Intramolecular dipolar cycloaddition reactions with azomethine ylides

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Intramolecular Dipolar Cycloaddition Reactions of Azomethine Ylides

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Contents

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1. Introduction

It was in 1963 that Huisgen laid out the classification of 1,3-dipoles and the concepts for 1,3-dipolar cycloaddition reactions, although it was not until 1976 that the first intramolecular 1,3-dipolar cycloaddition reaction of an azomethine ylide was reported. Since then, impressive developments have been described in this area, with the establishment of various useful methods for the formation of azomethine ylides and the determination of the requirements for a successful intramolecular cycloaddition reaction. Use of this methodology for the synthesis of pyrrolidine- and pyrrole-containing natural products has been expanding rapidly. This review aims to describe the background and mechanisms of azomethine ylide formation and intramolecular cycloaddition, giving a critical account including the very first example and covering to early 2005. It is hoped that this review will be a useful resource for chemists interested in cycloaddition reactions and will inspire further exciting developments in this area.

Cycloaddition reactions are one of the most important class of reactions in synthetic chemistry. Within

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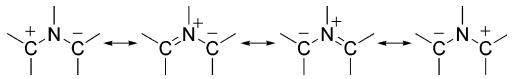
this class, the 1,3-dipolar cycloaddition reaction has found extensive use as a high-yielding and efficient, regio- and stereocontrolled method for the synthesis of many different heterocyclic compounds.[1−12] Indeed, the 1,3-dipolar cycloaddition reaction has been described as "the single most important method for the construction of heterocyclic five-membered rings in organic chemistry".[13] Placing the ylide dipole and the alkene or alkyne dipolarophile within the same molecule provides direct access to bicyclic (or polycyclic) products of considerable complexity.[14,15] The proximity of the reactants and the conformational constraints often lead to ready cycloaddition with very high or complete selectivity. For the preparation of five-membered cyclic amines, in particular pyrrolidines, dihydropyrroles, and pyrroles, cycloaddition of azomethine ylides with alkenes or alkynes is very effective and has been studied widely.[16−23] This review describes dipolar cycloaddition reactions of azomethine ylides that have been carried out intramolecularly. Such reactions have been gaining increasing popularity as a highly stereoselective method for natural product synthesis. Despite this, previous reviews of 1,3-dipolar cycloaddition reactions, with two recent exceptions,[22,23] have given very little or no attention to intramolecular cycloadditions with azomethine ylides. This review aims to provide a thorough coverage of these reactions, including reactivity and stereochemical issues and applications in synthesis. Cycloaddition reactions of 2-azaallyllithium species, which provide an alternative approach to pyrrolidine products, are not included, and readers should refer to a recent account of this area.[24]

Azomethine ylides have four π electrons spread over the three-atom C−N−C unit; as such, they must be represented by a zwitterionic (or diradical) form. Four zwitterionic resonance forms can be drawn, as shown in Chart 1. The most common representation has a positive charge located on the nitrogen atom and a negative charge distributed over the two carbon atoms.[25] The extent of negative charge on each carbon atom is determined by the nature and number of substituents at these carbons. Alternatively, two resonance forms with the positive and negative charges on the carbon atoms can be drawn to represent the 1,3-dipole.

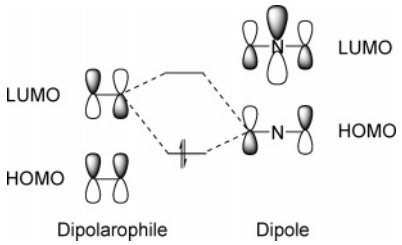
Chart 1



Cycloaddition of an azomethine ylide with a π-system involves a total of six π electrons [$_{\pi}4_s + {}_{\pi}2_s$] and takes place by a thermally allowed, suprafacial process according to the Woodward−Hoffmann rules.[26−28] For a suprafacial process, the two carbon−carbon bonds are formed to the same face of the azomethine ylide and to the same face of the dipolarophile. It is generally accepted that the cycloaddition is concerted with both carbon−carbon σ-bonds being formed at the same time, although not necessarily to the same extent. Evidence in favor of the concerted nature comes from the stereospecificity of the cycloaddition, in which the relative stereochemistry of the alkene dipolarophile is maintained in the pyrrolidine product. In addition, stereospecific intermolecular cycloadditions using azomethine ylides derived from cis and trans aziridines have been reported (however, compare with examples in section 4.1).[29] Depending on the electronic nature of the dipole and dipolarophile, a concerted process may not always be operative and a stepwise pathway, involving diradical or zwitterionic intermediates, cannot be ruled out.[30]

In terms of frontier molecular orbital (FMO) theory, in which reaction takes place by maximizing overlap of the HOMO and the LUMO,[31] azomethine ylides can be considered to be electron-rich, and the dominant interaction involves the HOMO of the azomethine ylide with the LUMO of the π-system (Chart 2).[32,33] This is borne out by the general preference for reaction of azomethine ylides with electron-poor alkenes. However, particularly in intramolecular cycloadditions, reaction can take place readily with an unactivated alkene and the best frontier orbital interaction is not necessarily obvious.

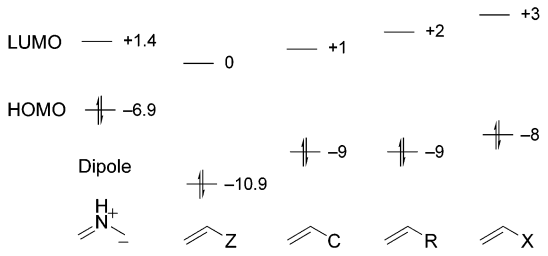
Chart 2



Calculations have been carried out by CNDO/2 and an estimation has been made of the energies of the frontier orbitals.[33,34] The parent azomethine ylide (CH_2NHCH_2) has approximate energies for the HOMO of −6.9 eV and for the LUMO of +1.4 eV. The relative energies of the frontier orbitals are illustrated in Chart 3. The most favorable interaction will be between the HOMO of an unstabilized azomethine ylide dipole and the LUMO of an electron-deficient dipolarophile (Z substituent), a conjugated dipolarophile (C substituent), or an alkyl-substituted dipolarophile (R substituent); however, the extent of interaction is similar between that of the HOMO of the dipole and the LUMO of an electron-rich dipolarophile (X substituent) and that of the LUMO of the dipole and the HOMO of the electron-rich dipolarophile and either could dominate. Such unstabilized ylide dipoles should react best with electron-deficient dipolarophiles, and examples in this review attest to this. The substitution pattern of the ylide or the presence of metal ions can alter the relative energies of the molecular orbitals, and care must be taken if invoking this theory. For example, the more electron-deficient azomethine ylide $RO_2CCH{=}N(Ar)$-$CHCO_2R$ has approximate energies for the HOMO of −7.7 eV and for the LUMO of −0.6 eV. Hence with this dipole, reaction should occur readily with any type of dipolarophile. Intramolecular dipolar cycloaddition reactions are common with electron-poor and with electron-rich alkenes and numerous examples are provided in this review. In addition to these

studies, other theoretical calculations using semi-empirical and ab initio methods have been investigated, providing evidence for concerted or stepwise processes, depending on the substitution pattern of the dipole and dipolarophile.[35−45]

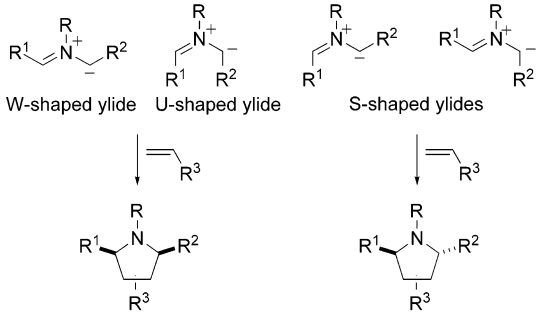
Chart 3



If the relative sizes of the atomic orbitals are known for the frontier orbitals of both the azomethine ylide and the dipolarophile, then a prediction of the regioselectivity in the cycloaddition reaction of an unsymmetrical dipole and dipolarophile can be made.[34] The preferred transition state will involve interaction of the larger terminal coefficients. Steric effects also typically play an important part in these cycloaddition reactions and may influence the regioselectivity. In intramolecular cycloaddition reactions, however, conformational constraints normally dictate that only one particular regioisomer can be formed, and this is clearly beneficial in terms of enhancing the selectivity of the process.

In addition to regioselectivity issues, the dipolar cycloaddition reaction can lead to mixtures of stereoisomers. Up to four new chiral centers are generated, and high levels of stereoselectivity are typically obtained. The chiral centers at carbon atoms 2 and 5 of the five-membered ring product derive from the azomethine ylide. There are four possible ylide geometries with the W- and U-shaped forms leading (for a suprafacial reaction) to the 2,5-cis-disubstituted cyclic amine product and the two S-shaped ylides leading to the 2,5-trans-disubstituted product (Chart 4). Azomethine ylides can isomerize, so mixtures of products can result. The question then arises as to whether reaction occurs through one of the ylide geometries to a significantly greater extent than through the others. An inspection of the examples given in this review perhaps shows some general preference for cycloaddition through an S-shaped ylide (see, for example, the extent of formation of the 2,5-trans-disubstituted pyrrolidines derived from aldehydes and unhindered secondary α-amino esters

Chart 4

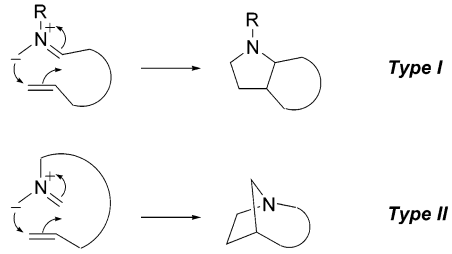


in section 2.1 or from aziridines in section 4.1), although care must be taken not to generalize because 2,5-cis-disubstituted products are not uncommon and subtle steric or conformational effects may have significant influence.

The chiral centers at carbon atoms 3 and 4 of the pyrrolidine product derive from the dipolarophile. The relative orientation of the substituents of the dipolarophile correlates with that in the cycloadduct such that cis-disubstituted alkenyl dipolarophiles lead to 3,4-cis-disubstituted pyrrolidine products and trans-disubstituted alkenyl dipolarophiles lead to 3,4-trans-disubstituted pyrrolidine products. This result is expected on the basis of a concerted cycloaddition reaction. In addition to this stereospecific aspect, the cycloaddition reaction is normally stereoselective, wherein the substituent(s) on the dipolarophile can select to adopt orientations endo or exo to the newly forming ring. The general preference is for the formation of the endo isomer, as found for the isoelectronic Diels−Alder reaction. A mixture of stereoisomers is not untypical, even in intramolecular cycloaddition reactions, although selectivities are often high.

For intramolecular cycloaddition reactions, the dipolarophile is tethered to the azomethine ylide. Two possibilities exist with the dipolarophile tethered to one of the carbon atoms or to the nitrogen atom of the azomethine ylide. The former is more common and leads to fused ring systems, whereas tethering to the nitrogen atom gives rise to bridged bicyclic rings (Chart 5). Both types of product have significant complexity, an attribute that arises inherently from the intramolecular nature of the reaction. Connecting the dipolarophile to the carbon atom of the dipole is analogous to the type I intramolecular Diels−Alder reaction, whereas connection to the nitrogen atom is analogous to the type II intramolecular Diels−Alder reaction.[46] In the former case, the normally relatively short tether restricts the ability for reaction to one conformer so that the transition state leading to one regioisomer is much preferred over the other (giving the fused bicyclic ring product). Indeed, all examples in which the dipolarophile is connected to a carbon atom of the azomethine ylide dipole, with only rare exception (see Schemes 27, 75, and 92), give exclusively the fused (rather than bridged) bicyclic amine product. Another important issue with this type of cycloaddition is the stereochemical outcome across the two new rings. Both cis- and trans-fused products can be formed, although the cis-fused product often predominates. With the type II arrangement in which the dipolarophile is tethered to the nitrogen atom, cycloaddition necessarily creates a bridged bicyclic product. There is of course no regioselectivity issue

Chart 5

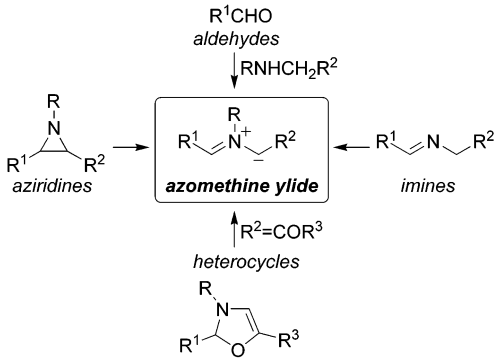


with a symmetrical dipole (as in Chart 5), but an unsymmetrical dipole may favor one regioisomeric product over the other. In both type I and type II cases, it is important to consider the length of the tether between the dipole and the dipolarophile. No cycloaddition occurs if the tether is too short (there are no examples of three-membered ring formation and only one of four-membered ring formation, see Scheme 26), although some examples of large ring systems have been reported (see section 4.2). It is prudent to consider the geometries and relative energies of the two regioisomeric transition states prior to attempting an intramolecular cycloaddition reaction.

Tethering the dipole and dipolarophile makes the reaction more favorable entropically, and conformational constraints normally limit the effective orbital overlap such that one regioisomer is much preferred over the other. This regioselectivity may be contrary to that normally obtained in the corresponding intermolecular reaction. These aspects provide significant advantages over the corresponding intermolecular reaction.[22,23] In addition, a distinct advantage of the intramolecular cycloaddition reaction is that it is effective for electron-rich dipolarophiles (R^3—see Chart 4—need not be an electron-withdrawing group). Alkyl-substituted dipolarophiles are unreactive in intermolecular cycloaddition reactions with azomethine ylides but are suitable in the intramolecular variant. Therefore a greater range of substituted pyrrolidine products is accessible using this chemistry. This aspect, combined with the often highly regio- and stereoselective nature of the reaction, the enhanced reactivity, and the ability to generate complex bicyclic or polycyclic ring systems in only a few steps, has helped to promote the use of this reaction in synthetic chemistry. Intramolecular cycloadditions with azomethine ylides have therefore received significant interest for the formation of substituted cyclic amine products, many of which form the basis of a variety of alkaloid natural products. It must be pointed out, however, that it is necessary to construct a substrate containing both a dipole and a dipolarophile within the same molecule. The various methods to prepare azomethine ylide dipoles do however allow ready access to such substrates.

This review is divided by virtue of the methods used to form the required azomethine ylide dipoles. One of the simplest methods to generate an azomethine ylide is the reaction of an amine with an aldehyde, followed by deprotonation of the iminium ion or prototropic shift of the imine. Other common approaches are the thermal ring-opening of aziridines or of heterocyclic compounds such as 4-oxazolines. Each of these methods (summarized in Scheme 1) and other methods are continuing to attract widespread use in synthetic chemistry.

Scheme 1

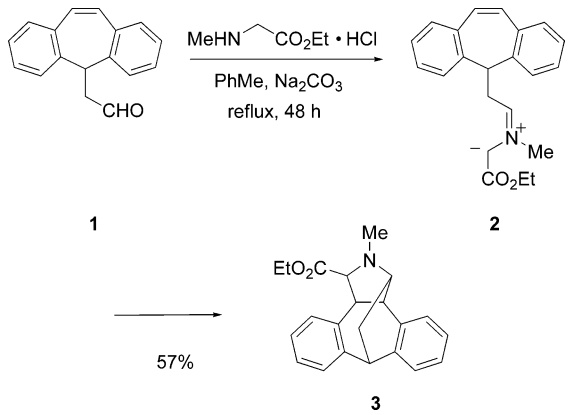


2. Ylides from Aldehydes

2.1. With Secondary α-Amino Esters

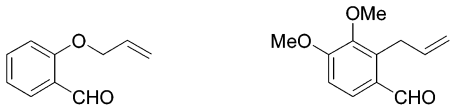
Perhaps the simplest approach to an azomethine ylide is the reaction of a secondary amine with an aldehyde. If the amine bears an electron-withdrawing group, such as a carboxylic ester on the α-carbon atom, then the initial iminium ion can undergo ready deprotonation to the required ylide.[16,19,22] This method was reported by Confalone and co-workers, who showed that a variety of different substituted aldehydes react with secondary amines such as *N*-methylglycine ethyl ester.[47−49] Reactions are typically carried out in nonpolar solvents such as toluene or xylene with removal of the water using, for example, a Dean−Stark trap. The use of nonpolar solvents is not normally a problem when aldehyde substrates are used with condensation by an amino ester but could be an issue with more polar or charged compounds. At high concentration (1 M) of both substrates, the rates of the reactions are normally fast, and increasing the concentration can result in improved yields of the cycloaddition products. The first reported example involved heating the aldehyde **1** with the hydrochloride salt of *N*-methyl-glycine ethyl ester (sarcosine ethyl ester) in toluene in the presence of sodium carbonate to give the cycloadduct **3** via the intermediate azomethine ylide **2** (Scheme 2).[47]

Scheme 2



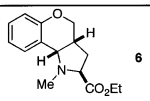
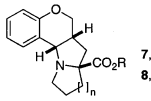
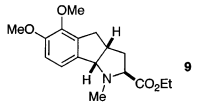
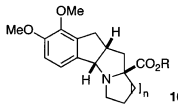
This chemistry was extended to the aldehydes **4** and **5**, which gave the required azomethine ylides and hence cycloaddition products **6**−**11** in high yield using *N*-methyl-glycine ethyl ester, proline methyl ester, or pipecoline ethyl ester as the secondary amine component (Chart 6, Table 1).[48] The stereochemistry of the products was determined by NMR spectroscopic analysis (on the basis of the magnitude of the coupling constants), and the analysis indicated that the product with the cis-fused ring junction predominated. The orientation of the ester group was assigned on the basis of the similarity of the products

Chart 6



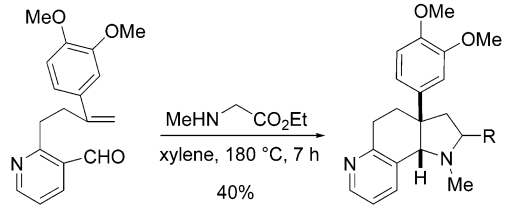
4 5

Table 1. Cycloaddition of α-Amino Esters and Aldehydes 4 and 5

Aldehyde	Amine	Major Product	Yield (%)	Ratio *cis:trans* ring fusion
4	MeHN CO_2Et	 **6**	97	10 : 1
4		 **7**, R=Me, n=1 **8**, R=Et, n=2	98	2.5 : 1
			99	11.5 : 1
5	MeHN CO_2Et	 **9**	89	all *cis*
5		 **10**, R=Me, n=1 **11**, R=Et, n=2	93	all *cis*
			99	all *cis*

with those from cycloaddition of the corresponding alkyne. This implies that the S-shaped ylide was involved in the cycloaddition reaction. Indeed, as this review illustrates, the S-shaped ylide geometry is often favored using secondary amino esters and aldehydes. The methodology was applied to a synthesis of *Sceletium* alkaloid A_4 **13a** (R = H) by reaction of the aldehyde **12** with *N*-methyl-glycine ethyl ester, followed by hydrolysis of the ester **13b** (R = CO_2Et) and decarboxylation (Scheme 3).

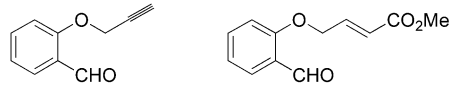
Scheme 3



12 **13a** R=H **13b** R=CO_2Et

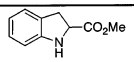
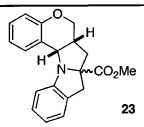
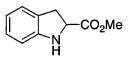
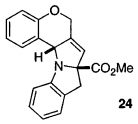
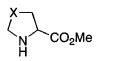
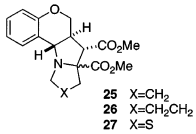
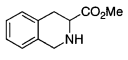
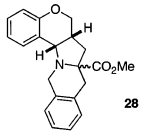
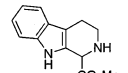
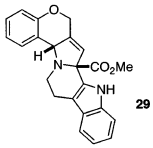
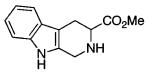
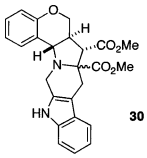
Intramolecular cycloaddition of azomethine ylides derived from the aldehydes **4**, **14**, and **15** (Charts 6 and 7) and various cyclic secondary amino esters **16**–**22** has been studied in some detail, and representative examples from the combinations of these alde-

Chart 7



14 15

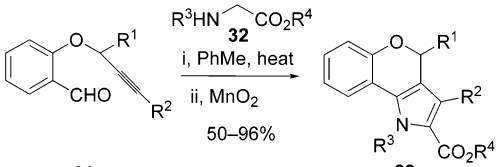
Table 2. Cycloaddition of α-Amino Esters 16–22 and Aldehydes 4, 14, and 15

Aldehyde	Amine	Major product	Yield (%)	Ratio of stereoisomers
4	 **16**	 **23**	55	2 : 1
14	 **16**	 **24**	48	1 : 0
15	 **17** X=CH_2 **18** X=CH_2CH_2 **19** X=S	 **25** X=CH_2 **26** X=CH_2CH_2 **27** X=S	86	4.6 : 1
			87	1.5 : 1
			60	1 : 1
4	 **20**	 **28**	72	3.2 : 1
14	 **21**	 **29**	85	1 : 0
15	 **22**	 **30**	63	2.2 : 1

hydes and amines are given in Table 2.[50] In general, yields of the cycloadducts were high, and mixtures of stereoisomers were formed (although the alkynyl substrate **14** typically gives a single product stereoisomer).

The aldehydes **31** underwent cycloaddition with *N*-alkyl glycine esters **32** (2 equiv) on heating in toluene to give, after cooling and treatment with manganese dioxide, the pyrroles **33** (Scheme 4).[51] The intermediate dihydropyrroles could be isolated if desired, but this was not necessary, and good yields of the pyrrole products were obtained after direct oxidation.

Scheme 4



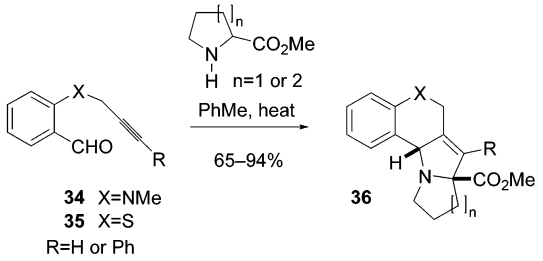
31 **33**

R^1=H or Me, R^2=H, Me or Ph
R^3=Me or Bn, R^4=Me or Et

This chemistry was extended further to give a selection of tetracyclic compounds using proline methyl ester and pipecolic acid methyl ester and the

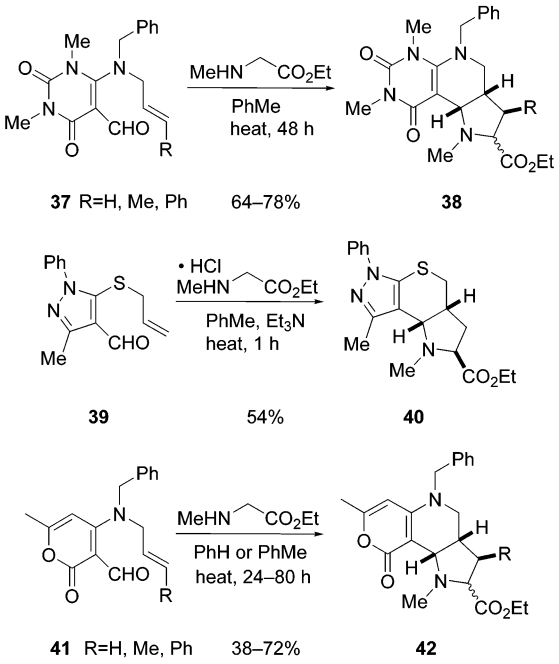
oxygen-tethered aldehydes **31**, the nitrogen-tethered aldehydes **34**, and the sulfur-tethered aldehydes **35** (Scheme 5).[52] In all cases (except with the substrate **31** ($R^1 = R^2 = Me$) in which a 1:1 mixture of the diastereomers was produced), only one stereoisomer of the products **36** was formed, corresponding to the cis stereochemistry of the ring junction hydrogen atom and the methyl ester group.

