) 1710, 1360, and 1150 cm^{-1}; δ_H (270 MHz) 7.76 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 6.42 (1H, t, J9Hz), 4.28-4.37 (2H, m), 3.30-3.40 (2H, m), 2.42 (3H, s), 2.25-2.38 (2H, m), 1.20-1.70 (8H, m); δ_c 147.8, 143.0, 137.1, 129.4, 127.5, 94.8, 53.0, 41.5, 28.4, 29.6, 27.9, 25.0, 21.8, 21.5; m/z (ci) 420 (M^++H).

(E)-isomer (203b) (33 mg, 25%) m.p. 109-110°C (from petrol-benzene) (Found: M^++H, 420.052. $C_{16}H_{22}INO_2S$+H requires 420.049); υ_{max} (Nujol) 1630, 1590, 1330 and 1150 cm^{-1}; δ_H (270 MHz) 7.67 (2H, d, J8Hz), 7.31 (2H, d, J8Hz), 6.31 (1H, t, J8Hz), 3.95-4.08 (2H, br.s), 3.06 (2H, t, J6Hz), 2.43 (3H, s), 2.30 (2H, dt, J7, 6.5Hz), 1.50-1.80 (4H, m), 1.30-1.50 (4H, m); δ_c 143.3, 141.6, 135.7, 129.7, 127.1, 99.8, 62.3, 47.4, 34.9, 27.4, 25.9, 24.6, 24.0, 21.5; m/z (ci) 420 (M^++H).

<u>(E)- and (Z)-N-(6,7-diiodo-5-heptenyl)-4-methylbenzenesulphonamide</u>

Only ^1H nmr data was obtained for the diiodo-intermediate

δ_H (300 MHz) 7.75 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 6.11 minor, 5.82 major (1H, t, J7Hz), 4.61 (1H, m), 4.35 major, 4.23 minor (2H, s), 2.91 (2H, q, J6Hz), 2.41 (3H, s), 2.02 (2H, q, J7Hz), 1.36-1.54 (4H, m).

<u>(Z,Z)-N,N-3,13-diiodo-bis[(4-methylphenyl)sulphonyl]</u>

<u>-1,11-diazacycloeicosa-3,13-diene (203d) and (E)- and</u>

<u>(Z)-1,2,3,4,5,6,7,10-octahydro-9-Iodo-1-[(4-methlphenyl)sulphonyl]azecine</u>

<u>(203b,c)</u>.

Using a similar procedure, to that described before, iodine was added to N-tosyl

nona-7,8-dienylamine (198) in THF and DMPU and sodium hydride was added to this solution. The three products (203b), (203c) and (203d) as a 1:1.5:5 mixture respectively and were separated by flash chromatography to give, on elution with CH_2Cl_2,(203b) and (203c) (data as before) and (203d) (560 mg, 40%) as a colourless solid, m.p. 205-206°C (from toluene) (Found: C, 46.1; H, 5.4; N, 3.5. $C_{32}H_{44}I_2N_2O_4S_2$ requires C, 45.8; H, 5.25; N, 3.3%); υ_{max} (Nujol) 1340 and 1150 cm^{-1}; δ_H (270 MHz) 7.69 (4H, d, J8Hz), 7.30 (4H, d, J8Hz), 5.92 (2H, t, J7Hz), 3.96 (4H, s), 2.98 (4H, t, J8Hz), 2.43 (6H, s), 2.18 (4H, q, J6Hz), 1.12-1.54 (16H, m); δ_c 143.3, 138.0, 136.3, 129.7, 129.2, 103.4, 60.6, 49.4, 35.5, 29.0, 28.4, 27.9, 27.3, 21.5; m/z (thermospray) 839.0955, requires 839.0912 (M^++H).

(E)- and (Z)-N-(8,9-diiodo-7-nonenyl)-4-methylbezenesulphonamide

Only ^1H nmr data was obtained for the diiodo-intermediate

δ_H (300 MHz) 7.75 (2H, d, J8Hz), 7.30 (2H, d, J8Hz), 6.20 minor, 5.88 major (1H, t, J7Hz), 4.39 major, 4.28 minor (2H, s), 4.30 (1H, br.s), 2.94 (2H, q, J7Hz), 2.42 (3H, s), 1.91-2.08 (2H, m), 1.20-1.50 (8H, m).

Octahydro-1-[(4-methylphenyl)sulphonyl]-1H-azonine (207)

A suspension of (E) and (Z) 2,3,4,5,6,9-hexahydro-8-iodo-1-(tosyl)-1H-azonine (188b,c) (12 mg, 0.03 mmol) and palladium on charcoal (12 mg) in ethanol (10 ml) was stirred under an atmosphere of H_2 gas for 18 h at room temperature. The mixture was then filtered through a small plug of celite and the filtrate was concentrated under reduced pressure to give (207) (6.5 mg, 81%) as a colourless solid, m.p. 104-105°C (from methanol), mixed m.p. 104-105°C, an authentic sample of (207) was prepared m.p. 105-106°C (from methanol), Lit., m.p. 103.5-104.5°C[111] (Found: C, 63.9; H, 8.1; N, 4.9. $C_{15}H_{23}NSO_2$ requires C, 64.1; H, 8.2; N 5.0%); υ_{max} (Nujol) 1330 and 1150 cm^{-1}; δ_H (300 MHz) 7.64

(2H, d, J8Hz), 7.26 (2H, d, J8Hz), 2.95-3.05 (4H, m), 2.39 (3H, s), 1.55-1.76 (12 H, m); δ_c 142.8, 135.1, 129.4, 127.2, 50.0, 27.15, 25.8 24.9, 21.4; m/z (ci) 282 (M^++H).