Scheme 5



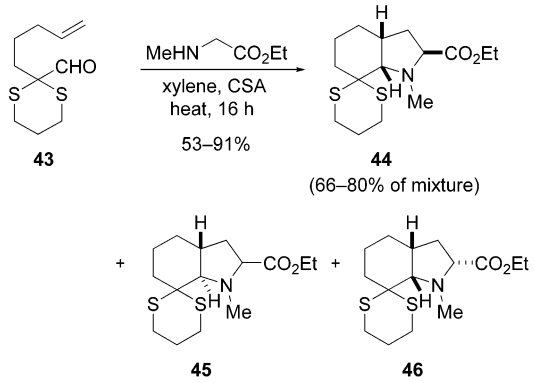
In addition to aromatic aldehydes such as **4**, **14**, and **15**, a number of heteroaromatic aldehydes have proven to be good substrates for condensation with secondary amines to give azomethine ylides. With a suitable alkenyl tether in the ortho position, intramolecular cycloaddition can take place to give cycloadducts such as **38**, **40,** and **42** (Scheme 6).[53−57] In each case, the major or exclusive isomer was that derived from the S-shaped ylide.

Scheme 6



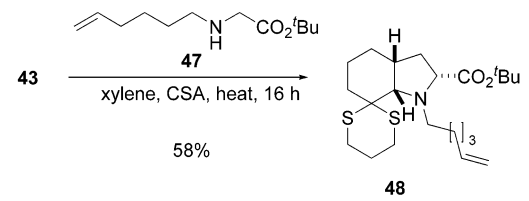
The majority of examples of this chemistry involve aromatic aldehydes, although there are a growing number of reports that use aliphatic aldehydes. In general, the reported examples involve substrates that cannot undergo enolization, and a drawback of this methodology seems to be that the reaction is normally limited to such nonenolizable aldehydes. For example, treatment of the aldehyde **43** with *N*-methyl-glycine ethyl ester has been shown to give predominantly the bicyclic product **44** (Scheme 7).[49,58]

Scheme 7



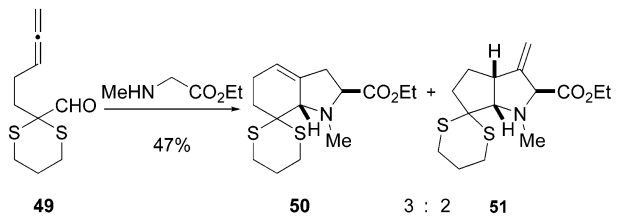
Optimum conditions involved heating the aldehyde and amine in xylene with 1−10 mol % camphor sulfonic acid (CSA) with removal of water (using a Dean−Stark trap). The major product **44** arises from an S-shaped ylide, although a reasonable amount of two other (inseparable) diastereomers was also obtained and these were tentatively assigned as the trans-fused isomer **45** and the isomer **46**. In contrast, attempted azomethine ylide formation and cycloaddition using the related (enolizable) substrate 6-heptenal and *N*-methyl-glycine ethyl ester failed, and a low yield of the self-aldol product was obtained. A variety of amino ester derivatives undergo cycloaddition with the aldehyde **43**. With *N*-benzyl-glycine ethyl ester, *N*-methyl-glycine *tert*-butyl ester, and *N*-allyl-glycine ethyl ester, the major products corresponded to the cycloadduct **44** with the ester group in the exo-orientation.[58] However, use of the amino ester **47** resulted in the formation of predominantly the product **48** with the ester group in the endo-orientation (Scheme 8). Presumably the bulkier N-substituent disfavors the S-shaped ylides and cycloaddition occurs via the U- or W-shaped ylide.

Scheme 8



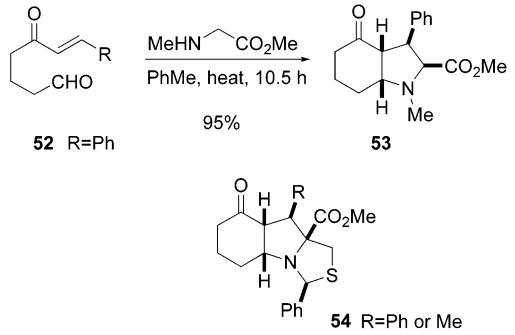
Cycloaddition with the allene **49** and *N*-methyl-glycine ethyl ester gave a mixture of products **50** and **51** (Scheme 9).[49] The major product **50** is the 6,5-fused ring system and results from cycloaddition on the terminal double bond. Cycloaddition on the internal double bond gives the product **51**.

Scheme 9



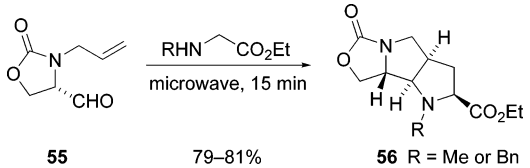
Because the cycloaddition with the substrate 6-heptenal failed, it is likely that the dithiane group present in substrate **43** aids the cycloaddition by preventing enolate or enamine formation. However, there are some reported examples of the successful use of enolizable aldehydes. In particular, condensation and cycloaddition has been achieved using the aldehydes **52**, which lack any blocking substituent α to the aldehyde group (Scheme 10).[59] A single stereoisomer of the pyrrolidine **53** and of the pyrrolidines **54** was obtained by treatment of the aldehydes **52** with *N*-methyl-glycine methyl ester or 2-phenyl-4-thiazolidinecarboxylate methyl ester, respectively.

Scheme 10

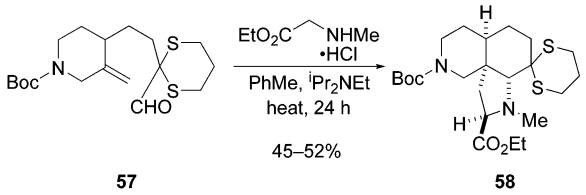


The aldehyde **55** has been reported to undergo intramolecular cycloaddition with *N*-methyl- and *N*-benzyl-glycine ethyl ester on the surface of silica gel in only 15 min using microwave activation (Scheme 11).[60] The crude aldehyde **55**, prepared by reduction (DIBAL-H) of the corresponding methyl ester, was mixed with silica gel (60 PF_{254}), placed on a Pyrex plate, and irradiated in a microwave oven for 15 min to complete the reaction. Good yields of the cycloadducts **56** were obtained by this procedure. Microwave irradiation has also been used to promote the cycloaddition of *O*-allylic and *O*-propargylic salicylaldehydes such as **4**, **14**, and **15** with *N*-alkyl glycine esters.[61,62] For example, the cycloadduct **6** (Table 1) was formed (93% yield) after only 15 min under microwave conditions (100 W, 130 °C), whereas thermal activation alone required 90 min, and the pyrrole **33** ($R^1 = R^2 = H$, $R^3 = R^4 = Me$, Scheme 4) was formed (after in situ oxidation of the intermediate dihydropyrrole using sulfur) in 70% yield after only 20 min.[61] Slightly more forcing conditions (300 W, 200 °C for 15 min) were found preferable for cycloaddition with *N*-benzyl glycine ethyl ester.[62] Bulkier N-substituents (*N*-isopropyl) were found to slow the rate of cycloaddition or prevent it all together (*N*-*tert*-butyl, *N*-adamantyl), and cycloaddition with *N*-phenyl glycine ethyl ester was unsuccessful. This study therefore demonstrated some of the limitations of this methodology, particularly in

Scheme 11



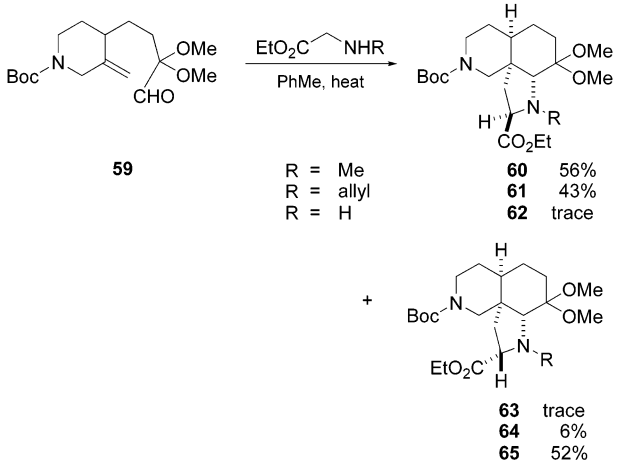
Scheme 12



relation to the use of α-amino esters bearing N-aryl or bulky N-alkyl substituents.

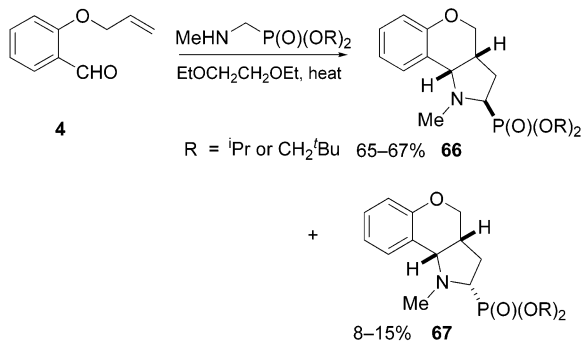
The condensation of a secondary α-amino ester with an aldehyde has found use in an efficient synthesis of the core ring system of manzamine A.[63] The aldehyde **57** was heated with *N*-methyl-glycine ethyl ester hydrochloride salt and diisopropylethylamine in toluene to give a single diastereomer of the cycloadduct **58** (Scheme 12).[63] The product **58** contains the ABC ring system of the manzamine alkaloids. Further work in this area demonstrated that the aldehyde **57** was a poor substrate for cycloaddition with other secondary amines.[64] The conditions outlined in Scheme 12 were the only ones suitable for successful reaction of aldehyde **57**. The alternative aldehyde **59**, with a dimethyl acetal in place of the dithiane, was shown however to be a good substrate and underwent cycloaddition with a variety of α-amino esters (Scheme 13). For example, condensation with *N*-methyl- or *N*-allyl-glycine ethyl ester gave the tricyclic products **60** or **61** as the major stereoisomer. In contrast, condensation with the primary amine glycine ethyl ester (see section 3.1 for related chemistry) resulted in the stereoisomer **65** as the major product.

Scheme 13



The examples described so far have involved secondary amines bearing a carboxylic ester as the anion-stabilizing group. Other anion-stabilizing groups have been reported to allow ylide formation and cycloaddition. For example, heating an amino phosphonate and the aldehyde **4** in ethylene glycol diethyl ether over molecular sieves gave the cycloadducts **66** and **67** (Scheme 14).[65] The stereochemistry of the major products **66** corresponds to that formed using the analogous carboxylic ester (compound **6**, Table 1). Use of toluene as solvent gave slightly lower yields. The use of a nitrile as the anion-stabilizing

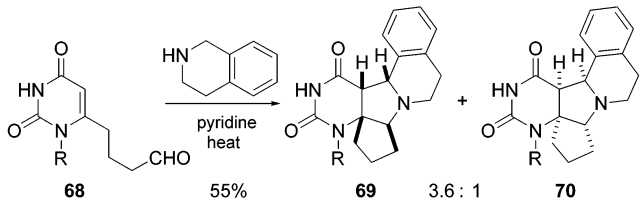
Scheme 14



group was also successful, although less stereoselective, and resulted in the formation of a mixture of cis-fused ring cycloadducts (26% and 37%), together with a small amount (7%) of two trans-fused adducts.

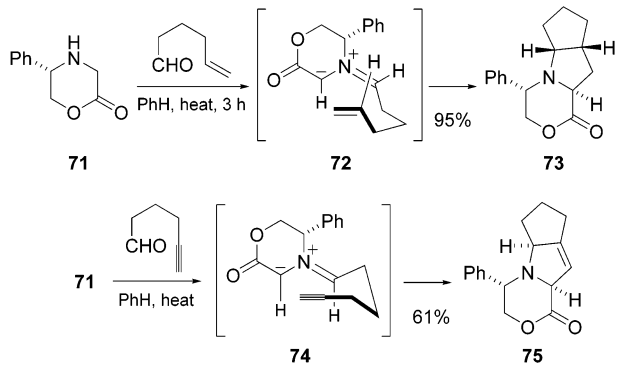
A single example of the use of an aromatic ring as the anion-stabilizing group for an intramolecular cycloaddition reaction of an azomethine ylide has been reported (Scheme 15).[66] Condensation of tetrahydroisoquinoline with the aldehyde **68** gave the cycloadducts **69** and **70**, which are diastereomeric due to the chiral substituent on the uracil group. The benzene ring must be a sufficiently activating group to allow deprotonation of the iminium ion to give the ylide (S-shaped), which undergoes cycloaddition to give the two diastereomers. This is a noteworthy result because the aldehyde **68** is enolizable and the secondary amine (tetrahydroisoquinoline) is not particularly activated; however, few other examples with such substrates have been reported (see Table 4 and Scheme 30), and the generality of this type of chemistry is unknown.

Scheme 15



With a chiral secondary amine, asymmetric induction is possible in the cycloaddition reaction. Despite the possibility of enolization/enamine formation, 5-hexenal could be heated in benzene with the morpholin-2-one **71** to give the cycloadduct **73** as a single diastereomer (Scheme 16).[67] Successful cycloaddition was also achieved between the amine **71** and 6-heptenal (90% yield) and 3-thia-5-hexenal (75% yield) at the higher temperature afforded by using toluene as the solvent. These cycloadducts were also formed as single diastereomers. In comparison, cycloaddition of the amine **71** and the alkyne 5-hexynal resulted exclusively in the diastereomer **75**.[68] The results indicate that cycloaddition with the alkenyl substrate occurs via the S-shaped ylide **72**, whereas with the alkynyl substrate the W-shaped ylide **74** is favored. These conclusions were supported by computational studies, in which the lowest energy transition states arise from these ylide geometries.[69] Interestingly, cycloaddition with the substrate 6-heptynal, in which there is one extra methylene unit in the linking chain, resulted in a single product derived from the usual S-shaped ylide. It appears that extending the chain length allows sufficient conformational freedom to permit cycloaddition from the S-shaped ylide.

Scheme 16



2.2. With Secondary α-Amino Acids

In the previous section, the condensation of aldehydes and α-amino esters to give proline derivatives was described. One of the drawbacks of this methodology is that a carbonyl group is required to stabilize the ylide and therefore ends up in the product where it may not be required. An alternative procedure that provides pyrrolidine products lacking the carbonyl group uses α-amino acids rather than their esters. These react with aldehydes to form, after decarboxylation, the required unstabilized azomethine ylide; cycloaddition then gives the pyrrolidine product.

The decarboxylative generation of azomethine ylides has been investigated extensively by Grigg and coworkers.[70−72] Heating the aldehyde **76** with phenylglycine or *N*-methyl-glycine in DMF gave the cycloadducts **77** and **78** as the only isomers (Scheme 17). The product **77**, R = H, R′ = Ph, arises from a W-shaped ylide. The reaction of the α-amino acid with the aldehyde is thought to lead to the oxazolidinone **79**, which on thermolysis releases carbon dioxide to give the "nonstabilized" ylide **80**, which then undergoes intramolecular cycloaddition.

Scheme 17

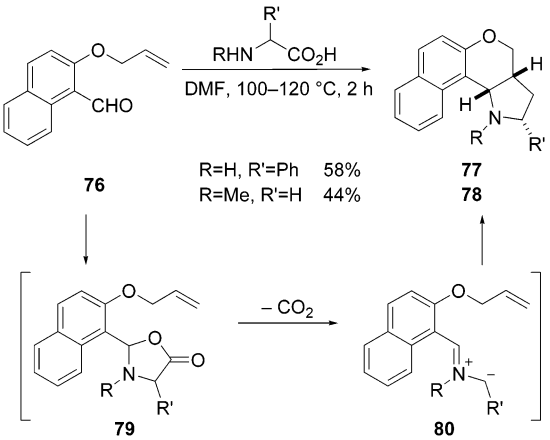
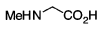
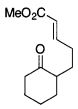
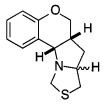
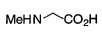
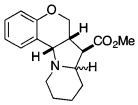
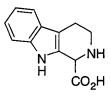
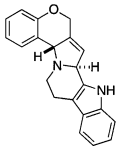


Table 3. Cycloaddition of α-Amino Acids and Aldehydes 4, 14, 15, 81, and 82

Aldehyde	Amine	Major product		Yield (%)	Ratio of stereoisomers
 81			83	65[a]	–
 82			84	65[a]	1 : 1
4			85	63	1 : 1
14			86	72	–
15			87	87	8.2 : 1[b]
14			88	62	1 : 0[c]

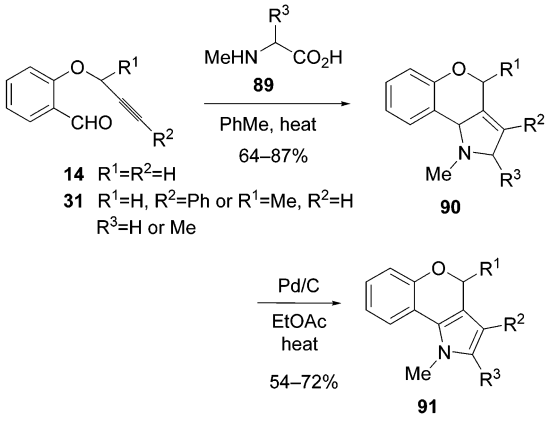
[a] In the presence of Bu_2SnCl_2. [b] Plus some of another *exo* adduct. [c] This ratio reflects the ratio of S-shaped/W-shaped ylides.

A variety of aldehydes and amino acids can be used for this process, as illustrated in Table 3.[72] Typically the substrates are heated in toluene or DMF, sometimes in the presence of the Lewis acid Bu_2SnCl_2. A mixture of stereoisomers is often formed, although the alkynyl substrate **14** gave only one product using a number of amino acids (for example, product **88**, arising from the S-shaped ylide). Combinations of other amino acids and aldehydes to give related products were also reported.[72]

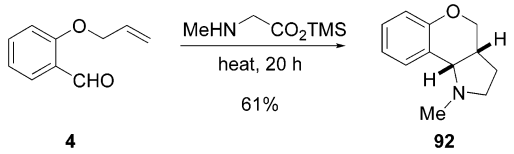
When the alkynyl aldehyde **14** and its substituted analogues **31** were used, cycloaddition with *N*-methyl glycine or *N*-methyl alanine **89** gave the products **90**, which could be oxidized to the pyrroles **91** by heating in EtOAc with palladium on charcoal (Scheme 18).[51] Similarly, cycloaddition with proline or pipecolic acid gave the expected tetracyclic adducts that could be aromatized to the pyrroles by heating with sulfur in toluene.[52]

The intramolecular dipolar cycloaddition reaction to give a pyrrolidine product from an α-amino acid was also reported by Confalone and Huie.[48] Treatment of the aldehyde **4** with the trimethylsilyl ester of *N*-methyl-glycine gave the product **92** (Scheme 19). The trimethylsilyl ester is thought to promote formation of the intermediate oxazolidinone. This type of reaction can often however be achieved with the free acid. Indeed reaction of the aldehyde **4** with *N*-*p*-methoxybenzyl-glycine (*N*-PMB-glycine) gave the analogous *N*-PMB product (53% yield).[73] More recently, condensation of methoxy-substituted derivatives of the aldehyde **4** with *N*-methyl-glycine and chlorotrimethylsilane gave methoxy-substituted analogues of the cycloadduct **92**, which were subsequently converted to compounds with activity against human acetylcholine esterase.[74]

Scheme 18

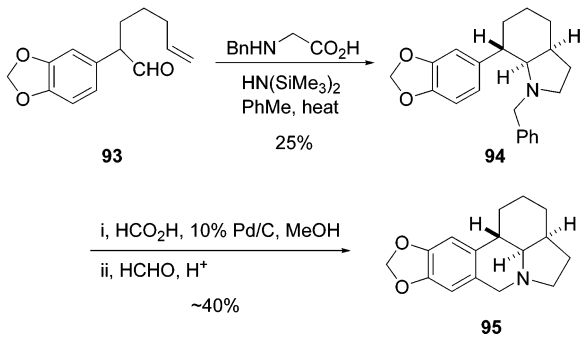


Scheme 19



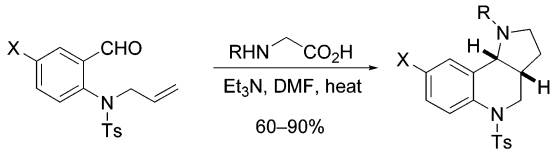
This chemistry was applied to a synthesis of α-lycorane **95** using the aldehyde **93** and *N*-benzyl-glycine, which had been pretreated with hexamethyldisilazane (Scheme 20).[75] The product **94** was formed as a single stereoisomer in low yield and was converted to α-lycorane **95** by hydrogenolysis and iminium ion cyclization.

Scheme 20



Similar chemistry has been reported with *o*-aminobenzaldehyde derivatives to provide an efficient synthesis of the core ring system of the *Martinella* alkaloids.[76–80] For example, heating the aldehydes **96** with *N*-methyl-, *N*-benzyl- or *N*-PMB-glycine (the latter two as their hydrochloride salts) in DMF and triethylamine gave the cycloadducts **97** (Scheme 21).[76,77] Unsurprisingly, treating the aldehyde **96** (X = H) with *N*-trityl-glycine or *N*-carboxybenzyloxy-glycine failed to give any cycloaddition products. However glycine itself did give the *NH*-pyrroloquinoline (X = R = H) in low yield (17%), which could alternatively be prepared by hydrogenolysis of **97** (R

Scheme 21



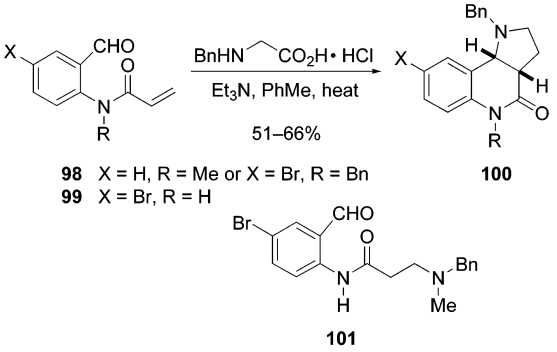
96 X = H or Br
R = Me, Bn, PMB

97

= Bn or PMB). Therefore, to prepare N-unsubstituted cycloadducts, it may be possible to use the simplest amino acid glycine in these cycloaddition reactions, perhaps more effectively with activated dipolarophiles, although this has not, to our knowledge, been investigated.

More recent studies have shown that an acrylamide group can be used as the dipolarophile, as long as the amide is tertiary rather than secondary.[78] Thus, heating the aldehydes **98** with the hydrochloride salt of *N*-benzyl-glycine in toluene and triethylamine gave the cycloadducts **100** (Scheme 22). Attempts to promote reaction with the aldehyde **99**, in which the amide is secondary (R = H), resulted in the Michael addition product **101** (68%), equivalent to adding *N*-methylbenzylamine to the acrylamide. It is thought that the intermediate oxazolidinone is generated and undergoes decarboxylation to give the azomethine ylide. However this ylide must be protonated at a rate that is faster than cycloaddition, thereby resulting in the formation (after hydrolysis) of *N*-methylbenzylamine, which then adds to the acrylamide to give **101**. This result suggests that it is prudent to avoid the presence of a relatively acidic proton when forming the desired "nonstabilized" azomethine ylide.

Scheme 22



98 X = H, R = Me or X = Br, R = Bn
99 X = Br, R = H

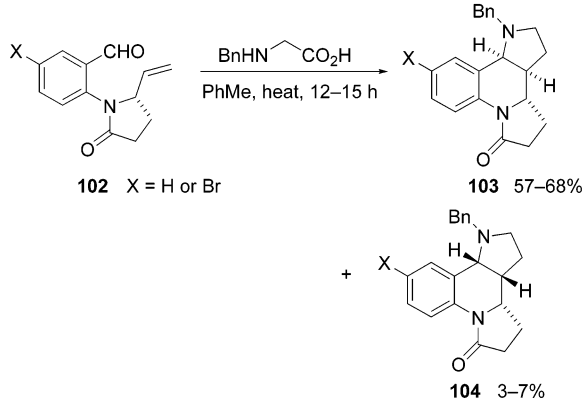
100

101

In a separate study toward the same ring system, the aldehydes **102** were treated with excess *N*-benzyl-glycine in toluene to give the cycloadducts **103** and **104** (Scheme 23).[79] The stereochemistry of the major product **103** (X = H) was assigned on the basis of the magnitude of coupling constants in the ^{1}H NMR spectrum and of X-ray crystal structure analysis. When the bromo derivative **102** (X = Br) was used, the major diastereomer **103** was used in a total synthesis of martinellic acid.[80]

Application of this chemistry toward the synthesis of an annulated nicotine analogue was achieved using the aromatic aldehyde **105** (Scheme 24).[81] Heating the aldehyde **105** with *N*-methyl-glycine in DMF for

Scheme 23



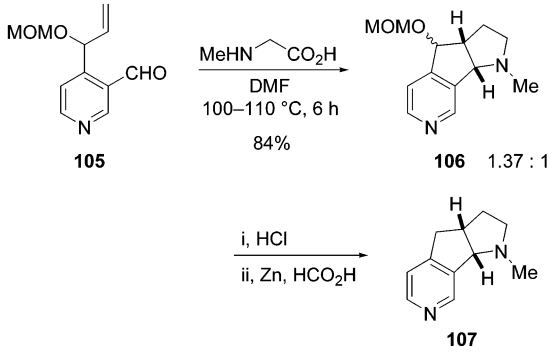
102 X = H or Br

103 57–68%

104 3–7%

6 h resulted in the formation of the cycloadducts **106**, epimeric at the carbon atom bearing the alkoxy group, in a ratio 1.37:1. Acidic hydrolysis and reductive dehydroxylation gave the nicotine analogue **107**. A more efficient and direct synthesis of the product **107** was achieved by allylation (in the 4-position) of pyridine-3-carboxaldehyde (using Comins' methodology) followed by heating with *N*-methyl-glycine in DMF.[82]

Scheme 24



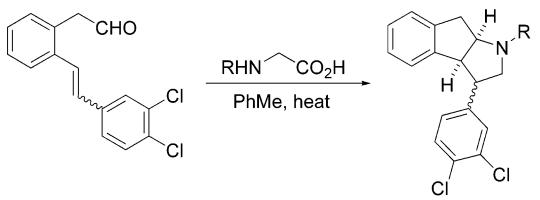
105

106 1.37 : 1

107

Conformationally constrained analogues of aminoindane neuronal calcium antagonists have been prepared using intramolecular cycloaddition reactions of azomethine ylides generated from α-amino acids and the aldehydes **108** (Scheme 25).[83] The cycloaddition was stereospecific as illustrated by the formation of the exo- and endo-isomers of the product **109** from the separate *E*- and *Z*-isomers of the aldehyde **108**. A mixture of the *E*- and *Z*-geometrical isomers gave a mixture of the stereoisomeric pyrrolidines **110** (R = PMB) using *N*-*p*-methoxybenzyl-glycine.

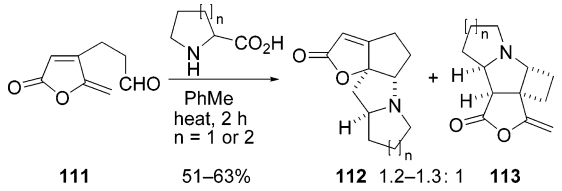
Scheme 25



E-**108**	R=Me	73%	*exo*-**109**
Z-**108**	R=Me	81%	*endo*-**109**
E- + *Z*-**108**	R=PMB	47%	**110**

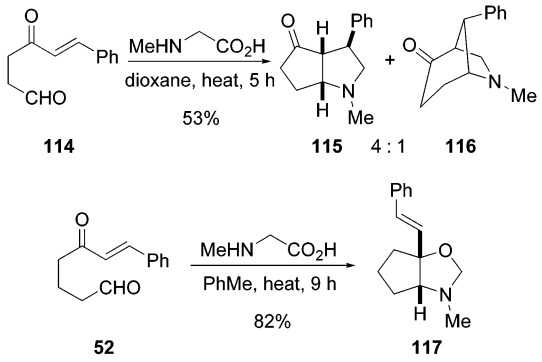
Addition of proline or pipecolic acid to the 4-substituted protoanemonin **111** resulted in the formation of the tetracyclic products **112** and **113** (Scheme 26).[84] Both alkene double bonds act as dipolarophiles to give a mixture of products in approximately equal ratio. The stereochemistry of the cycloadducts **112** and **113** ($n = 1$) was based on ^{1}H NMR NOESY data and analogy to those for $n = 2$, which were determined by X-ray crystal structure analyses. The stereochemistry indicates that the cycloaddition occurs through ylides with S-shaped geometry. Unusually, the lower boiling solvent acetonitrile was also successful, providing the two products **112** and **113** ($n = 2$) in a similar overall yield (58%) and with a slight preference (ratio 2.1:1) for reaction at the more reactive γ,δ-double bond.

Scheme 26



Ylide formation from the aldehyde **114** and cycloaddition onto the carbon−carbon double bond of the enone gave predominantly the bicyclic product **115** (Scheme 27).[59] A small amount of the amine **116** was also formed, representing the less common regioisomeric combination of the ylide dipole and dipolarophile to give the bridged bicyclic product. Both **115** and **116** are formed as single stereoisomers with the expected relative stereochemistry. Similar products arise from condensation of the aldehyde **114** with cyclic α-amino acids such as 4-thiazolidinecarboxylic acid.

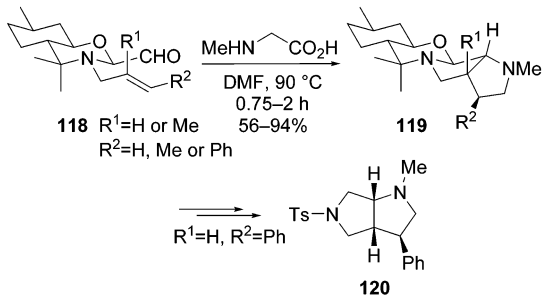
Scheme 27



In contrast, heating the aldehyde **52** (which has a longer chain length between the aldehyde and the enone functional groups) with *N*-methyl-glycine in toluene for 9 h resulted in the formation of the cycloadduct **117** (Scheme 27). The product **117** arises from cycloaddition of the azomethine ylide onto the ketone, rather than the alkene double bond. This result also contrasts with the cycloaddition of the aldehyde **52** with α-amino esters, in which the normal reaction with the alkene double bond occurs (see Scheme 10). A possible explanation for this change in selectivity lies in the fact that nonstabilized azomethine ylides (formed from condensation of aldehydes with α-amino acids followed by loss of CO_2) have a high-energy HOMO and prefer, when geometrically possible, to interact with the carbonyl group, which is more electrophilic and has a lower-energy LUMO. It remains to be seen whether this type of reaction will be successful with other carbonyl functional groups, although some success in this area has been reported using ylides generated from the addition of difluorocarbene to imines (see Scheme 75).

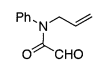
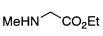
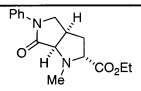
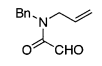
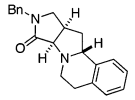
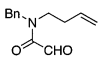
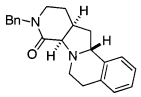
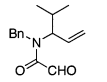
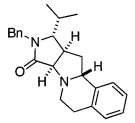
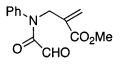
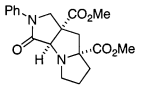
Intramolecular cycloaddition of azomethine ylides bearing a chiral auxiliary or in the presence of a chiral catalyst has so far received little attention. It is possible to achieve asymmetric induction using a chiral aldehyde or a chiral amine; some examples of which are given in Schemes 16 and 28. For example, heating the chiral aldehydes **118** with *N*-methylglycine in DMF gave a single diastereomer of the cycloadducts **119** (Scheme 28).[85] The best yields of the products were obtained in DMF at 90 °C, except with aldehyde **118** ($R^1 = H$, $R^2 = Ph$), for which the use of refluxing DMF and addition of triethylamine was preferable (76% rather than 56% yield). The chiral auxiliary was removed for cycloadduct **119** ($R^1 = H$, $R^2 = Ph$) over a series of steps (AlH_3, THF; PCC, NaOAc; TsCl, NaOH) to give the enantiomerically pure octahydro-pyrrolo[3,4-*b*]pyrrole **120**. The stereoisomers **119** arise from a preference for cycloaddition to give the cis-fused five-membered rings with the connecting alkene dipolarophile tether in an endo arrangement (R^1 and R^2 exo).

Scheme 28



The direct synthesis of octahydro-pyrrolo[3,4-*b*]-pyrroles can be achieved by reacting activated amines with *N*-allyl-glyoxamides such as **121**−**125** and triethylamine at reflux in toluene (Table 4).[86] The secondary amine tetrahydroisoquinoline or a variety of α-amino esters (but not unactivated amines such as pyrrolidine or the acyclic *N*-methyl-benzylamine) can be used to give a selection of bicyclic amine products including **126**−**130**. In most cases, a single stereoisomer is produced, resulting from an S-shaped azomethine ylide. This stereochemical outcome contrasts with that reported for a similar aldehyde under microwave conditions (see Scheme 11), in which the product (**56**) arises from a W-shaped ylide. The difference in selectivity presumably arises from the presence of a carbonyl group α to the aldehyde in substrates **121**−**125**. Intramolecular cycloaddition reactions with the analogous alkynyl glyoxamides could be accomplished in low yield (20−45% yield of the isolated dihydropyrrole or pyrrole products).

Table 4. Cycloaddition with *N*-Allyl-glyoxamides 121−125

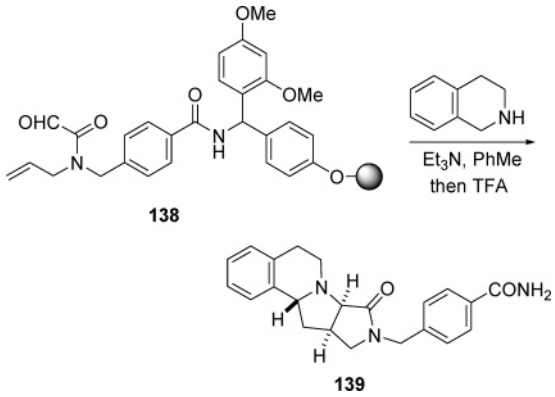
Aldehyde		Amine	Major product		Yield (%)
	**121**			**126**	65[a]
	**122**			**127**	72
	**123**			**128**	64
	**124**			**129**	56
	**125**			**130**	56

[a] Ratio exo/endo = 5:1.

The products, such as **126**, from cycloaddition with the glyoxamides have a trans relationship between the substituents at C-2 and C-5 of the pyrrolidine ring, indicative of an S-shaped ylide. There are two possible S-shaped ylides and an interesting competition experiment was carried out to determine the extent, if any, of equilibration between these ylides using the two glyoxamides **121** and **134** (Scheme 29).[86] Reaction with the amine components **131** and **135** might be expected to give the two S-shaped ylides **132** and **136**, respectively, which could lead to different cycloaddition products. However, only the cycloadduct **133** was formed in both reactions, implying that the ylides are fully equilibrated and that there is a preference for cycloaddition onto the *N*-allyl rather than *N*-homoallyl group.

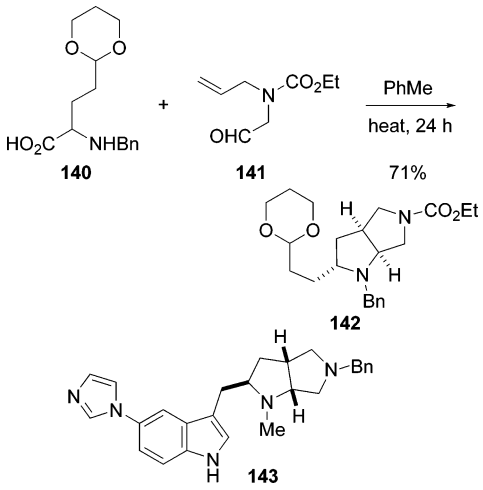
The chemistry was applied to the solid phase by preparing the glyoxamide **138** with the nitrogen atom connected to the Rink linker via a benzamide spacer (Scheme 30). Treatment of the linked glyoxamide with tetrahydroisoquinoline and triethylamine in refluxing toluene, followed by release from the resin with trifluoroacetic acid gave the product **139**. Varying the secondary amine or the *N*-allyl unit provided a total of nine different cycloadducts.

Scheme 30



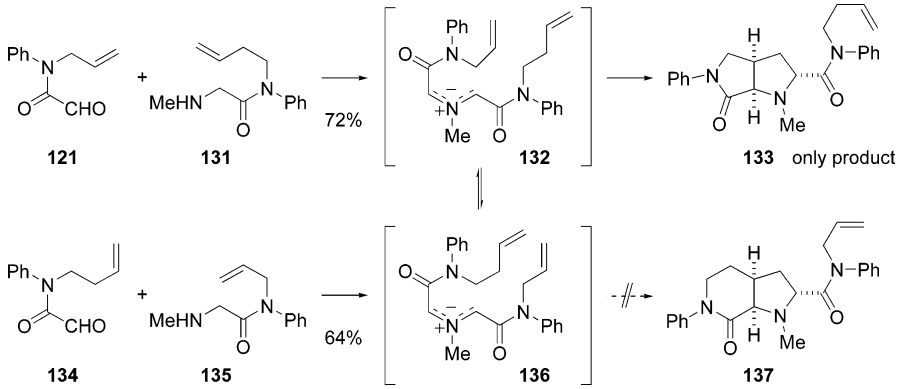
A number of high affinity conformationally restricted 5-HT receptor agonists with the octahydropyrrolo[3,4-*b*]pyrrole ring system have also been prepared using a related intramolecular cycloaddition reaction.[87] Heating the α-amino acid **140** with the aldehyde **141** in toluene gave the cycloadduct **142** as a single diastereomer (via an S-shaped ylide). The adduct **142** was converted over a number of steps to the targets such as **143** (Scheme 31).

Scheme 31



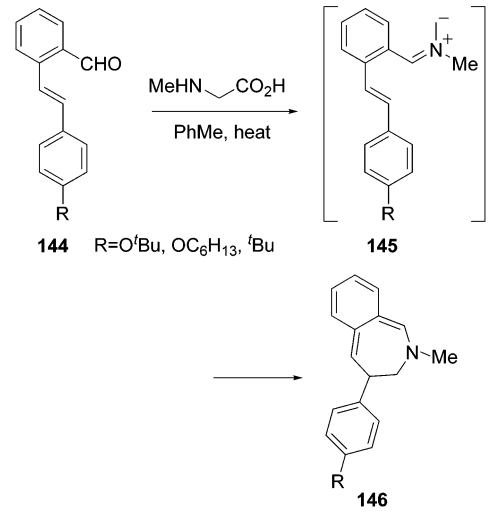
While an *inter*molecular cycloaddition of an unactivated azomethine ylide onto C_{60} was attempted, the aldehydes **144** were treated with *N*-methyl-glycine in toluene (Scheme 32).[88] The alkene tether in the substrate is only two atoms from the azomethine

Scheme 29



ylide (intermediates **145**), and it was not anticipated that intramolecular cycloaddition would take place, because this would result in a four-membered or a bridged bicyclic ring system. Indeed intramolecular cycloaddition does not take place, but cyclization does occur to give the diene **146**, which acts as a 4π component in a subsequent Diels–Alder type cycloaddition with C_{60}.

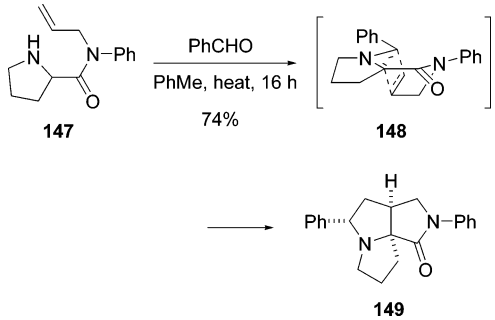
Scheme 32



2.3. Dipolarophile Tethered to the Amine

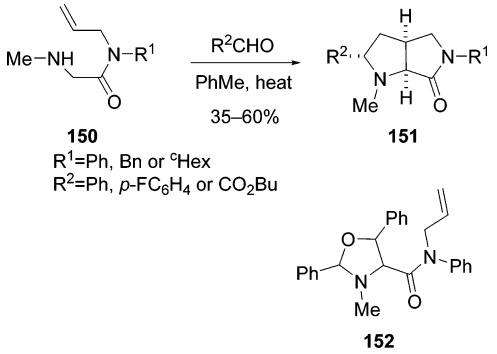
Only a few examples have been reported of the intramolecular cycloaddition reaction of an azomethine ylide derived from a secondary alkenylamine and an aldehyde. These require, for formation of the ylide, an anion-stabilizing group (or a carboxylic acid for decarboxylation) on the carbon atom α to the nitrogen atom. This group could be part of the chain carrying the dipolarophile or attached to the α-carbon atom of this chain, or it could be on the α′ atom. So far, only examples of the first of these have been reported. Heating the amine **147**, bearing a carboxylic amide group in the dipolarophile chain, with benzaldehyde in toluene gave the tricyclic product **149** (Scheme 33).[86] A single stereoisomer of the product was formed, as judged by ^{1}H NMR NOE spectroscopy, which had the cis fused ring and the *C*-phenyl group in the exo orientation. This must arise from an intermediate S-shaped ylide **148** with the carbonyl group exo to the five-membered ring transition state. This stereoselective reaction is clearly an efficient entry to such tricyclic products, although access to other stereoisomers is not possible using this chemistry.

Scheme 33



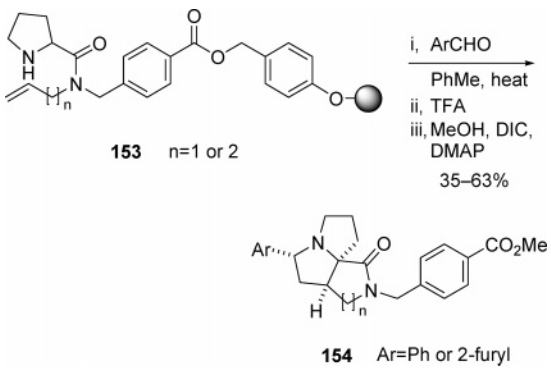
A selection of amines **150** and aldehydes were studied, as illustrated by the examples in Scheme 34. The reaction is successful for a variety of *N*-alkyl or aryl (but not *N*-H) substituents on the amide nitrogen atom; however, the reaction only tolerated *N*-methyl or pyrrolidine (from proline as in **147**) as the secondary amine unit (*N*-H, Ph, Bn, Bu, and ^{c}Hex all failed). Aromatic aldehydes (R^2 = Ar) are suitable components, but formaldehyde and aliphatic aldehydes failed to give cycloaddition products, although butyl glyoxylate gave the cycloadduct **151** (R^1 = Ph, R^2 = CO_2Bu) in moderate yield. Ketones were generally unsuccessful, with the exception of methyl pyruvate and isatin, which gave low yields of the cycloadducts with a quaternary center. A side product in a number of these reactions is the adduct such as **152** in which two aldehyde components have combined with the amine. The formation of this product appears to be irreversible (at least under these conditions), and substantial amounts of this 2:1 adduct can be formed, thereby diminishing the yield of the desired cycloadduct.

Scheme 34



In the same way as the alkenyl aldehydes described in the previous section (Scheme 30), alkenylamines can be linked, via an amide nitrogen atom, to a solid support (Scheme 35). The Wang resin was found preferable and was used to prepare the amines **153**, which were treated with benzaldehyde or furfural in refluxing toluene to give the cycloadducts. Acidic cleavage from the resin and esterification to ease purification gave the products **154**. Comparable yields to the solution phase were obtained. The chemistry was also amenable to the use of sarcosine

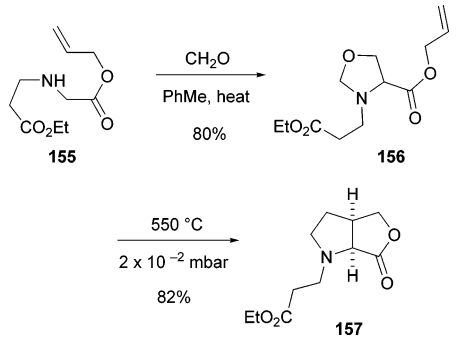
Scheme 35



(as well as proline) as the linked amino acid component.