Hexahydro-1-[(4-methylphenyl)sulphonyl]-1H-azepine (205)

Using a similar procedure to that described for (207), (200b) was reduced, to give (205) as a colourless solid m.p. 75-76°C (from methanol), Lit m.p. 75-76°C[111] (Found: C, 62.1; H, 7.9; N, 5.7. $C_{13}H_{19}NO_2S$ requires C, 61.7; H, 7.5; N, 5.5); υ_{max} (Nujol) 1330 and 1155 cm^{-1}; δ_H (300 MHz) 7.62 (2H, d, J8Hz), 7.24 (2H, d, J8Hz), 3.20 (4H, t, J7Hz), 2.38 (3H, s), 1.50-1.70 (8H, m); m/z (ci) 254 (M^++H).

Octahydro-1-[(4-methylphenyl)sulphonyl]azocine (206)

Using a similar procedure to that described for (207), (201b) was reduced, to give (206) as a colourless solid m.p. 80-81°C (from methanol), Lit m.p. 81-82°C[111] (Found: C, 63.2; H, 7.9; N, 5.2. $C_{14}H_{21}NO_2S$ requires C, 62.9; H, 7.9; N, 5.2%); δ_H (300 MHz) 7.65 (2H, d, J8Hz), 7.26 (2H, d, J8Hz), 3.10 (4H, J7Hz), 2.40 (3H, s), 1.55-1.83 (10H, m); m/z (ci) 268 (M^++H).

Decahydro-1-[(4-methylphenyl)sulphonyl]azecine (208)

Using a similar procedure to that described for (207), (203b,c) was reduced to give, N-tosyl azecane (208) as a colourless solid, m.p. 106-108°C (from methanol), Lit m.p. 109.5-110.5°C[111] (Found: C, 65.1; H, 8.8; N, 4.8. $C_{16}H_{25}NO_2S$ requires C, 65.1; H, 8.5; N, 4.75%); υ_{max} (thin film) 1330 and 1160 cm^{-1}; δ_H (300 MHz) 7.62 (2H, d, J8Hz), 7.28 (2H, d, J8Hz), 2.94-3.02 (4H, m), 2.40 (3H, s), 1.40-1.78 (14H, m); m/z (ci) 296 (M^++H).

1-[(4-methylphenyl)sulphonyl]azacycloundecane (209)

Using a similar procedure to that described for (207), (204c) was reduced to give, (209) as a colourless solid, m.p. 117-118°C (from methanol), Lit m.p. 115-116°C[111] (Found; C, 65.8; H, 8.9; N, 4.4. $C_{17}H_{27}NO_2S$ requires C, 66.0; H, 8.7; N, 4.5%); υ_{max} (Nujol) 1330 and 1160 cm^{-1}; δ_H (270 MHz) 7.68 (2H, d, J8Hz), 7.29 (2H, d, J8Hz), 2.98 (4H, t, J7Hz), 2.42 (3H, s), 1.40-1.78 (16 H, m); m/z (ci) 310 (M^++H).

1,9-Bis[(4-methylphenyl)sulponyl]-1,9-diazacyclohexadecane (210)

Using a similar procedure to that described for (207), (201d) was reduced to give, (210) as a colourless solid, m.p. 190-191°C (from methanol), Lit m.p. 192°C[112] (Found: C, 63.0; H, 8.0; N, 5.0. $C_{28}H_{42}N_20_4S_2$ requires C, 62.9; H, 7.9; N, 5.2); δ_H (270 MHz) 7.67 (4H, d, J8Hz), 7.30 (4H, d, J8Hz), 2.99 (8H, t, J7Hz), 2.42 (6H, s), 1.49-1.68 (8H, m), 1.32-1.47 (12H,).

1,11-Bis[(4-methylphenyl)sulphonyl]-1,11-diazacycloeicosane (211)

Using a similar procedure to that described for (207), (203d) was reduced to give, (211) as a colourless solid, m.p. 178-179°C (from methanol), Lit m.p. 178-179°C[112] (Found: C, 65.1; H, 8.3; N, 5.0. $C_{32}H_{50}N_20_4S_2$ requires C, 65.1; H, 8.5; N, 4.75); υ_{max} (Nujol) 1320 and 1160 cm^{-1}; δ_H (270 MHz) 7.66 (4H, d, J8Hz), 7.26 (4H, d, J8Hz), 3.00 (8H, t, J7Hz), 2.42 (6H, s), 1.63-1.48 (8H, m), 1.20-1.43 (20H, m).