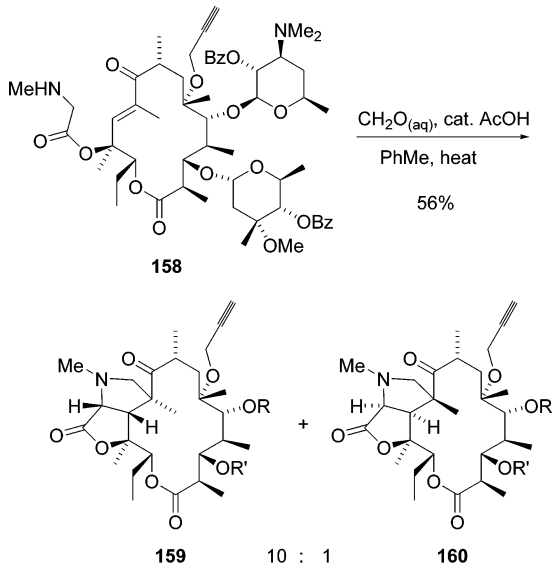
In another example of intramolecular cycloaddition with a dipolarophile-tethered amine, the amine **155** was treated with formaldehyde (Scheme 36).[89] This lead to the 2:1 adduct **156**, rather than the product of cycloaddition onto the alkene. However, flash vacuum pyrolysis (FVP) of the oxazolidine **156** gave the desired bicyclic product **157** as a single diastereomer. The use of FVP may therefore provide a solution should the 2:1 adducts be the major products in such attempted cycloaddition reactions.

Scheme 36



Recently the addition of formaldehyde to the α-amino ester **158** was used for the preparation of novel tricyclic macrolides as potential antibacterial agents (Scheme 37).[90] Using just one equivalent of formaldehyde avoided oxazolidine formation (cf. **156**) and resulted in the desired cycloadduct **159** together with a small amount of the diastereomer **160**. The structure of the cycloadduct **159** was deduced from 2D NMR spectroscopic studies. Lower levels of stereoselectivity were obtained with some other O-protected derivatives. This example illustrates the usefulness of dipolar cycloaddition reactions with azomethine ylides for the preparation of complex ring systems in multifunctional compounds.

Scheme 37

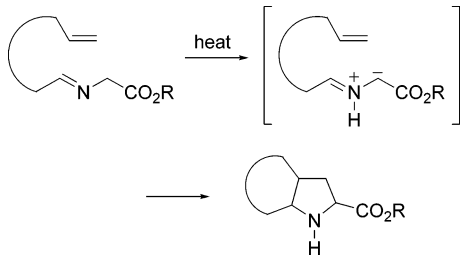


3. Ylides from Imines

3.1. By Prototropy

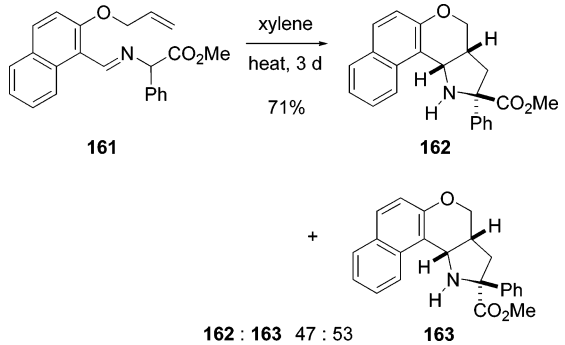
One of the drawbacks of the methodology described in section 2 is that it uses a secondary amine to condense with an aldehyde (to give the azomethine ylide); such amines may not be readily available and the pyrrolidine product formed after cycloaddition necessarily contains an alkyl group on the nitrogen atom. To form directly an N-unsubstituted product, a hydrogen atom (or a metal atom—see section 3.2) must be attached to the nitrogen atom of the azomethine ylide. These ylides are accessible from imines by migration of a proton from the α-carbon to the nitrogen atom, a so-called 1,2-prototropic shift (Scheme 38).[18,19,21]

Scheme 38



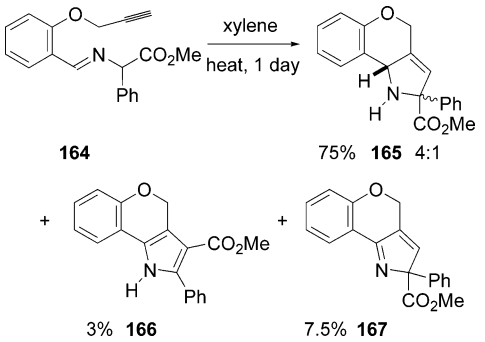
This approach was developed by Grigg and coworkers, who found that the 1,2-prototropic shift could be promoted on heating imines derived from aromatic aldehydes and α-amino esters. The derived azomethine ylide was then able to undergo intramolecular cycloaddition.[91,92] For example, heating the imine **161** in xylene gave the diastereomeric adducts **162** and **163** (Scheme 39). The stereochemistry of the adduct **163** was verified by X-ray crystallography. In a similar way, the corresponding substrate with an alkyne dipolarophile also gave a mixture of diastereomeric cycloadducts.

Scheme 39



The related imine **164** was heated in xylene to give the adducts **165**, as a mixture of stereoisomers, together with a small amount of the pyrrole **166** and some of the diene **167** (Scheme 40).[92] The major stereoisomer of the adduct **165** was found to have the methoxycarbonyl group trans to the ring junction hydrogen atom (as found for the related product **163**). The pyrrole **166** arises from the product **167**, as the isolated diene **167** rearranged quantitatively to the pyrrole **166** on heating. The ester group has a higher

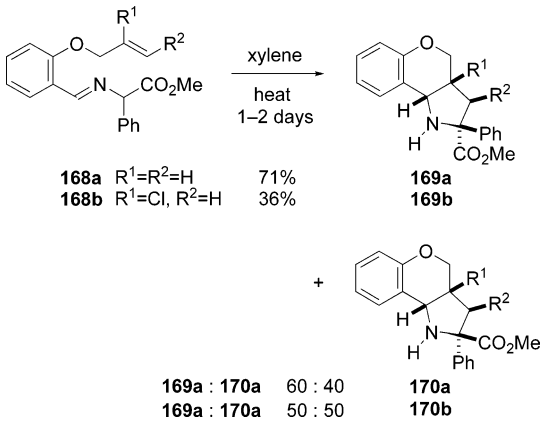
Scheme 40



migratory aptitude than the phenyl group and undergoes preferential 1,5-shift. The diene **167** presumably arises by dehydrogenation of the cycloadduct **165**.

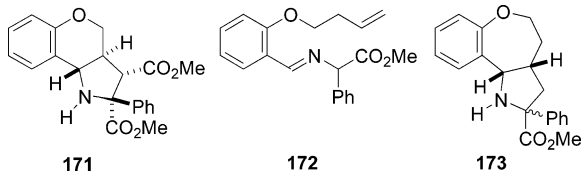
Other examples of such cycloadditions with an imine derived from phenylglycine are shown in Scheme 41.[92] Mixtures of stereoisomers **169** and **170** were obtained after heating the imines **168** in xylene for up to 2 days. It was possible to effect cycloaddition with the vinyl chloride **168b**, but the substrate in which the chlorine atom is replaced by a methyl group ($R^1 = Me$, $R^2 = H$) did not undergo reaction, and the imine decomposed. Likewise the terminal methyl-substituted compound, $R^1 = H$, $R^2 = Me$ failed to undergo reaction. The activated dipolarophile with $R^1 = H$ and $R^2 = CO_2Me$ reacted successfully and gave the adduct **171** (Chart 8) as the major product with, unusually, the trans-fused ring junction (compare with section 3.2). In all cases, the assignment of stereochemistry was made on the basis of ^1H NMR NOE spectroscopy and the magnitude of the coupling constants. The rate of these intramolecular reactions is determined by the slow step, which is thought to be the cycloaddition rather than the 1,2-prototropic shift. This is in contrast to the corresponding intermolecular reaction with activated dipolarophiles such as *N*-phenyl-maleimide, in which ylide formation is rate-determining (and in which the rate is accelerated by adding acetic acid). The rate of (intermolecular) cycloaddition was slowed (in comparison with that using **168a**) by the presence of an electron-donating ethoxy group on the aromatic ring para to the imine, and no intramolecular cycloaddition took place. With the homologue **172** (Chart 8), cycloaddition was also considerably slower, and a mixture

Scheme 41



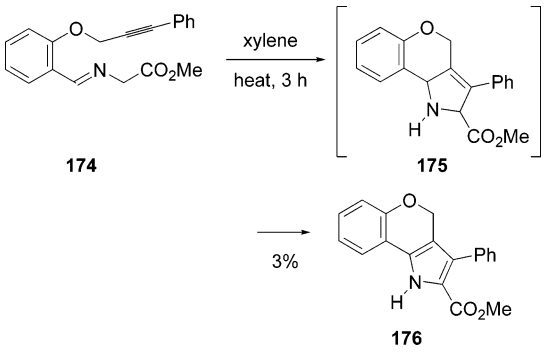
(1:1) of the cycloadducts **173** was formed in low yield (the isomer with the methoxycarbonyl group trans to the ring junction hydrogen atoms was isolated in 20% yield).

Chart 8



At a similar time to the first reports by Grigg on the intramolecular dipolar cycloaddition reaction by 1,2-prototropic shift, Tsuge and co-workers described the same type of chemistry with the formation of the adduct **165** (together with a small amount of the pyrrole **166** and some of the aldehyde arising from hydrolysis of unreacted imine **164**).[93] This result was compared with that obtained using the substrate **174**, lacking the phenyl group to stabilize the azomethine ylide (Scheme 42). The substrate **174** was much less reactive toward 1,2-prototropic shift/cycloaddition and gave only a very low yield of the adduct **176**, which had already undergone aromatization and was found to be isomeric to the pyrrole **166**.

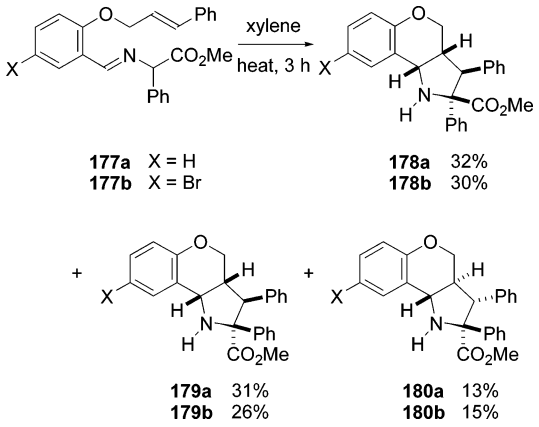
Scheme 42



In the same way, the intramolecular dipolar cycloaddition reaction was effective for the similar substrates **177a** and **177b**, which gave a mixture of the cycloadducts **178**−**180** (Scheme 43).[94] The two cis-fused stereoisomers **178** and **179** were formed as the major products in approximately equal amounts. There appears therefore to be no significant preference for the formation of either the W- or the S-shaped ylide geometry in these cycloaddition reactions.

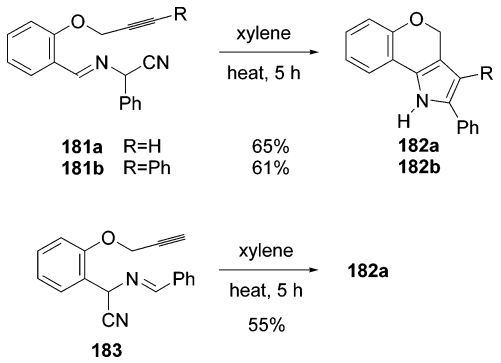
The 1,2-prototropic shift and intramolecular cycloaddition of the resulting azomethine ylide has also been extended to substrates bearing a nitrile rather than a carboxylic ester as the anion-stabilizing group. For example, heating the imines **181** in xylene gave the pyrroles **182** (Scheme 44).[95] Evidently, the intermediate dihydropyrrole cycloadducts eliminate hydrogen cyanide in situ to give the pyrrole products. The pyrrole product **182a** could alternatively be prepared from the imine **183**, which is isomeric to the imine **181a**. Cycloadditions of the corresponding substrates with an alkene rather than an alkyne as

Scheme 43



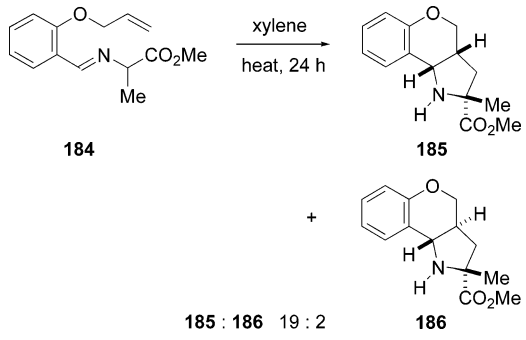
the dipolarophile (*O*-allyl, crotyl, cinnamyl, or 3-cyclohexenyl) were less successful (26−44% yield).

Scheme 44



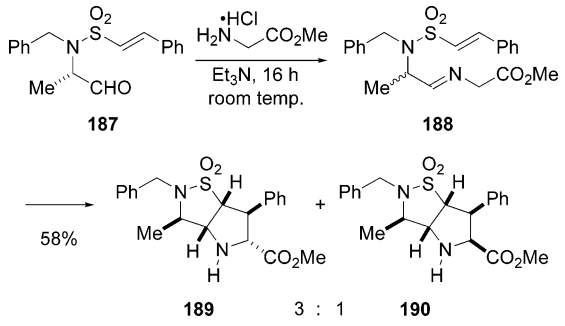
In contrast to results such as that in Scheme 39, Grigg and co-workers found that it was not necessary to use imines of phenylglycine. For example, the imine **184** from alanine, on heating in xylene, underwent successful prototropic shift and intramolecular cycloaddition (Scheme 45).[92] A mixture of stereoisomers was formed, in which the major product was the cycloadduct **185** (admittedly isolated in only 24% yield) and the minor product was tentatively assigned as the trans-fused isomer **186**.

Scheme 45



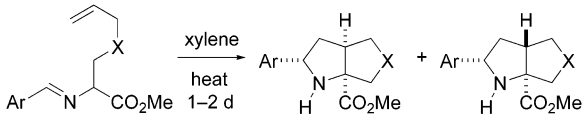
Unfortunately, imines of aliphatic aldehydes bearing α-protons were not stable to heating, and no intramolecular cycloaddition products were obtained with such substrates. Indeed, the majority of examples of cycloaddition reactions from imines are derived from aromatic aldehydes, in which enolization is not possible. This is a serious limitation of this methodology, although aliphatic aldehydes can be used if enolization is not possible, such as that shown in Scheme 13 (to give compound **65**). There is, however, one reported example with a substrate that can enolize, shown in Scheme 46.[96] Treatment of the aldehyde **187** with glycine methyl ester hydrochloride salt and triethylamine gave the imine **188**, which undergoes prototropic shift and cycloaddition to give a mixture of the bicyclic adducts **189** and **190**. The products were found to be racemic, indicating that racemization occurs prior to cycloaddition.

Scheme 46



The examples so far in this section have involved the use of substrates in which the dipolarophile is tethered to the imine carbon atom. An alternative strategy involves tethering the dipolarophile to the imine nitrogen atom (the amino acid moiety), and there are several examples of this class of intramolecular cycloaddition by 1,2-prototropic shift. The first such report described heating the imines **191** in xylene to give a mixture of the adducts **192** and **193** (Scheme 47).[92] The major products **192** arise from a W-shaped ylide and were assigned on the basis of their ^{1}H NMR NOE spectroscopic data. The minor products **193** were assigned as the trans-fused ring systems (also arising from W-shaped ylides) as judged by signals in their ^{1}H NMR spectra. No cycloaddition products were obtained on heating the homologue that would lead to the 5,6-fused ring system.

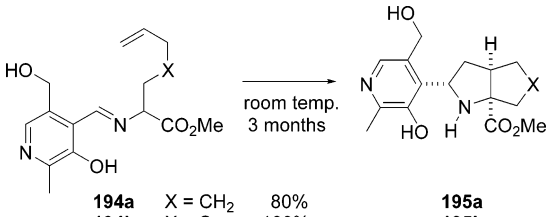
Scheme 47



[a] Crude yield (63% of **192b** isolated).

The related imines **194** of pyridoxal were found to undergo cycloaddition on heating in deuterioacetonitrile at 80 °C for 18 h in NMR tube experiments, although extensive decomposition took place and only low yields (20−30%) of the products **195** were obtained (Scheme 48).[97] The intermediate azomethine ylides, formed by 1,2-prototropic shift, were present under these conditions, as demonstrated by intermolecular quench with *N*-phenylmaleimide. Interestingly, keeping the imines **194** at room temperature for 3 months promoted cycloaddition to give the solid products **195** in high yield.

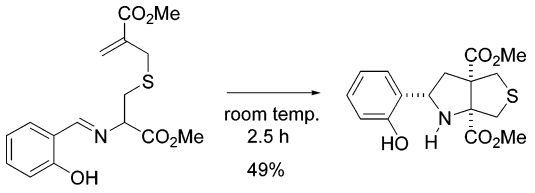
Scheme 48



194a X = CH_2 80% **195a**
194b X = S 100% **195b**

During an attempt to prepare substrates for intramolecular Diels–Alder cycloaddition reactions, the imine **196** was prepared, and on standing at room temperature, it gave rise to the pyrrolidine **197** (Scheme 49).[98] The structure of the product was established by X-ray crystallographic analysis. A 1,2-prototropic shift followed by intramolecular cycloaddition of the intermediate azomethine ylide was postulated to account for the formation of the product **197**, which concurs with the results reported by Grigg and co-workers. The ease of cycloaddition of this substrate (and that of imines **194**) under mild conditions may be due to the presence of an *ortho*-hydroxy group, capable of hydrogen-bonding to the imine nitrogen atom and promoting the formation of the azomethine ylide.

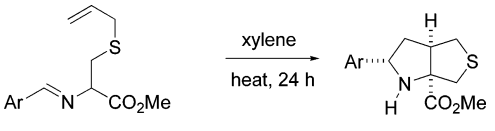
Scheme 49



196 **197**

In the absence of a hydroxy group in the ortho-position, cycloaddition is very slow at room temperature, although successful azomethine ylide formation and cycloaddition occurs on heating (Scheme 50).[99] At room temperature in $CDCl_3$, the adduct **199** (Ar = Ph) was formed in only 18% yield after 25 days but in 82% yield after 130 days. Aryl-substituted compounds **198** were studied and gave adducts **199** in moderate to good yield on heating in xylene. The isomeric products with the trans-fused ring systems could not be isolated but could be detected (less than 5% yield) in the ^{1}H NMR spectra of the crude reaction mixtures.

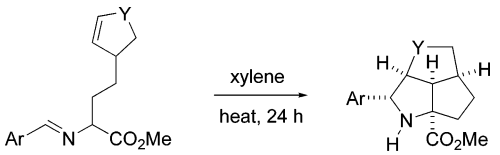
Scheme 50



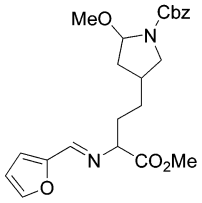
198 Ar=Ph, 1-Npth, 2-$MeOC_6H_4$ or 4-$Me_2NC_6H_4$ 37–71% **199**

The use of cyclic dipolarophiles leads to tricyclic products, as demonstrated by the thermal cycloaddition of the imines **200** (Scheme 51).[100] The yields quoted are for the combined alkylation of the glycine methyl ester imines followed by cycloaddition. The imine **200d** was formed in situ from the hemiaminal **202**. In all cases, only a single stereoisomer of the products **201a–d** was formed. The reactions of the 2-furyl derivatives **200c** and **200d** were less clean than those of the phenyl derivatives **200a** and **200b** and resulted in several additional byproducts. The structure and stereochemistry were confirmed by X-ray crystallographic analysis of the 3,5-dinitrobenzoyl derivatives of the pyrrolidines **201a** and **201b**.

Scheme 51



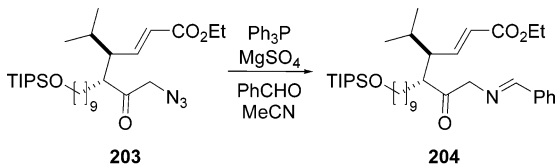
200a Ar = Ph Y = CH_2 51% **201a**
200b Ar = Ph Y = NTs 86% **201b**
200c Ar = 2-furyl Y = NTs 24% **201c**
200d Ar = 2-furyl Y = NCbz 48% **201d**



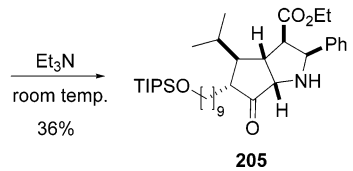
202

The 1,2-prototropic shift and intramolecular cycloaddition reaction has been used as the key step in synthetic approaches to various natural products. A route to the core ring system of the anticancer compound roseophilin was achieved by cycloaddition of the ylide derived from the imine **204**, itself formed from the azide **203** (Scheme 52).[101] The product **205** was formed in moderate yield as a single diastereomer. The stereochemistry of the product **205** was determined from ^{1}H NMR NOESY studies and arises from an S-shaped ylide. A route to the alkaloid sarain A has been reported that uses 1,2-prototropy and intramolecular cycloaddition of the resulting azomethine ylide.[102] Addition of paraformaldehyde to the amine **206** and heating in toluene gave the intermediate azomethine ylide **207** and hence the cycloadduct **208** (Scheme 53, *cf.* Scheme 88). This reaction could be carried out on a reasonable scale (7.6 g of the amine **206**) and demonstrates versatility of this chemistry because it avoids the typical aromatic imine and allows the formation of pyrrolidines unsubstituted in the 2-position.

Scheme 52

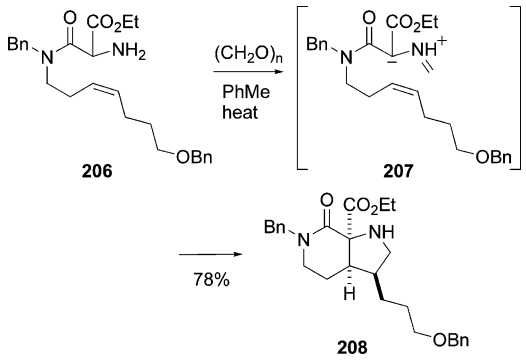


203 **204**



205

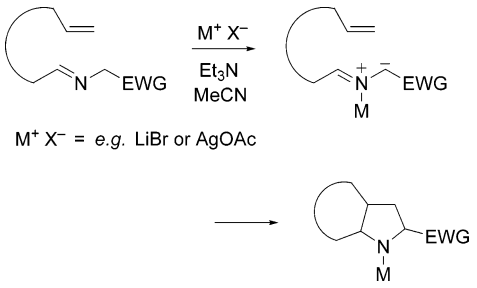
Scheme 53



3.2. By Metalation

An alternative to thermal activation of imines for the formation of the required azomethine ylide is the addition of a metal salt.[20] Typically, an imine bearing an electron-withdrawing group (EWG) in the position α to the nitrogen atom is treated with a metal salt such as lithium bromide (LiBr) or silver acetate (AgOAc) and a base such as triethylamine in a polar aprotic solvent such as acetonitrile (Scheme 54). Coordination of the imine nitrogen atom to the metal activates the substrate to deprotonation, thereby resulting in the *N*-metalated azomethine ylide. Alternatively, it should be possible (although to our knowledge has been reported only for intermolecular examples) to treat the activated imine with a strong base such as lithium diisopropylamide (LDA) to give the *N*-metalated azomethine ylide. In the absence of an electron-withdrawing group to stabilize the ylide, metalation is said to give a 2-azaallyllithium species, which undergoes so-called anionic cycloaddition with nonactivated dipolarophiles.[24]

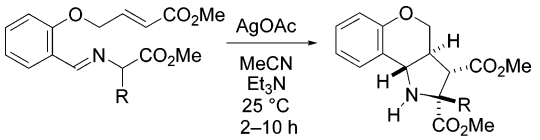
Scheme 54



The *N*-metalated azomethine ylides seem to have similar properties to azomethine ylides that have been generated in other ways. They undergo ready cycloaddition with electron-poor dipolarophiles; hence these ylides can be classified as electron-rich, and the major frontier orbital interaction could be assumed to be the HOMO of the ylide and the LUMO of the dipolarophile. However they can show different reactivities and selectivities to *N*-H or *N*-alkyl substituted azomethine ylides. For example, cycloaddition often occurs at lower temperature with *N*-metalated azomethine ylides, and this could be beneficial, particularly for sensitive substrates. Differences in selectivities tend to be more pronounced in intermolecular examples because conformational constraints dictate that only one regioisomer is formed in intramolecular cycloadditions. Stereoselectivities can, however, vary when *N*-metalated azomethine ylides are employed (see, for example, Scheme 58), and it is worth adopting this methodology, particularly if low selectivity or the undesired stereoisomer is obtained. The chemistry lends itself to asymmetric induction using a chiral ligand complexed with the metal, and high enantiomer ratios have been obtained in recent years in intermolecular cycloadditions,[103−106] although examples have not yet been reported for the related asymmetric intramolecular cycloaddition of azomethine ylides.[107]

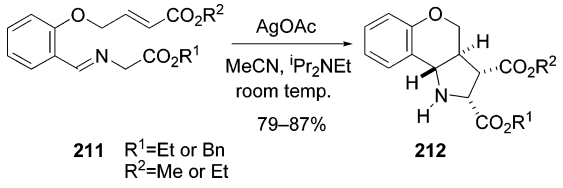
Grigg and co-workers were the first to report successful intramolecular cycloaddition reactions of *N*-metalated azomethine ylides. Treatment of the imines **209** with silver acetate and triethylamine at room-temperature resulted in the formation of the cycloadducts **210** and **171** in high yield (Scheme 55).[108] The ability of these ylides to undergo cycloaddition with unactivated dipolarophiles appears to be reduced, since the cycloaddition was unsuccessful under these conditions using a dipolarophile lacking the electron-withdrawing ester substituent (such as compound **184**, Scheme 45). However, the metal salt-promoted cycloaddition protocol allows cycloaddition at ambient temperature, which could have distinct advantages, particularly for sensitive substrates. The stereochemistry of the products **210** and **171** indicates that cycloaddition occurs through a W-shaped ylide. The stereochemistry at the ring junction was trans, as found under thermal conditions (see Chart 8). The same substrate, **209a**, could be activated for cycloaddition using (^{i}PrO)$_3$TiCl or (^{i}PrO)$_2$TiCl$_2$ in CH_2Cl_2 at room temperature to give the product **210** (ca. 65% yield).[109]

Scheme 55



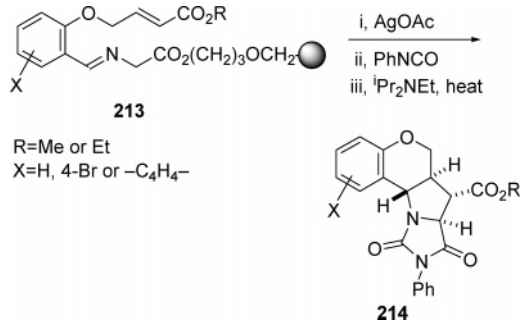
Related chemistry was reported by Kurth and coworkers using the substrates **211** (Scheme 56).[110,111] The products **212** were formed as single stereoisomers, the major product being that shown as determined by X-ray crystallographic analysis of the phenyl urea derivative of the cycloadduct **212** (R^1 = Et, R^2 = Me).

Scheme 56



Extension to the solid phase was performed using an extended Merrifield resin, which was connected

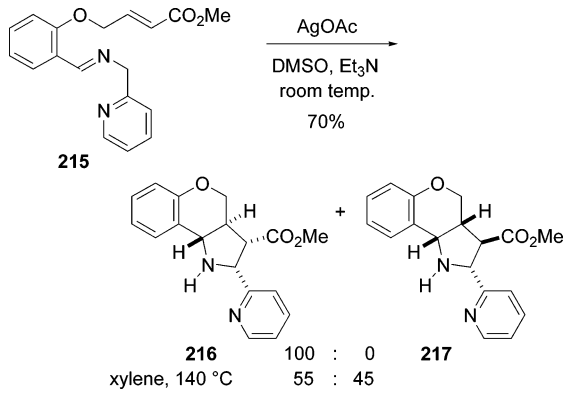
Scheme 57



to the glycine ester functional group.[111] The polymer-bound substrates **213** were treated with silver acetate and diisopropylethylamine in acetonitrile to effect cycloaddition. Subsequent urea formation and cyclization with $^{i}Pr_2NEt$ (which promoted epimerization at C-2 of the pyrrolidine) released the products **214** from the polymer support in overall 10−15% yield (Scheme 57).

It is not a necessity to have a carboxylic ester as the anion-stabilizing group, as shown by the successful cycloaddition of the substrate **215** (Scheme 58).[112] The cycloaddition occurs selectively in the presence of silver acetate and triethylamine in DMSO to give only the adduct **216**, whereas under thermal conditions a mixture of the adducts **216** and **217** is formed.

Scheme 58



By use of the imines **218**, it was shown that intermolecular Michael addition with divinyl sulfone precedes cycloaddition with activation by lithium bromide and triethylamine (Scheme 59).[113] The Michael adduct **220**, prepared separately, was found to give the same product **219a** on treatment with

Scheme 59

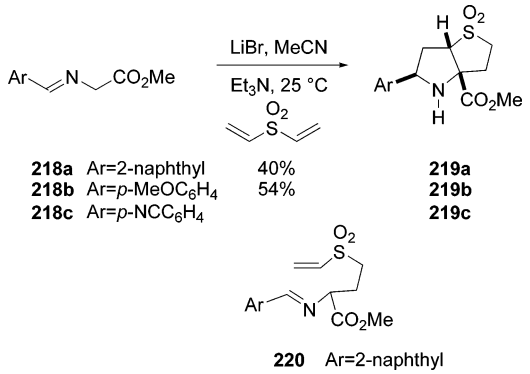
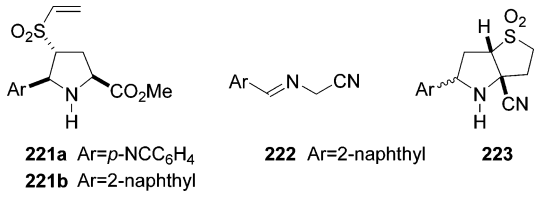


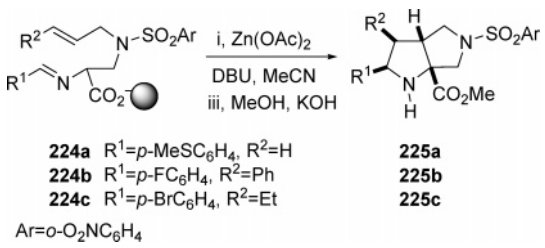
Chart 9



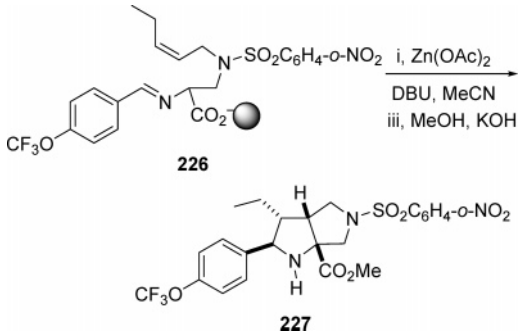
lithium bromide and triethylamine. Less successful were the imines **218c**, which gave the product **219c** together with the cycloadduct **221** (Chart 9) (25%, 1:1), and **222**, which gave a mixture of stereoisomers **223** (20%, 1:1). The use of silver acetate in DMSO to activate the reaction of the imine **218a** with divinyl sulfone was found to give the cycloadduct **221b** (27%), rather than **219a**. Therefore, the choice of metal salt and solvent can be influential in the course of reaction, Michael addition competing more effectively with cycloaddition under lithium bromide activation.

Successful cycloadditions have been reported using the imines **224**, in which the carboxylic ester group is attached to a hydroxymethyl polystyrene resin.[114] Of a variety of conditions to promote cycloaddition, zinc acetate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) proved optimal, resulting in the formation of the products **225** after cleavage from the resin with potassium methoxide (Scheme 60). In each case, only a single diastereomer of the products was formed. The relative stereochemistry was assigned on the basis of ^{1}H NMR NOESY data and corresponds to cycloaddition through a W-shaped ylide. The process is stereospecific in regard to the geometry around the dienophile, as shown by the formation of the diastereomer **227** from the *Z*-alkene **226** (Scheme 61).

Scheme 60



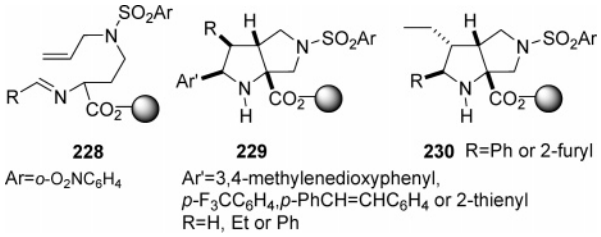
Scheme 61



Extension of this chemistry to the homologue **228** (Chart 10) was attempted but was found to be unsuccessful. The products from cycloaddition of the imines **224** and **226**, together with further examples **229** and **230** (Chart 10), were however used to provide a library of products after sequential func-

tionalization of the nitrogen atoms and hydantoin formation to cleave from the resin.

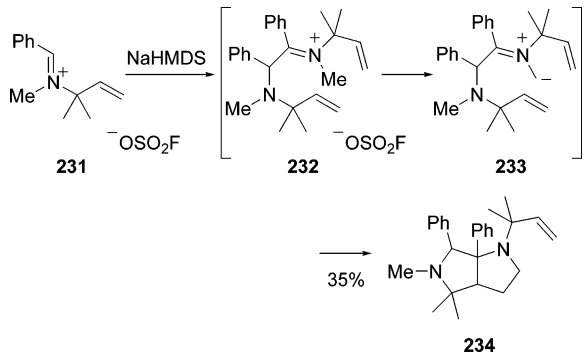
Chart 10



3.3. By Alkylation

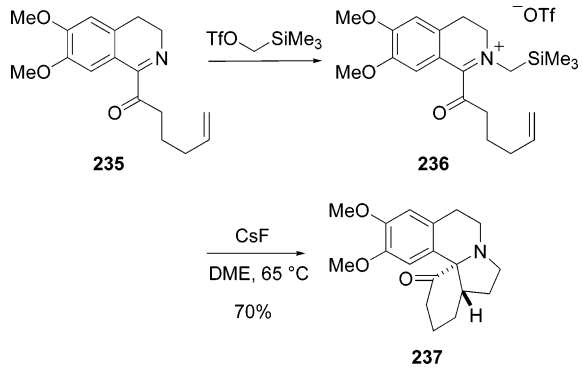
Alkylation of the nitrogen atom of an imine provides a method to prepare an iminium ion and hence, after subsequent deprotonation or desilylation, an azomethine ylide. A drawback of the methodology is that a relatively stable imine is required and therefore this chemistry has so far been limited to aromatic imines or formamidines. Despite this, one of the first reported examples of an intramolecular dipolar cycloaddition with an azomethine ylide involved formation of the iminium salt **231** from the corresponding aromatic imine and $MeOSO_2F$, followed by treatment with a strong base (Scheme 62).[115] Initial deprotonation occurs preferentially at the methine carbon of the iminium ion **231**. Addition of the ylide to another molecule of the iminium ion provides the dimer **232**. A second deprotonation then occurs at the methyl group to give the azomethine ylide **233** and hence the cycloadduct **234**. Assignment of the structure of the product **234** was aided by the preparation of an isotopically labeled dideutero analogue. The formation of the product **234** was used as confirmation of the presence of intermediate azomethine ylides in related chemistry lacking the internal dipolarophile.

Scheme 62



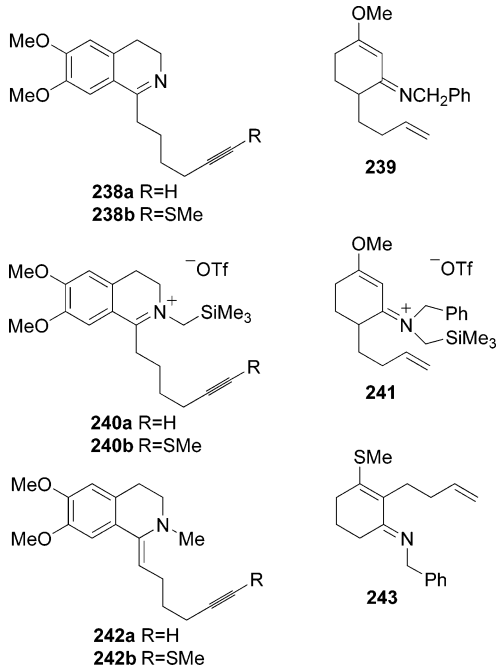
Livinghouse and co-workers have described examples of alkylation of an imine followed by ylide formation and cycloaddition that have been more successful. Alkylation of the dihydroisoquinoline **235** with trimethylsilylmethyl triflate gave the intermediate iminium salt **236**, which was treated with cesium fluoride to give the cycloadduct **237** (Scheme 63).[116] Similar chemistry was successful with the related alkyne as the dipolarophile. The fluoride ion promotes desilylation of **236** to give a stabilized azomethine ylide, which was able to undergo cycloaddition with the unactivated alkene or alkyne dipolarophiles. Only a single stereoisomer of the product **237** was obtained and the relative stereochemistry was assigned from ^1H NMR NOESY analysis.

Scheme 63



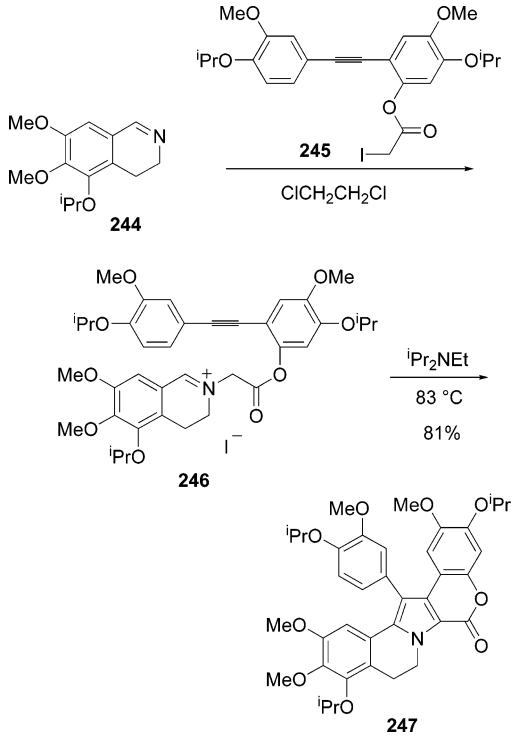
In contrast, however, formation of a nonstabilized ylide by this methodology did not promote successful cycloaddition. Alkylation of the imines **238** and **239** with trimethylsilylmethyl triflate gave the desired ylides **240** and **241** (Chart 11); however these did not undergo cycloaddition on treatment with fluoride ion under a variety of conditions.[117,118] The enamines **242** were isolated from the attempted cycloaddition of the ylides **240**.[117] This observation indicates that enamine formation occurs in preference to cycloaddition in these cases and therefore that it may be prudent to avoid the presence of a proton α to the imine if this method of azomethine ylide formation is adopted. Another potential difficulty lies in the ability to effect *N*-alkylation. For example, no alkylation of the imine **243** took place on treatment with trimethylsilylmethyl triflate, probably due to steric factors.[118]

Chart 11



Some more recent examples make use of this chemistry for the synthesis of the lamellarin alkaloids. Alkylation of the substituted 3,4-dihydroiso-

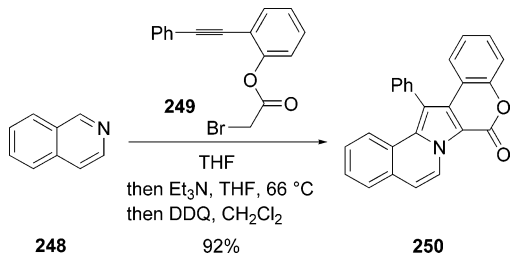
Scheme 64



quinoline **244** with the iodide **245** gave the salt **246**, which was not isolated but treated immediately with base and heated in 1,2-dichloroethane (Scheme 64).[119] This promoted azomethine ylide formation and cycloaddition, followed by in situ aromatization, to give lamellarin K triisopropyl ether **247**. A very similar sequence was used to prepare lamellarin α and lamellarin H.[120]

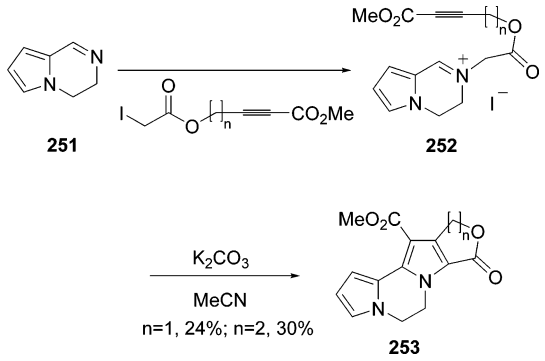
It was shown that isoquinoline (**248**) could be used in this process, by alkylation with the bromide **249** followed by heating in the presence of the base triethylamine (Scheme 65).[119] The product **250**, representing the parent ring system of the lamellarins, was isolated after oxidation of the mixture of dihydropyrroles with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Further examples of the alkylation of nitrogen-containing heteroaromatics are given in Scheme 67 and in section 5.3.

Scheme 65



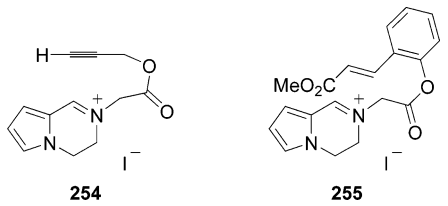
The chemistry could be extended, although less successfully, to the 3,4-dihydropyrrolo[1,2-*a*]pyrazine **251**. The salts **252** were prepared by *N*-alkylation of the imine **251**, and on treatment with potassium carbonate they gave, in low yields, the cycloadducts **253** (Scheme 66).[121] Unsuccessful attempts to improve the yields of the cycloadducts were ascribed to the instability of the salts **252**. No cycloaddition

Scheme 66



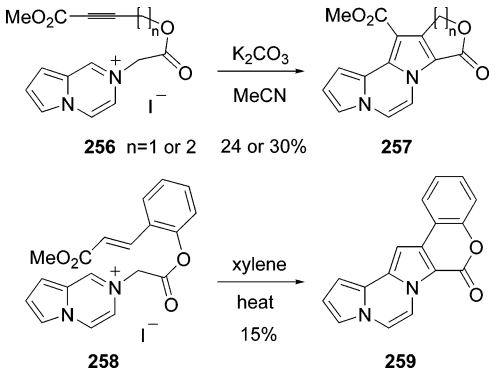
products were obtained using the salts **254** or **255** (Chart 12).

Chart 12



Alkylation of pyrrolo[1,2-*a*]pyrazine itself gave the analogous salts **256** and **258** (Scheme 67).[122] These gave, in low yields, the polycyclic products **257** on treatment with potassium carbonate or **259** on heating in xylene. In each case the initial cycloadduct has oxidized (and also decarboxylated during the formation of **259**) to give the fully aromatized ring system.

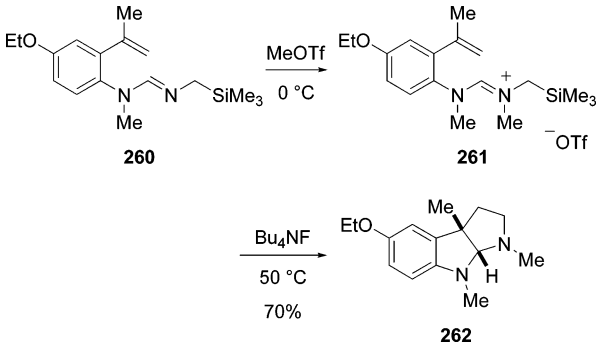
Scheme 67



Formamidines are good substrates for *N*-alkylation or *N*-acylation to give an iminium ion and hence the required azomethine ylide. This is exemplified in approaches to the physostigmine alkaloids. Hence, *N*-alkylation of the formamidine **260** with methyl trifluoromethanesulfonate gave the iminium salt **261**, which was added to tetra-*n*-butylammonium fluoride to effect desilylation and azomethine ylide formation (Scheme 68).[123] Heating at 50 °C for 12 h provided the cycloadduct eserethole **262** in 70% yield. Only the cis isomer was formed in the cycloaddition reaction.

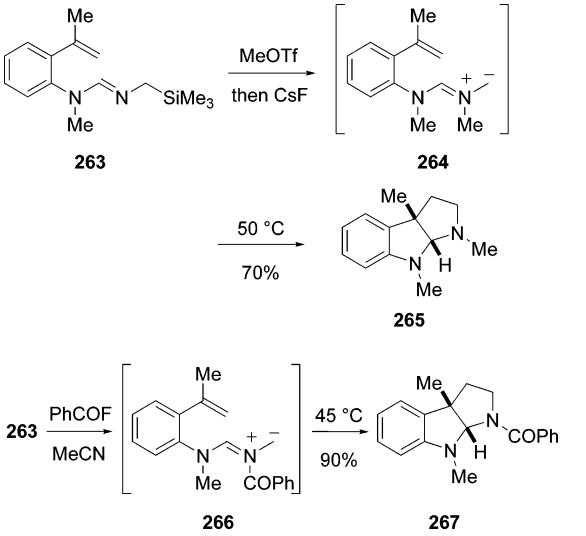
A similar sequence was carried out to give the corresponding de-ethoxy compound **265** from the formamidine **263** (Scheme 69).[117,124] Addition of methyl trifluoromethanesulfonate to the formamidine **263** was followed by (inverse) addition to cesium fluoride

Scheme 68



(in 1,2-DME) to give the azomethine ylide **264** and hence the cycloadduct **265**. Attempted (normal) addition of cesium fluoride to the intermediate iminium salt resulted in the formation of dimers and other undesired products. Interestingly, as an alternative approach, acylation of the formamidine with benzoyl fluoride gave the azomethine ylide **266**, which was capable of cycloaddition to give the adduct **267** in high yield. The direct formation of such *N*-acyl pyrrolidines is rare in cycloaddition chemistry, and the mild conditions and high yield augur well for further use of this methodology.

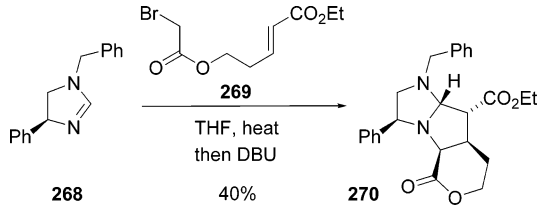
Scheme 69



Dihydroimidazoles can also act as suitable substrates for *N*-alkylation followed by subsequent ylide formation. Treatment of the dihydroimidazole (*S*)-**268** with the unstable bromo-ester **269**, followed by slow addition of the base DBU gave the cycloadduct **270** (Scheme 70).[125] Likewise the enantiomeric (*R*)-**268** gave the enantiomeric cycloaddition product (31% yield). The structure of the adduct **270** was determined by NMR spectroscopic studies and by X-ray crystal structure analysis. The stereochemistry of the adduct is consistent with an S-shaped ylide and cycloaddition by an endo approach of the dipolarophile.