N-Methyl-O-prop-2-enylbenzenesulphonimidate (212)

N-Methyl sulphonimidoyl chloride[119](1.22 g, 6.4 mmol) in CCl_4 (10 ml) was added to a stirred suspension of the sodium salt of allyl alcohol (8 g, 0.13 mol) in toluene (10 ml) at 0°C. The reaction mixture was stirred at room temperature for 30 min and then quenched with ether (20 ml). The reaction mixture was

filtered and the filtrate concentrated under reduced pressure, to give (212) (1.1 g, 85%) as a pale yellow oil which was used without purification (Found: M^++H, 212.075. $C_{10}H_{13}NO_2S$+H requires 212.0745); υ_{max}(thin film) 1440, 1290 and 1185 cm^{-1}; δ_H (300 MHz) 7.92-8.00 (2H, m), 7.46-7.60 (3H, m), 5.80 (1H, m), 5.25 (1H, d, J16Hz), 5.18 (1H, d, J10Hz), 4.31-4.40 (2H, m), 2.95 (3H, s); m/z (ci) 212 (M^++H).

N-Methyl-O-(1-deuteriumprop-2-eny)lbenzenesulphonimidate (215)

Using a similar procedure to that described for (212), N-methyl sulphonimidoyl chloride reacted with the sodium salt of 2-deuterium-prop-2-en-1-ol[122] to give (215) (1.8 g, 95%) (Found: M^++H, 213.082. $C_{10}DH_{12}NO_2S$+H requires 213.081); υ_{max} (thin film) 1440, 1290 and 1185 cm^{-1}; δ_H (300 MHz) 7.91-8.00 (2H, m), 7.45-7.62 (3H, m), 5.79 (1H, ddd, J6, 10, 16Hz), 5.28 (1H, d, J16Hz), 5.20 (1H, d, J10Hz), 4.35 (1H, m), 2.95 (3H, s); m/z (ci) 213 (M^++H).

N-Methyl-O-(2-iodoprop-2-enyl)benzenesulphonimidate (217)

Using a similar procedure to that described for (212), N-methyl sulphonimidoyl chloride reacted with the sodium salt of 2-iodoprop-2-ene-1-ol[123] to give (217) (1.5 g, 93%) (Found: M^++H, 337.972. $C_{10}H_{12}INO_2S$+H requires 337.971); υ_{max} (thin film) 1610, 1600, 1440, 1290 and 1170 cm^{-1}; δ_H (300 MHz) 7.48-8.00 (5H, m), 6.30-6.50 (2H, m), 4.48 (2H, d, J5Hz), 2.96 (3H, s); m/z (ci) 338 (M^++H).

N-methyl-N-prop-2-enylbenzenesulphonamide (213)

A solution of O-allyl-N-methyl benzenesulphonimidate (212) (35 mg, 0.16 mmol) in toluene (20 ml) was heated at 110°C for 40 h. The solution was then concentrated under reduced pressure to give, without further purification, (213) (35 mg, 100%) as a colourless oil (Found: C, 57.2; H, 6.2; N, 6.7. $C_{10}H_{13}NO_2S$

requires C, 56.9; H, 6.2; N, 6.6%); υ_{max} (thin film) 1440, 1335 and 1165 cm^{-1}; δ_H (300 MHz) 7.76-7.82 (2H, m), 7.50-7.62 (3H, m), 5.70 (1H, m), 5.14-5.24 (2H, m), 3.63 (2H, d, J5Hz), 2.67 (3H, s); m/z (ci) 212 (M^++H).

N-Methyl-N-(3-deuteriumprop-2-enyl)benzenesulphonamide (216)

Using a similar procedure to that described for (213), the rearrangement was conducted to give, without purification, (216) (0.20 g, 100%) as a colourless oil (Found: M^++H, 213.082. $C_{10}DH_{12}NO_2S$+H requires 213.081; υ_{max} (thin film) 1620, 1580, 1340 and 1160 cm^{-1}; δ_H (300 MHz) 7.50-7.80 (5H, m), 5.70 (1H, m), 5.16 (1H, m), 3.60 (2H, d, J5Hz), 2.68 (3H, s); δ_c 137.4, 132.5, 132.3, 128.9, 127.3, 118.8 (dd, J_{CD}24, 23Hz), 52.9, 34.1.

N-Methyl-N-(2-iodoprop-2-enyl)benzenesulphonamide (218)

Using a similar procedure to that described for (213), the rearrangement was conducted to give, after purification, (218) (25 mg, 10%) (Found: M^++H, 337.971. $C_{10}H_{12}INO_2S$+H requires 337.971); δ_H (300 MHz) 7.75-7.82 (2H, m), 7.50-7.62 (3H, m), 6.46 (1H, dt J7.5, 1.5Hz), 6.18 (1H, dt J7.5, 6.5Hz), 3.77 (2H, dd, J6.25, 1.25 Hz), 2.72 (3H, s); m/z (ci) 338 (M^++H).

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