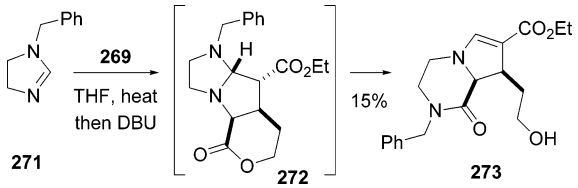
Alkylation using the bromide **269** was also successful using *N*-benzyl-dihydroimidazole (**271**) (Scheme 71).[126] However, in this case the lactam **273** was isolated rather than the cycloadduct **272**. Elimination followed by cyclization of the released amine onto the

Scheme 70



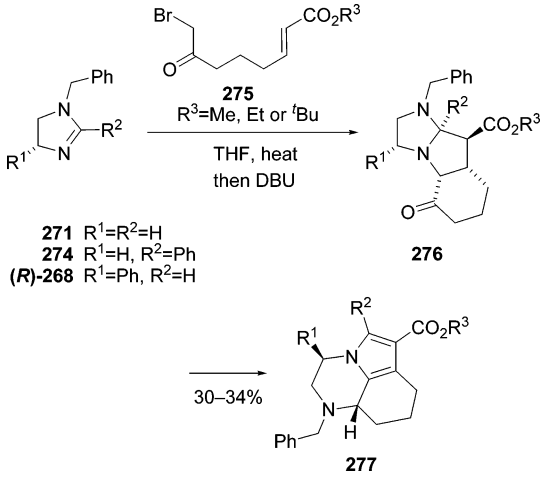
lactone group can be invoked to explain the formation of the product **273**.

Scheme 71



A similar intramolecular cycloaddition followed by elimination and subsequent cyclization occurs with the corresponding α-bromo-ketone alkylating agents **275** (Scheme 72).[127] In this case the initial cycloadducts **276** (except R^1 = Ph, R^2 = H, R^3 = ^{t}Bu) undergo elimination and cyclization, followed by prototropic shift to give the heterocycles **277**. With the substrate (*R*)-**268** and the alkylating agent **275** bearing a *tert*-butyl ester group, the initial cycloadduct **276**, rather than **277**, was isolated. The structures of several of the adducts were confirmed by X-ray crystal structure analysis. The product **277** (R^1 = R^2 = H, R^3 = Me) was also formed using the *Z*-stereoisomer of the dipolarophile **275**, albeit in reduced yield.

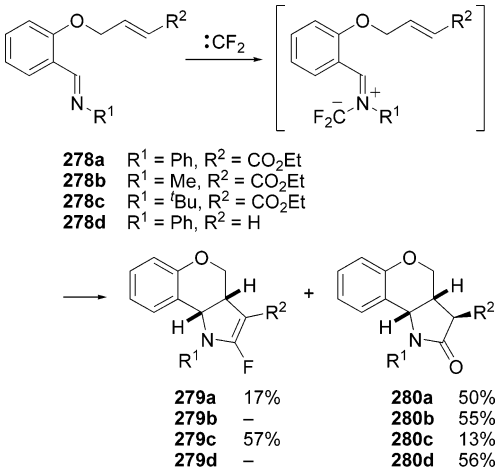
Scheme 72



An alternative approach to the formation of azomethine ylides from imines involves the addition of a carbene. The only successful report of such chemistry uses difluorocarbene, generated in situ by reduction of CF_2Br_2 with active lead in the presence of tetrabutylammonium bromide.[128] Thus, the imines **278** (Scheme 73) were mixed with lead (freshly prepared from lead acetate and sodium borohydride) and tetrabutylammonium bromide in CH_2Cl_2 and then treated with CF_2Br_2 and stirred at 45 °C until the lead had been consumed. Purification by chromatog-

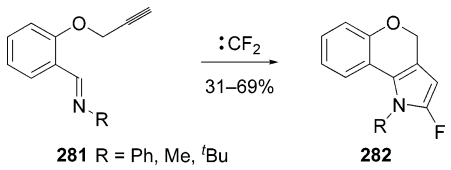
raphy gave the fluoropyrrolines **279a** and **279c** and the lactams **280a**−**d** (due to hydrolysis on silica).

Scheme 73



The cycloaddition reaction was also successful using the substrates **281**, bearing an unsubstituted alkyne as the dipolarophile to provide, after elimination of HF, the products **282** (Scheme 74).

Scheme 74



Unexpectedly, attempted cycloaddition with the substrate **283a** gave the bridged cycloadduct **284a** as a result of addition of the azomethine ylide to the ester carbonyl group rather than addition to the alkene (Scheme 75, Table 5).[129,130] This example represents the first report of an intramolecular cycloaddition of an azomethine ylide to the double bond of an ester carbonyl group (for cycloaddition onto an internal ketone, see Scheme 27). The structure of the product **284a** was confirmed by X-ray crystallographic analysis. A selection of examples were studied (including **283a**−**j**), and the reaction was found to be successful with a range of α,β-unsaturated or aromatic esters combined with *N*-aryl or, in some cases, *N*-alkyl imines to give the adducts **284a**−**i** and **285** (Table 5). The azomethine ylide generated from the imine **286**, in which an additional

Scheme 75

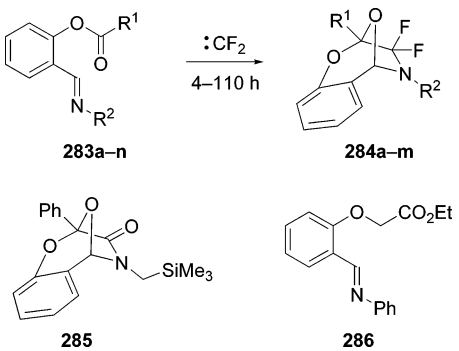


Table 5. Cycloadditions onto Ester Carbonyl Groups

283	R^1	R^2	284	yield (%)
a	C(Me)=CH_2	Ph	**a**	77
b	Ph	Ph	**b**	74
c	4-$MeOC_6H_4$	Ph	**c**	92
d	4-NCC_6H_4	Ph	**d**	70
e	(*E*)-CH=CHMe	Ph	**e**	68
f	(*E*)-CPh=CHPh	Ph	**f**	70
g	2-furyl	4-BrC_6H_4	**g**	75
h	Ph	2,4-$Cl_2C_6H_3$	**h**	70
i	Ph	$(4\text{-}ClC_6H_4)_2CH$	**i**	88
j	Ph	CH_2SiMe_3	**285**	67

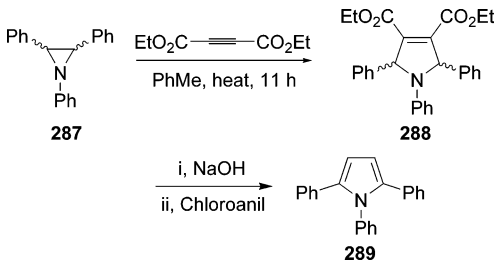
one-carbon unit was present in the chain connecting the imine to the carbonyl group, failed to undergo cycloaddition.

4. Ylides from Aziridines

To discuss the intramolecular cycloaddition of azomethine ylides derived from aziridines, it is helpful to review how the concept arose that aziridines could be precursors of azomethine ylides and to consider some of the theory behind the processes involved in the aziridine ring-opening reaction. Unsurprisingly, azomethine ylides derived from aziridines were first postulated as intermediates by trapping experiments in the presence of external dipolarophiles, that is, through an intermolecular cycloaddition reaction.

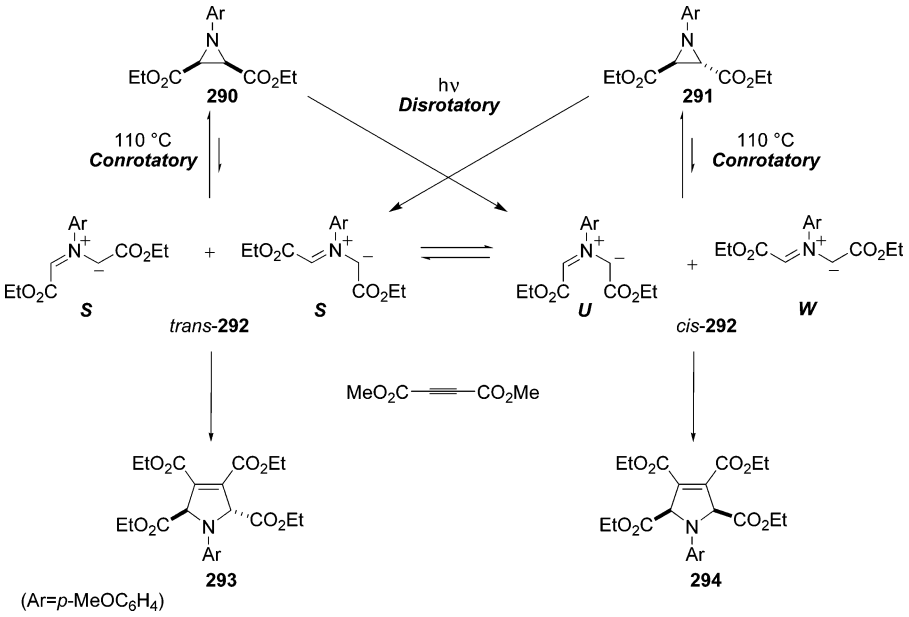
It was the group of Heine in 1965 who first reported that heating the aziridine **287** with diethylacetylene dicarboxylate in toluene under reflux gave a crystalline product purported to be the pyrrolidine **288**, which was isolated in 98% yield (Scheme 76).[131] Hydrolysis of the intermediate **288** followed by simultaneous oxidation and decarboxylation with chloroanil gave the pyrrole **289**, the physical properties of which were identical in all respects to that of an authentic sample.

Scheme 76



Although no reference to the intermediacy of an azomethine ylide was made, it was noted by Heine that a "new reaction involving carbon−carbon bond cleavage of the aziridine ring was observed" rather than carbon−nitrogen bond scission as, presumably, was the expected outcome. Only a year later, through the pioneering work of Huisgen and co-workers, the thermolysis of aziridines was linked with the existence of reactive azomethine ylide intermediates.[29,132] More importantly, this study also made the connection between the method used to promote ylide formation and the stereochemical course of their reactions with dipolarophiles. Huisgen found that

Scheme 77



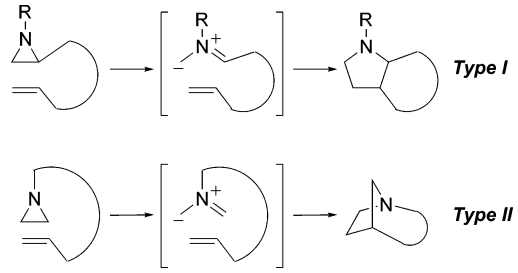
pure samples of either aziridine **290** or **291**, when heated at 100 °C in carbon tetrachloride in an NMR tube, apparently interconverted to give an equilibrium mixture comprising **290** and **291** in the ratio of 1:4 (Scheme 77). The mechanism for this interconversion was thought to proceed through azomethine ylide intermediates.

According to the Woodward−Hoffmann theory on the stereochemical outcome of electrocyclic reactions (published only one year earlier in 1965), thermolysis of the cis-aziridine **290** (which is isoelectronic with the cyclopropyl anion) should proceed with conrotatory ring-opening to give the trans (or S-shaped—see section 1) ylides *trans*-**292**.[133] Since rotation about the N−C bond can occur, both forms of *trans*-**292** can interconvert to their cis-counterparts, namely, *cis*-**292** (U and W), and hence on to the aziridine **291** by virtue of the reversible nature of the thermolysis process. When a reactive dipolarophile was introduced into the system, the rate of ylide interconversion relative to the rate of 1,3-dipolar cycloaddition was negligible, thus allowing the cycloaddition pathway to predominate. In this case, the dipolarophile used was dimethylacetylene dicarboxylate, which reacted with the cis-aziridine **290** to give exclusively the trans-pyrrolidine **293**. Likewise the trans-aziridine **291** gave exclusively the cis-pyrrolidine **294**.

In a separate experiment, a solution of the trans-aziridine **291** in the dipolarophile was subjected to irradiation from a mercury lamp to produce the trans-pyrrolidine **293** in 40% yield. Ring-opening of the trans-aziridine **291** now took place in a *disrotatory* sense to give the ylides trans-**292**; this result, which is opposite to that obtained via thermolysis, provided one of the first experimental verifications of the Woodward−Hoffmann theory of stereochemistry in electrocyclic reactions.[134]

The observations made by Heine and Huisgen in the 1960s have lead to many studies of intermolecular reactions involving azomethine ylides derived from aziridines with dipolarophiles such as alkenes and alkynes, and these lie outside the scope of this review.[22,23] Here we describe the intramolecular process, which can be brought about by tethering the carbon−carbon multiple bond to the aziridine using a suitable linkage (Chart 13). With the dipolarophile tethered to either of the ring carbons of the aziridine (type I) or to the nitrogen of the aziridine ring (type II), a series of complex nitrogen-containing heterocyclic systems can be produced. Typically an electron-withdrawing group, normally a carbonyl group, is attached to one or both carbons of the aziridine, and this aids the ylide formation.

Chart 13

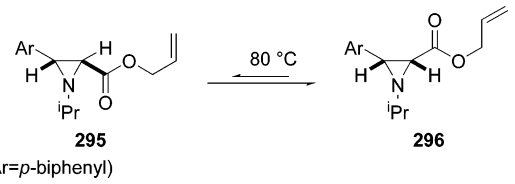


4.1. Cycloadditions onto Alkenes to Form 5,5 and 5,6 Ring Systems

Early attempts to induce azomethine ylide generation and concomitant cycloaddition onto an appendant terminal carbon−carbon multiple bond were not, at first, successful. When a 1:1 mixture of the trans- and cis-aziridines **295** and **296** were heated at 80 °C in benzene, trans−cis isomerization took place to give a product mixture that was enriched with the thermodynamically more stable cis isomer (ratio **295/296** = 3:7) (Scheme 78).[135] No trace of the product derived from an intramolecular cycloaddition was detected.

The mechanism for cis−trans isomerization is the same as that described above (Scheme 77) for the aziridines **290** and **291**. The absence of any cycloadduct was thought to be a result of the relatively large

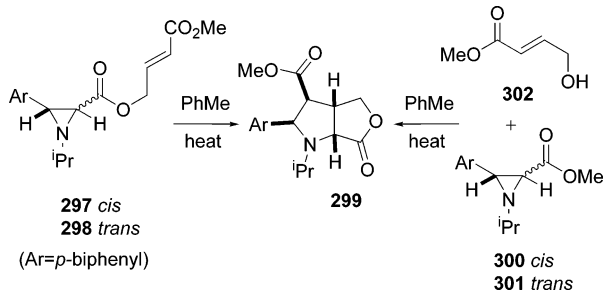
Scheme 78



difference in energy between the LUMO of the 1,3-dipole and the HOMO of the dipolarophile. As a result of the lack of favorable orbital interactions, the only course of reaction remaining was that of trans−cis isomerization.

By this reasoning, appending an electron-withdrawing substituent to the alkene terminus would promote cycloaddition through a more favorable HOMO−LUMO interaction with the lower-energy LUMO of the dipolarophile. Padwa and Ku employed this strategy in the first intramolecular cycloaddition reaction of an azomethine ylide generated from an aziridine (Scheme 79).[135]

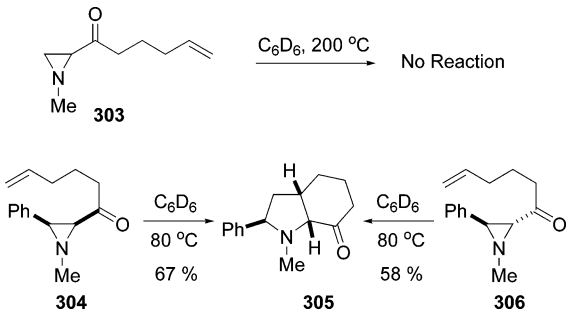
Scheme 79



Heating the aziridines **297** or **298** resulted in their conversion to the pyrrolidine **299** as a single stereoisomer in yields of 73% and 81%, respectively. The structure of the pyrrolidine **299** was established by ^{1}H NMR correlation spectroscopy and confirmed by synthesis using the intermolecular reaction of the aziridines **300** or **301** with the alkene **302** followed by lactonization. The fact that a single product, **299**, was formed via intra- or intermolecular pathways suggests that the reactive azomethine ylide intermediate adopts a predominantly S-shaped geometry. This in turn suggests that the rate of isomerization of the ylide interconversion is faster than the rate of cycloaddition in this system.

Similar trends in reactivity were found when a related series of 2-acyl aziridines were studied (Scheme 80).[136] Thermolytic experiments conducted on the 3-unsubstituted aziridines such as **303** in

Scheme 80

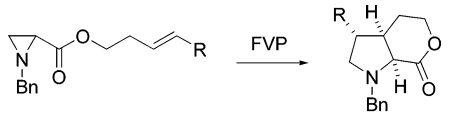


degassed d^6-benzene in sealed NMR tubes at 200 °C showed that no cyclization had occurred, even after several hours of heating. Upon substitution at the 3-position of the aziridine ring with a phenyl group however (compounds **304** and **306**), intramolecular cycloadditions did take place to give the corresponding cycloadduct **305**, even at reduced temperatures and reaction times. Moreover, a single diastereomer was produced from both the cis- and the trans-aziridines.

This result suggests that an aromatic substituent enhances ring-opening of the aziridine at relatively low temperatures. Whether the aromatic group serves to stabilize any transient ylide intermediate through conjugative effects was not discussed, but it is clear from this and the results described by Padwa and Ku (Schemes 78 and 79) that aziridine ring substitution goes only part way to determining whether cycloaddition will take place by simple thermolysis. Other contributory factors such as tether length (cf. Schemes 78 and 80) and the nature of the dipolarophile (discussed earlier) must also be taken into account.

It is also clear that a significant energy barrier needs to be surmounted to promote ylide formation and intramolecular cycloaddition of unsubstituted aziridines. Using a technique known as flash vacuum pyrrolysis (FVP), in which a higher reaction temperature could be used without causing undue decomposition of either starting materials or products, DeShong and co-workers were able to promote intramolecular cycloaddition of aziridines carrying a single carboxylic ester-olefin tether (Scheme 81).[137]

Scheme 81

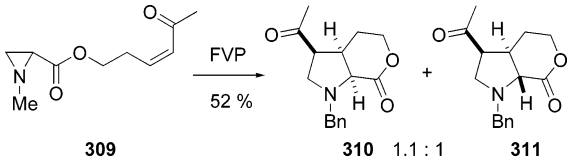


Cycloaddition could be achieved without the presence of an activating aromatic substituent on the aziridine ring; hence the aziridines **307a** and **307b** could be converted to the pyrrolidines **308a** and **308b** in excellent yield. Furthermore, deactivating groups on the dipolarophile were tolerated. The aziridine **307c** bearing an ethyl substituent on the terminus of the alkene underwent intramolecular cycloaddition to the pyrrolidine **308c**, albeit in poor yield (a possible indication of how energetically unfavorable the transformation had become). A significant amount of the reaction mixture (25−30%) comprised 1,2-diphenylethane, which was thought to arise from radical-based degradation of the starting materials.

Another interesting observation made during the course of these studies came as a result of subjecting the *Z*-alkene **309** to FVP (Scheme 82). In this instance, a mixture of diastereomeric lactones **310** and **311** was formed, indicating that the azomethine ylide was reacting through two conformations in the transition state. Presumably the orientation of the acetyl group influences the transition state geometry

through steric effects to promote the formation of a mixture of products.

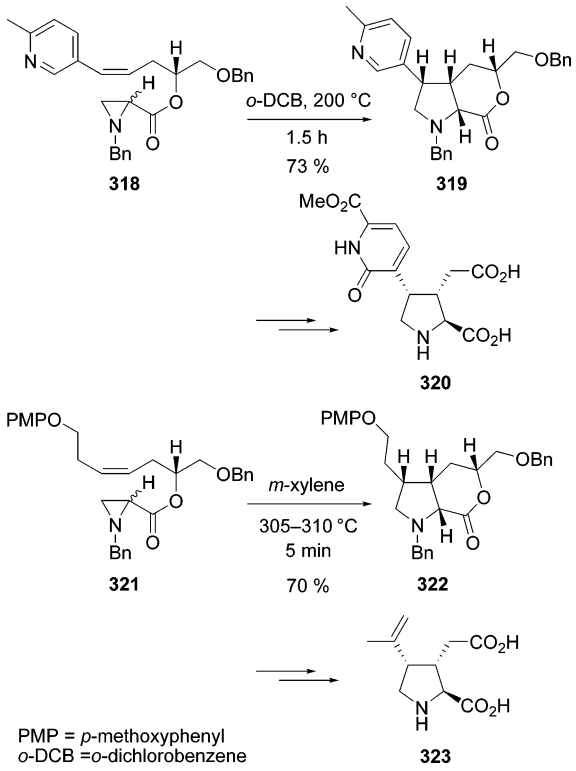
Scheme 82



A similar result was obtained by Padwa and Ku when investigating the synthesis of bridged bicyclic amines.[135] Thus, heating the aziridines **312** or **313** gave the azabicyclo[2.2.1]heptanes **315** and **317** in 37% and 30% yields from either aziridine (Scheme 83). The regiochemistry of the cycloaddition reaction in this example was explained by considering the interaction of the frontier molecular orbitals between the dipole and dipolarophile. Conrotatory ring-opening of the cis-aziridine **312** gives rise to the S-shaped ylide **314**, in which the interaction of the larger orbital of the dipole HOMO (at the carbon atom bearing the methyl ester group) with the larger orbital of the alkene LUMO ultimately directed the cycloaddition. In a similar way, the trans-aziridine **313** gives the intermediate **316**, which could interconvert with the ylide **314** via a process similar to that shown in Schemes 77 and 78, so both cycloadducts **315** and **317** were obtained from either aziridine. This observation implied that the rate of interconversion between the two dipoles was comparable to or faster than the rate of cycloaddition.

The intramolecular cycloaddition of azomethine ylides derived from aziridines has been used to synthesize two of the kainoids, a group of naturally occurring pyrrolidine-based amino acids that are, among other things, potent neuroexcitors. The high diastereoselectivity of intramolecular cycloadditions combined with the direct formation of complex substituted pyrrolidine ring systems from relatively simple starting materials renders this process ideal for assembling the framework common to this class of natural product. The two kainoids, acromelic acid A **320** and kainic acid **323**, were synthesized using the aziridine precursors **318** and **321**, respectively (Scheme 84).[138,139] The cis-stereochemistry across C-3/C-4 of the natural products was present in the *Z*-alkene tether of the aziridine precursors **318** and **321** and the absolute configuration of three new

Scheme 84



stereocenters formed in the cycloaddition were directed from the common starting material (*S*)-*O*-benzylglycidol. The epimerization of stereochemistry at C-2 was effected using NaH/DBU during the latter stages of the synthesis.

Both cycloadditions were carried out by heating the precursors in sealed tubes using either *o*-dichlorobenzene or xylene as solvent, giving the pyrrolidine **319** or **322** in good yield and as single diastereomers. The high diastereoselectivity was thought to be a result of the highly ordered chairlike transition state adopted by the transient azomethine ylides (**324** and **325**, Chart 14), wherein the larger benzyloxymethyl group is placed in a pseudo-equatorial position.

By adoption of the same methodology, the alkaloid (−)-mesembrine **328** was synthesized (Scheme 85).[140] The aziridine precursor **326** was heated in xylene at 250 °C in a sealed tube to give the intermediate **327** as a single diastereomer. In this process, the quaternary carbon center found in (−)-mesembrine **328**

Scheme 83

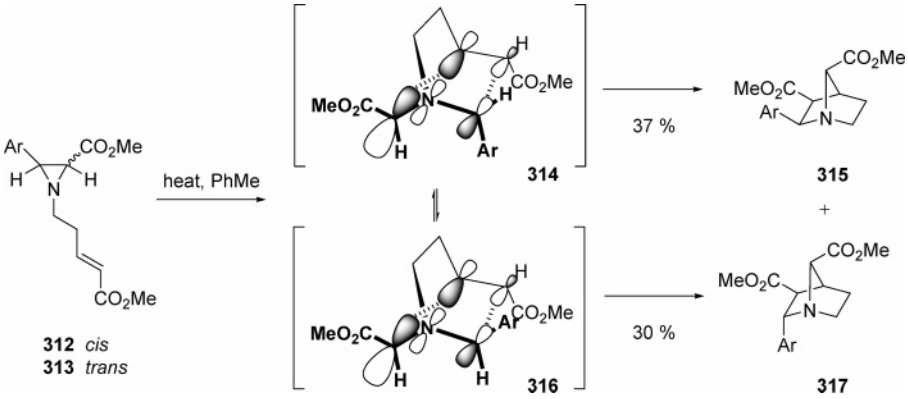
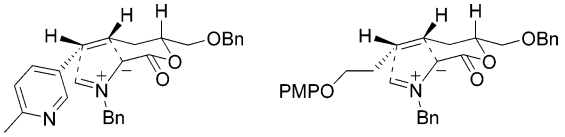


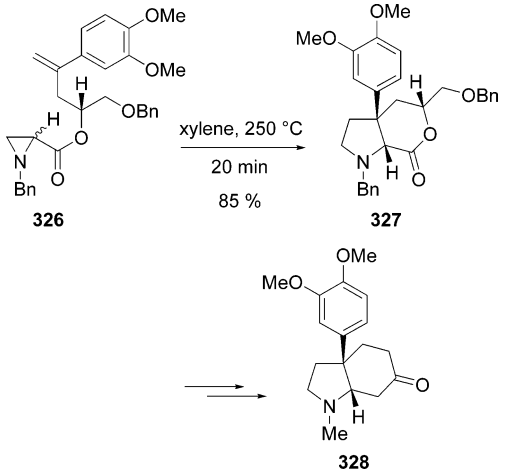
Chart 14



324 **325**

was established in a stereoselective manner, thus highlighting the usefulness of this process.

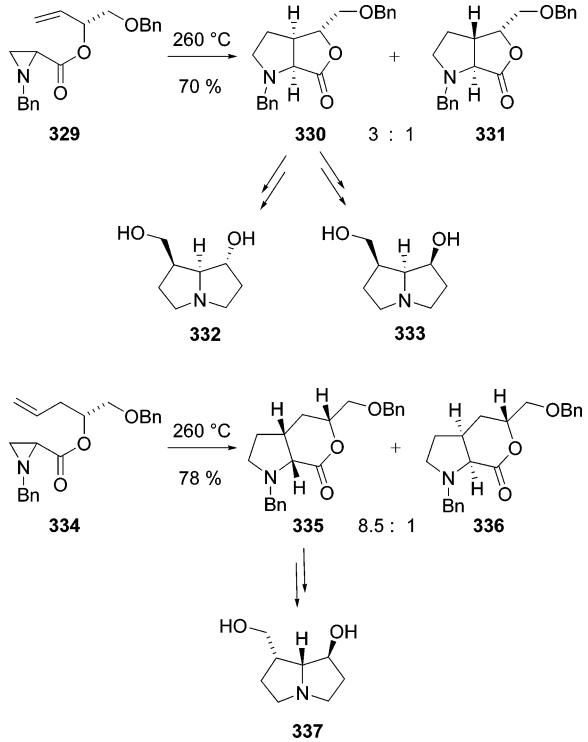
Scheme 85



326 **327** **328**

In a later communication, Ogasawara and coworkers showed that the aziridine **329** underwent cycloaddition to form an inseparable mixture of pyrrolidines **330** and **331** (Scheme 86) in good overall yield.[141] Formation of the major diastereomer **330** was thought to occur via the ylide **338** (Chart 15), which was postulated to adopt an envelope-like transition state conformation. The formation of two diastereomers during the course of the reaction

Scheme 86



329 **330** 3 : 1 **331** **332** **333** **334** **335** 8.5 : 1 **336** **337**

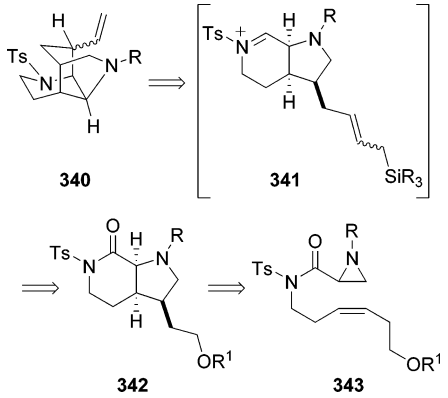
contrasts with the results of experiments using the related aziridine **307a** (Scheme 81), its shorter homologue, in which cycloaddition using FVP proceeded stereoselectively.[136] The homologous aziridine precursor **334** was also subjected to the same reaction conditions and gave the cycloadducts **335** and **336** in good yield with an improved diastereomeric ratio. As in earlier work, the chairlike conformation of the transient ylide **339** (Chart 15) was used to explain the formation of the major diastereomer **335** and that the facial selectivity of the dipole for the dipolarophile was enhanced by increasing the chain length of the tether. The pyrrolidine **335** was then used as an intermediate in the synthesis of (−)-dihydroxyheliotridane **337**, whereas both (+)-dihydroxyheliotridane **332** and (−)-platynesine **333** were synthesized by way of the pyrrolidine **330**.

Chart 15

338 **339**

Sarain A, a complex alkaloid isolated from the marine sponge *Reniera sarai*, has been a focus of attention by the groups of Weinreb and Heathcock.[142−147] At about the same time, both research groups independently devised a route to the core of this complex and structurally unique macrocycle, which relied upon the synthesis of a suitably functionalized, cis-fused bicyclic lactam intermediate, a product of an intramolecular azomethine ylide cycloaddition reaction. A summary of the strategy adopted by the Weinreb group is shown in Scheme 87 and involves the formation of the core ring system **340** by an intramolecular Mannich reaction of a tethered allyl silane onto the iminium ion **341**, itself formed from the lactam **342**, the product from cycloaddition of the aziridine precursor **343**.

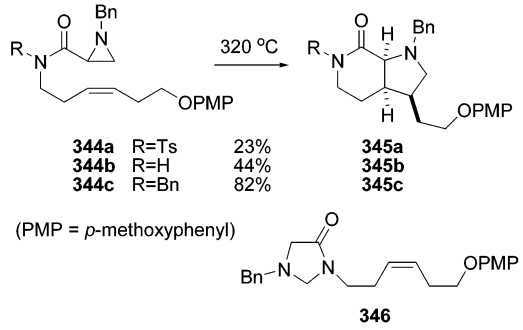
Scheme 87



340 **341** **342** **343**

Preliminary studies showed that heating the aziridine **344a** in *o*-dichlorobenzene in a sealed tube at 320 °C made it possible to synthesize the lactam **345a** in a stereospecific manner, albeit in poor yield (Scheme 88).[143] The choice of substituent on the side-chain oxygen atom (PMP was slightly preferably to THP or Bn) and on the amide nitrogen atom was

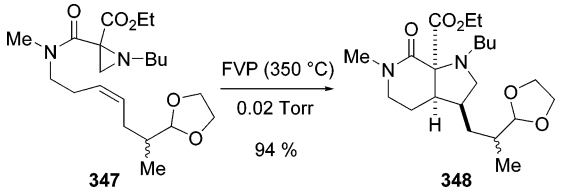
Scheme 88



crucial, presumably because the conditions employed for the cycloadditions demanded robust, nonlabile protecting groups. Best yields were obtained with the *N*-benzyl protecting group (**344c**, R = Bn). Interestingly, thermolysis of the unsubstituted amide **344b** (R = H) gave a high proportion of the imidazolidinone **346** (52%) together with the desired cycloadduct **345b** (44%). The imidazolidinone was thought to have formed by reaction of the amide nitrogen atom with the terminal carbon atom of the intermediate azomethine ylide, although subsequent attempts to convert the product **346** to the desired cycloadduct **345b** by thermolysis failed.

In an independent study into the synthesis of sarain A, Heathcock and co-workers elected to synthesize the aziridine **347** (Scheme 89) as a precursor for their cycloaddition experiments.[145] As well as providing functionality from which to build later on in the synthesis, the ester group present at C-2 of the aziridine **347** also served to stabilize the azomethine ylide intermediate. Flash vacuum pyrolysis was used as a means of achieving efficient ylide generation/cycloaddition of the aziridine **347** and gave the bicyclic lactam **348** in excellent yield.

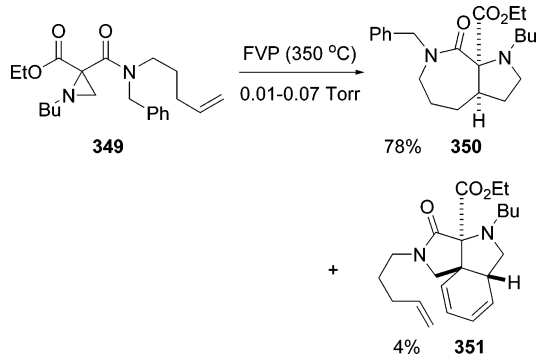
Scheme 89



A wider study of this type of reaction was carried out using aziridines in which the chain length of the olefin tether was varied.[145] Other than one successful example (to give the 5,5-fused ring system), substrates containing a secondary amide failed to undergo cycloaddition and decomposition occurred. For those cases that failed, it was postulated that the amide proton may quench the intermediate azomethine ylide (compare with the result of heating the aziridine **344b**) or that the reactive intermediate may adopt a conformation in which the alkene side-chain is distant from the ylide. The latter of these two explanations was thought more likely.

During the course of these studies the aziridine **349** containing an *N*-benzyl group was assayed (Scheme 90). As well as the expected diazabicyclo[5.3.0]decane derivative **350**, a small quantity of the tricyclic compound **351** was isolated, a result of cycloaddition

Scheme 90



of the intermediate ylide onto the π-system of the *N*-benzyl group.

This reaction was explored further by eliminating the olefin tether completely from the aziridine precursor. A series of aziridines incorporating several "symmetrical" and "nonsymmetrical" bis-substituted benzyl groups were then prepared and subjected to FVP to test the scope of this hitherto unknown transformation (Scheme 91, Table 6).

Scheme 91

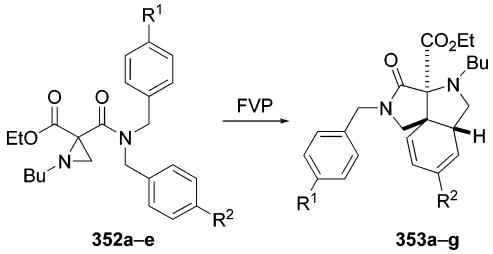


Table 6. Cycloadditions of the Aziridines 353a–e

352	R^1	R^2	353	yield (%)
a	H	H	**a**	67
b	CF_3	CF_3	**b**	68
c	OMe	OMe	**c**	42
d	H	OMe	**d** (R^1 = H, R^2 = OMe)	21
			e (R^1 = OMe, R^2 = H)	21
e	H	CF_3	**f** (R^1 = H, R^2 = CF_3)	50
			g (R^1 = CF_3, R^2 = H)	21

Preliminary experiments involving the dibenzyl amide **352a** gave the tricyclic lactam **353a** in 67% yield when subjected to FVP. Similar results were obtained for the bis[*p*-(trifluoromethyl)benzyl]amide **352b**. This is an important result because it established the feasibility of reaction of an electron-deficient aromatic dipolarophile with an azomethine ylide. The product derived from thermolysis of the dimethoxybenzyl amide **352c** proved to be thermally unstable and liable to decomposition on silica gel. Both of these factors were used to explain the lower yield of this derivative when compared to the results obtained for **352a** and **352b**. The bis(*p*-cyanobenzyl)-amide failed to react under the conditions described.

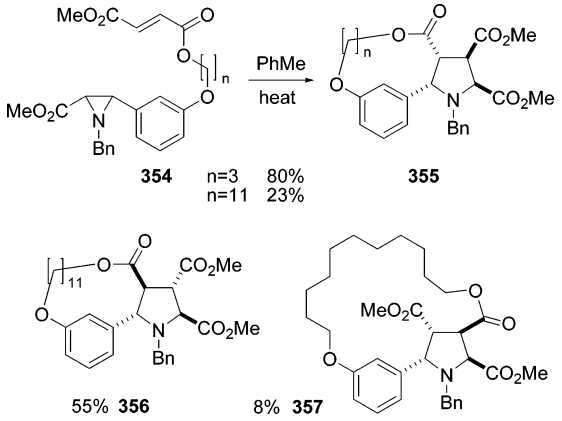
Two "unsymmetrical" aziridine precursors were synthesized (**352d** and **352e**) to determine what effects, if any, differing aromatic substituents would have on the regioselectivity of the cycloaddition reaction. Thermolysis of the aziridine **352d** (benzyl

versus *p*-methoxybenzyl) gave a 1:1 mixture of the tricyclic amides **353d** and **353e** with a combined yield of 42%. Thermolysis of **352e** gave a higher yield of products (71%) and a product mixture in the ratio of 7:3 (**353f/353g**) wherein the azomethine ylide appears to undergo preferential reaction with the more electron-deficient dipolarophile *p*-(trifluoro)benzyl group rather than the benzyl substituent. The latter of these two results indicates that the azomethine ylide can be considered to be the electron-rich component (despite the two carbonyl substituents) and that predictions based on FMO theory would make use of the HOMO of the ylide. However, the cycloaddition was shown to be reversible under the conditions of FVP such that heating either **353f** or **353g** gave a 7:3 mixture of **353f/353g**, thereby indicating that the product ratio is a reflection of the relative thermodynamic stability of the products rather than a kinetic preference for reaction at the less electron-rich dipolarophile.

4.2. Cycloadditions onto Alkenes to Form Large Ring Systems

Discussions so far in this section into the scope of the intramolecular 1,3-dipolar cycloaddition reaction of azomethine ylides derived from aziridines have shown that ring sizes of up to seven atoms could be synthesized using alkene-containing tethers of the appropriate length (Scheme 90). Work by Eberbach and co-workers demonstrated that aziridines tethered to alkenes could be used to synthesize much larger ring systems, in particular, metacyclophanes.[148] A series of aziridines **354** ($n = 2-6$ and 11) were prepared and were heated under reflux in benzene to initiate azomethine ylide formation and cycloaddition (Scheme 92). The most notable result of these investigations is that an aziridine with a tether containing 11 methylene units (**354**, $n = 11$) underwent thermolysis to form a variety of products, including a small amount of the pyrrolidine **357**, which contains a 20-membered ring.

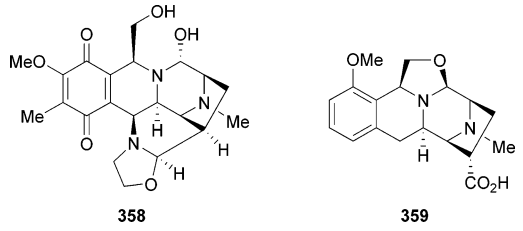
Scheme 92



As might be expected, the length of the olefin tether had a significant effect, not only on the yield of the reaction but also on the stereo- and regioselectivity of the intramolecular cycloaddition process. An optimum tether size of $n = 3$ resulted in a good yield of the metacyclophane **355** ($n = 3$) in a diastereoselective manner. As the chain length was shortened or lengthened, the yields of isolated products diminished, as did the facial selectivity. With the aziridine containing 11 methylene units ($n = 11$), the length of the chain allowed for (in part) a reaction pathway with inversion of regioselectivity in the cycloaddition.

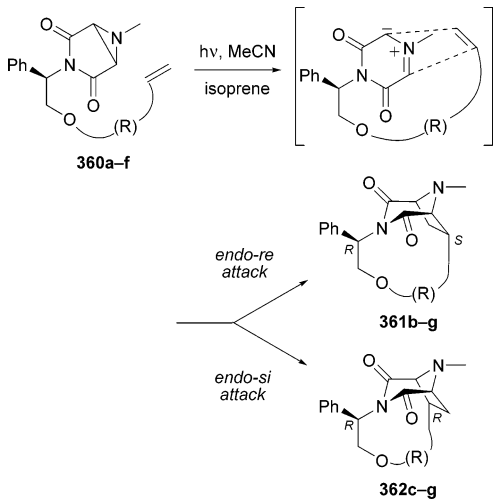
As part of their investigations into the synthesis of naphthyridinomycin **358** and quinocarcin **359** (Chart 16), Garner and co-workers studied a system containing a dipolarophile tethered to an azomethine ylide precursor that would provide a route into the 3,8-diazabicyclo[3.2.1]octane framework of these natural products.[149−151] A previous publication by the group had outlined a strategy for synthesizing the core ring system, which relied upon *intermolecular* 1,3-dipolar cycloadditions of prochiral dipolarophiles with chiral azomethine ylides.[152] This route however gave little of the desired endo-product and an alternative approach was sought. A tethered arrangement was devised to direct the mode of cycloaddition by enforcing a defined transition state geometry through which the dipolarophile could react with the azomethine ylide. In addition, the tether was devised to invoke a degree of facial selectivity by incorporating a chiral directing group and was designed to be removed easily to unmask functionality that could be built on to at a later stage. With these constraints in mind, a series of aziridines **360** (Scheme 93) containing varied tethers and tether lengths was prepared from (*S*)-phenylglycidol and subjected to photolysis.

Chart 16



Initial experiments using the acrylate **360a** (Table 7) failed to give any cycloaddition products. However when the substrate was converted to the mixed acetal **360b**, there was sufficient flexibility in the tether to

Scheme 93



allow cycloaddition to occur, giving exclusively the desired endo−re cycloadduct in moderate yield. The use of silyl tethers was found to produce the right balance of flexibility and functionality to enable the desired endo−re attack to take place with favorable yields (**360c**−**g**). Optimum results were obtained by incorporating either a dimethylsilylmethylene subunit (**360c**) or a diphenylsilylmethylene subunit (**360d**) into the tether to produce cycloadducts containing nine-membered rings. The desired endo−re cycloadducts **361c** and **361d** were formed in preference to the endo−si cycloadducts **362c** and **362d** in good yields and with good selectivities. As the length of the tether was increased, a reversal of diastereoselectivity occurred, with the endo−si isomer becoming the major product of the cycloaddition reaction with long chain lengths (**362e**−**g**). In an attempt to explain the observed diastereoselectivities, a crude transition state model was computed, which did predict a reversion from endo−re to endo−si with increasing tether length. More detailed transition state models failed to predict quantitatively the observed endo−re/endo−si selectivities based on calculated relative energies.

Table 7. Cycloadditions of the Aziridines 360a−f

360	R (tether)	ring size	ratio[a] re/si	yield (%)[b]
a	CO	8		
b	CH(OMe)	8	1:0	35−42
c	$Si(Me)_2CH_2$	9	16:1	62
d	$Si(Ph)_2CH_2$	9	10:1	71
e	$Si(Ph)_2OCH_2$	10	1:5	79
f	$Si(^iPr)_2OSi(^iPr)_2OCH_2$	12	1:2.5	60
g	$Si(Ph)_2OCH_2CH_2OCO$	13	1:12	72

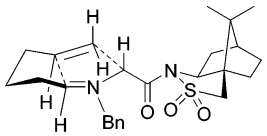
[a] Ratio of products obtained from ^1H NMR spectra of unresolved mixtures. [b] See ref 151.

4.3. Auxiliary-Controlled Cycloadditions

Although asymmetric variants of the intramolecular cycloaddition of aziridine-derived azomethine ylides have been discussed,[138−141,149−152] the approaches described above utilize a localized chiral center contained within the olefin tether to invoke a degree of asymmetry during the course of the cycloaddition. An alternative approach makes use of a chiral auxiliary attached to one of the carbon atoms of the aziridine framework to influence the stereochemical outcome of the cycloaddition onto an achiral alkene tether (Scheme 94). Thus, the racemic aziridines *cis*-**363** and *trans*-**363** were coupled with Oppolzer's sultam **364** using Me_3Al to give the cycloaddition precursors *cis*- and *trans*-**365** as 1:1 mixtures of diastereomers.[153] The diastereomeric pairs were then separated and each diastereomer subjected to thermolysis at 190−195 °C (sealed tube, toluene) for 3 h. In all cases, a single pair of diastereomers (ratio 3:1) was isolated from the reaction mixtures in 72% yield, with the structure of the major diastereomer shown to be that of the cycloadduct **366** (the structure of the minor diastereomer was not reported).[154]

The formation of the major diastereomer **366** was thought to occur via the transition state **367** (Chart 17) in which the 1,3-dipole approaches the olefin from the re face. The fact that all four aziridines **365** reacted to give the same products was explained by assuming that the intermediate ylides derived from thermolysis of these aziridines could interconvert by isomerization in a similar way to that described previously for the interconversion of aziridines **290** and **291** (Scheme 77).

Chart 17



367

4.4. Cycloadditions onto Alkynes

The use of aziridines for intramolecular azomethine ylide cycloadditions onto alkynes is confined to but a few examples in the literature. The earliest report of this type of transformation came from the group of DeShong who, as part of their study into the scope of the intramolecular cycloaddition onto alkenes also used alkynes as dipolarophiles.[137] For example, the aziridine **368** was subjected to FVP to give the expected dihydropyrrole **371** in moderate yield together with a small amount of the pyrrole **372**, the latter cycloadduct formed via aromatization of **371** (Table 8). The extent to which the pyrrole **372** was produced depended upon the reaction conditions

Scheme 94

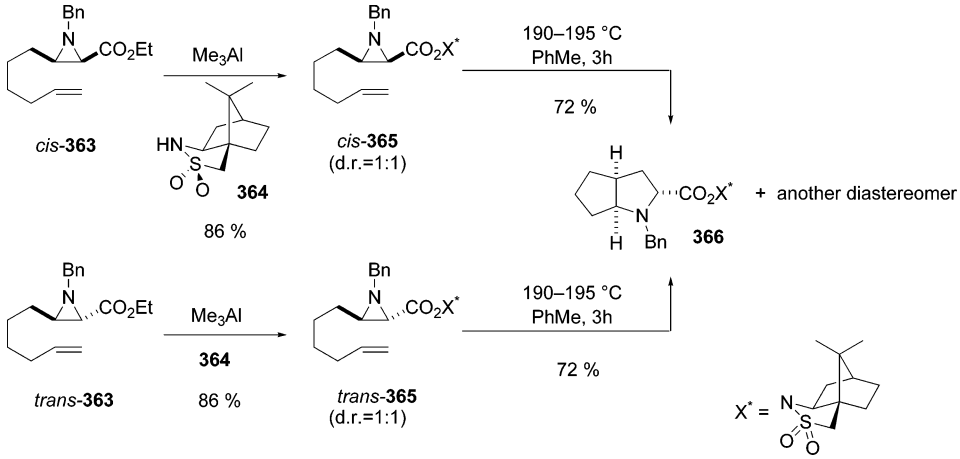
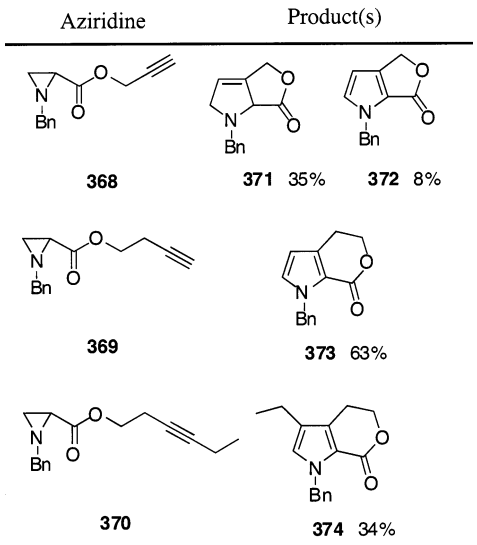


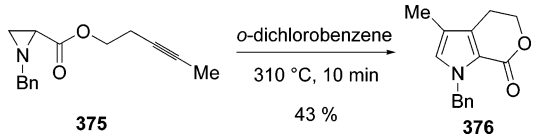
Table 8. Cycloadditions of the Aziridines 368−370



employed, and it was found that conversion of **371** to **372** could be achieved by exposure of the crude reaction mixture to oxygen for 24 h. In the same way, the aziridine **369** underwent thermolysis and concomitant oxidation to form the pyrrole **373** in good yield. Adding an alkyl group to the terminus of the alkyne (**370**) served only to diminish the yield of the resultant cycloadduct **374**, presumably by raising the energy of the LUMO of the dipolarophile and thereby reducing the extent of its interaction with the HOMO of the dipole.

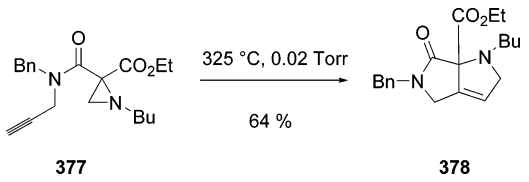
During a similar study, Fukumoto and co-workers showed that the aziridine **375**, which possesses an alkyne substituted with a terminal methyl group, underwent cycloaddition at 310 °C to form the pyrrole **376** in moderate yield (Scheme 95).[155] Cycloaddition experiments were conducted in *o*-dichlorobenzene at temperatures ranging from 180 to 310 °C. Radical scavengers were also employed but had a negative effect upon the outcome of the reaction.

Scheme 95



As outlined previously, Heathcock and co-workers used a 1,3-dipolar cycloaddition of an azomethine ylide generated from an aziridine as a means of constructing the core of sarain A (Scheme 89).[145] As part of their investigations into the scope of this process, the aziridine precursor **377**, incorporating an alkyne as the internal dipolarophile, was subjected to FVP at 300−350 °C. The resultant highly functionalized lactam **378** was obtained in good yield (Scheme 96).

Scheme 96

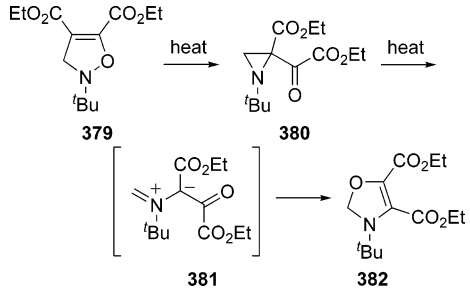


5. Ylides from Heterocycles

5.1. Ylides from Oxazolines and Isoxazolines

In section 4, the formation of azomethine ylides from aziridines by pyrolysis was discussed. By virtue of their structure and the reaction conditions employed, these ylides undergo intramolecular cycloaddition onto appendant dipolarophiles. In the absence of a dipolarophile and with suitable substituents in place, ylides derived from *N*-acyl-aziridines have been shown to undergo valence bond tautomerization to their isomeric 4-oxazolines. During their studies into the rearrangement of 4-isoxazolines, Baldwin and coworkers showed that the aziridine **380**, derived from thermal rearrangement of the 4-isoxazoline **379**, could undergo further pyrolysis to give the 4-oxazoline **382,** presumably via the azomethine ylide **381** (Scheme 97).[156]

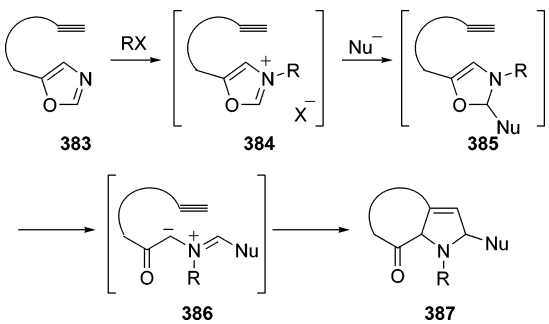
Scheme 97



The discovery of this aziridine/ylide/4-oxazoline tautomeric relationship has inspired other groups to investigate the rearrangement of 4-oxazolines as an alternative method for the generation of azomethine ylides. However, examples of 4-oxazolines in the literature are scarce and those that are isolable species normally contain undesired stabilizing substituents. A method for preparing "nonstabilized" 4-oxazolines was therefore sought.

Vedejs and co-workers were among the first to pioneer such an approach. Their strategy was to prepare the "nonstabilized" 4-oxazolines in situ. These would then tautomerize to the azomethine ylide and form cycloaddition products with dipolarophiles, initially in an intermolecular fashion.[157−159] Later, the intramolecular variant was attempted successfully, an outline of which is shown in Scheme 98.[160]

Scheme 98

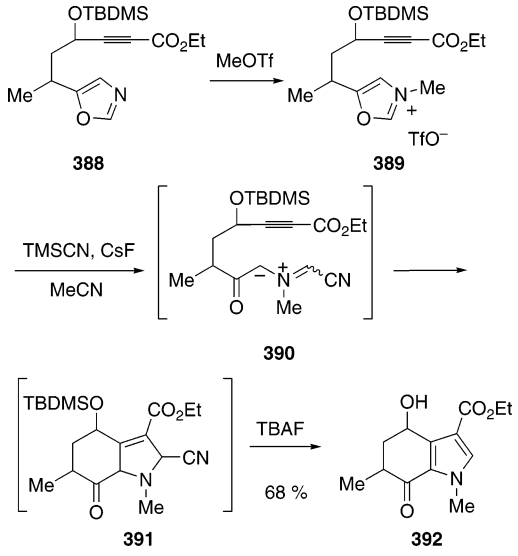


Formation of the 4-oxazoline intermediates in situ was accomplished using nucleophilic addition to 4-oxazolium salts. An oxazole **383**, bearing a suitable tether at the 5-position, was activated for nucleophilic addition by formation of its salt **384**. Introduction of a nucleophile (such as a reducing agent, in which case Nu=H) furnishes the desired oxazoline precursor **385**, which rearranges to the ylide **386**. The ylide **386** can then react with a dipolarophile in the usual way to give cycloadducts such as **387** (illustrated in Scheme 98 for the intramolecular process).

This method of azomethine ylide generation is particularly useful when selective hydride donors are used to generate the intermediate 4-oxazolines. Due to the instability of the resultant oxazolines, rearrangement to the ylide takes place readily, and consequently, mild reaction conditions can used. This method allows the formation of ylides that possess a potentially labile C−H bond adjacent to the iminium carbon atom. These intermediates commonly undergo competing side-reactions (due to enolization or enamine formation) when synthesized from aldehydes or aziridines (see previous sections).

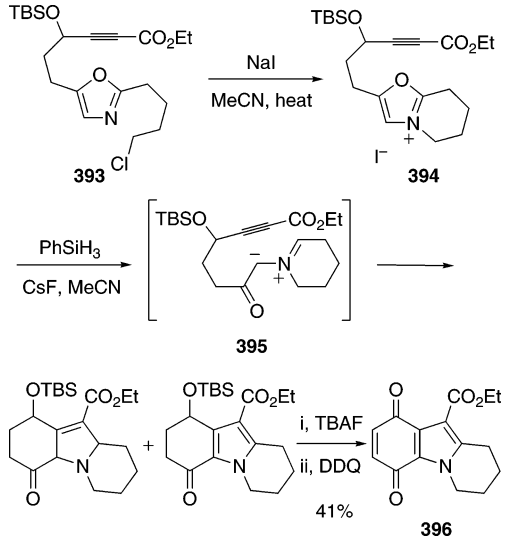
The first intramolecular example of this process to be published involved the oxazole **388**, in which the 5-position was substituted with an alkyne-containing tether. Treatment of **388** with methyl triflate gave the oxazolium intermediate **389** (Scheme 99), which was subsequently reacted with an excess of trimethylsilyl cyanide to form the ylide **390**. Intramolecular cycloaddition with the alkyne ensued to give the pyrroline **391**. Aromatization through expulsion of hydrogen cyanide, followed by silyl ether cleavage resulted in the formation of the tetrahydroindolone **392** in 68% overall yield.

Scheme 99



An extension to this methodology was later published in which an intermediate oxazolium salt was formed by internal *N*-alkylation rather than *N*-alkylation from an external source.[161] The oxazole **393**, which contained a chlorobutyl side-chain, was treated with sodium iodide to form the transient oxazolium intermediate **394**. The crude reaction mixture was treated with phenylsilane and cesium fluoride to generate the azomethine ylide **395**, which, in turn, reacted with the internal dipolarophile to form a mixture of cycloadducts comprising partially desilylated products, aromatized products, and dihydropyrrole isomers. Complete desilylation of this mixture was achieved using tetrabutylammonium fluoride (TBAF) and aromatization was carried out using 2,3-dicyano-5,6-dichloro-*p*-benzoquinone (DDQ) to give the indolquinone **396** in 41% yield (based on the oxazole **393**, Scheme 100). Azomethine ylides such as **395** contain a C−H bond α to the iminium carbon atom and may therefore be susceptible to enamine formation, especially if the conditions for cycloaddition involve high temperature.

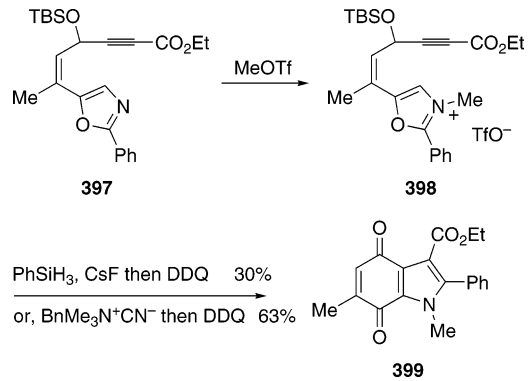
Scheme 100



Hydride donors other than phenylsilane were found to cause over-reduction, especially when reagents that contained some Lewis acid character were used. The use of protic solvents such as methanol gave lower yields.

To optimize the cycloaddition process, Vedejs and co-workers sought to minimize the amount of side reactions by eliminating the possibility of enamine formation and constraining the dipolarophile tether to enhance the prospect of cycloaddition. For the purposes of such a study, the oxazole **397** (Scheme 101) was synthesized, which had the added advantage that the 2-phenyl group could be used as a label to detect any fragmentation products.[162]

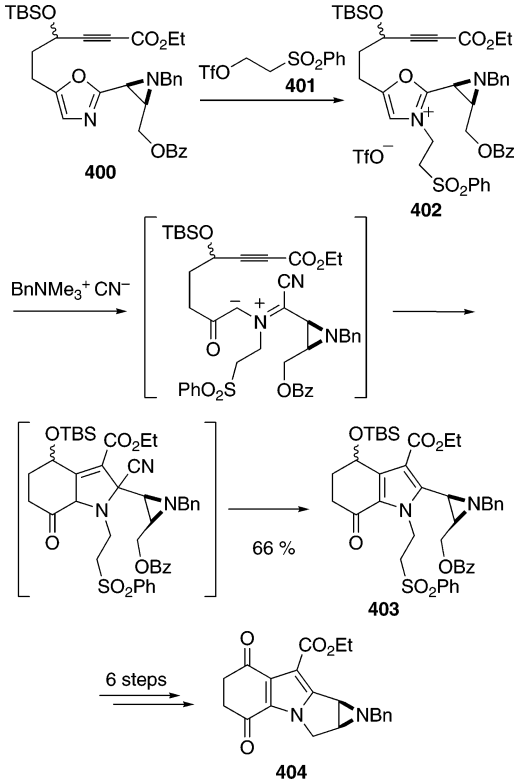
Scheme 101



Despite the features outlined above, conversion of the oxazole **397** to the oxazolium salt **398** with methyl triflate followed by treatment with Ph_3SiH/CsF and subsequent DDQ oxidation gave only 30% yield of the indolquinone **399**. A complex mixture of air-sensitive reaction products was formed through three competing reaction pathways, thus provoking the search for an alterative set of reaction conditions. Activation of the oxazolium intermediate **397** using cyanide anion in the form of TMSCN/CsF or NaCN in acetonitrile gave similar (low) yields of the DDQ-oxidized product **399**, but fewer byproducts were obtained, a consequence of more rapid aromatization through loss of HCN.

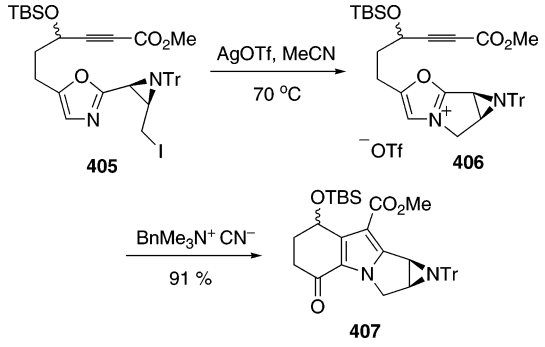
Based on the assumption that the oxazolium salt **398** might be reacting with active intermediates in the reaction mixture, experiments then focused upon maintaining low concentrations of **398** to avoid unwanted byproducts. These experiments lead ultimately to the use of benzyltrimethylammonium cyanide ($BnMe_3NCN$), a more soluble cyanide source that induced much faster reaction than the more heterogeneous alkaline earth metal cyanides and gave an improved yield (63%) of the indoloquinone **399** after DDQ oxidation (Scheme 101). The methodology was used later in the synthesis of several aziridinomitosene derivatives.[163] Reaction of the oxazole **400** with the 2-(phenylsulfonyl)ethyl triflate **401** (a removable *N*-alkyl group) gave the 4-oxazolium salt **402**, which was then treated with benzyltrimethylammonium cyanide to give the pyrrole **403** in 66% yield. This key intermediate was then used to synthesize the racemic aziridinomitosene derivative **404** in six steps (Scheme 102).

Scheme 102



In later publications, a modification to the aziridinomitosene synthetic strategy was outlined.[164,165] Silver triflate-promoted internal alkylation of the 4-oxazole **405** with the iodide subunit [a process similar to that described earlier (Scheme 100)], gave the 4-oxazolium triflate salt **406**, which then underwent ylide generation/cycloaddition/HCN loss in the presence of benzyltrimethylammonium cyanide to give the pyrrole **407** in 91% yield (Scheme 103).[165] It was therefore shown that the aziridine could be incorporated into the framework of the 4-oxazolium salt **406** and subsequent reactive intermediates en route to the tetracycle **407** without undergoing decomposition.

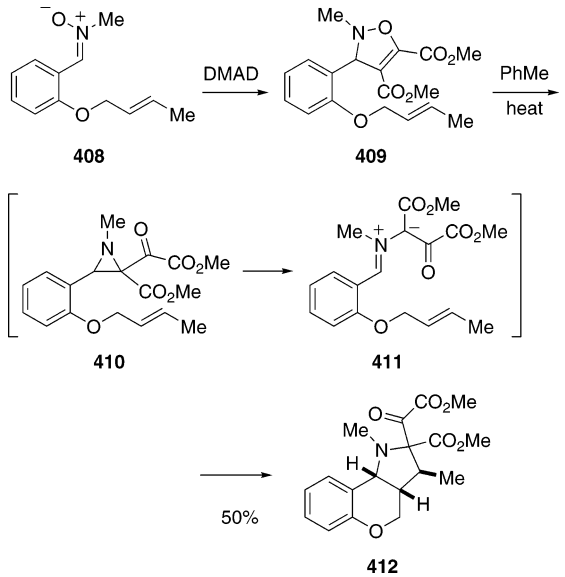
Scheme 103



At the start of this section, we described that 4-isoxazolines can undergo thermal rearrangement to azomethine ylides via aziridine intermediates (Scheme 97). Intermolecular cycloadditions of the resultant azomethine ylides have been reported, but there are few examples of the intramolecular process described in the literature.

The nitrone **408** was converted into the 4-isoxazoline **409** by reaction with dimethyl acetylene-dicarboxylate (DMAD) (Scheme 104). When the isoxazoline **409** was heated under reflux in toluene, a mixture (1.3:1 ratio) of diastereomers of the tricyclic compound **412** was obtained in 50% overall yield.[166] Rearrangement of 4-isoxazolines has long been known to produce acyl aziridines, which may subsequently undergo thermal rearrangement to azomethine

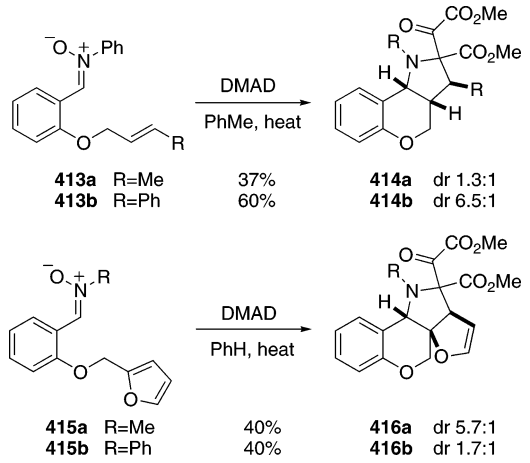
Scheme 104



ylides.[156] It is not surprising then that formation of the tricycle **412** arises through an intramolecular cycloddition reaction of the azomethine ylide **411** onto the crotyl group present in the intermediate **411**, which itself originated via thermolysis of the aziridine **410**.

Further studies on this type of system were carried out using *N*-phenylnitrones containing crotyl and cinnamyl groups (**413a** and **413b**) as the internal dipolarophile (Scheme 105).[166] No significant improvements were noted except when the terminus of the alkene was substituted with a phenyl group, in which case the yield and diastereomeric ratio of the cycloadducts **414b** was increased.

Scheme 105



413a R=Me 37% **414a** dr 1.3:1
413b R=Ph 60% **414b** dr 6.5:1

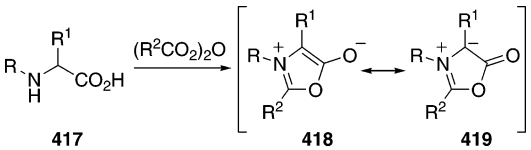
415a R=Me 40% **416a** dr 5.7:1
415b R=Ph 40% **416b** dr 1.7:1

Replacement of the *O*-allyl tether with an *O*-(2-furylmethyl) tether allowed cycloaddition across the C-2,C-3 double bond of the furan (Scheme 105). Thus, treating the nitrones **415a** and **415b** with DMAD and then heating the resultant 4-isoxazolines under reflux in toluene gave the complex tetracyclic cycloadducts **416a** and **416b**.

5.2. Ylides from MUnchnones

Münchnones, or meso-ionic Δ^2-oxazolium-5-oxides, are known to behave like cyclic azomethine ylides and can undergo 1,3-dipolar cycloaddition reactions with alkynes and alkenes to form pyrroles and pyrrolines, respectively, through expulsion of carbon dioxide.[167,168] They are commonly synthesized by heating symmetrical acid anhydrides with amino acid derivatives **417** (Scheme 106), a process that establishes the oxazolium oxide (or münchnone) framework. The tautomeric form of the münchnone, **419**, is in all respects an azomethine ylide and is able to undergo cycloaddition chemistry with reactive dipolarophiles. The intramolecular cycloaddition process usually takes place with the dipolarophile tethered via the nitrogen atom of the ring (R group) or at the 2-position of the ring (R^2).

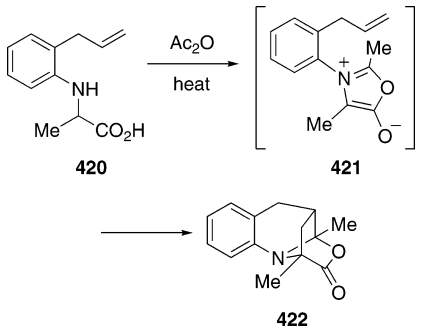
Scheme 106



417 **418** **419**

The first published account of an intramolecular 1,3-dipolar cycloaddition using such a heterocycle involved heating *N*-(2-allylphenyl) alanine **420** with acetic anhydride to form the münchnone **421**.[169,170] This transient intermediate reacted with the appended alkene to form the oxazoloquinolinone **422** (Scheme 107), a hitherto unknown transformation that was interesting because the münchnone had undergone a regioselective internal [3+2] cycloaddition with an unactivated alkene, in which the elements of carbon dioxide were still present in the cycloadduct.

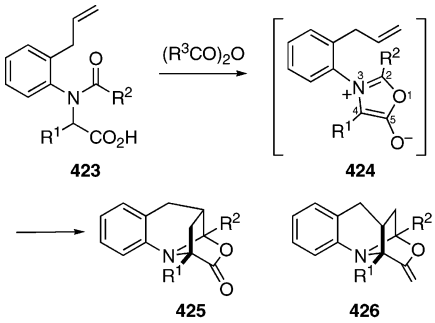
Scheme 107



420 **421** **422**

In this and subsequent work,[171] a series of amino acid derivatives **423** (Scheme 108) were assessed for their ability to undergo intramolecular cycloaddition reactions and to see what influence, if any, the substituents at C-2 and C-4 of the münchnone ring would have upon the outcome of the cycloaddition process. The intermediate münchnones **424** were synthesized from *N*-(2-allylphenyl) glycine, alanine, or phenylglycine derivatives using an excess of the appropriate cyclodehydrating agent (the anhydride). Because of their reactive nature, the münchnones **424** were not isolated.

Scheme 108



423 **424** **425** **426**

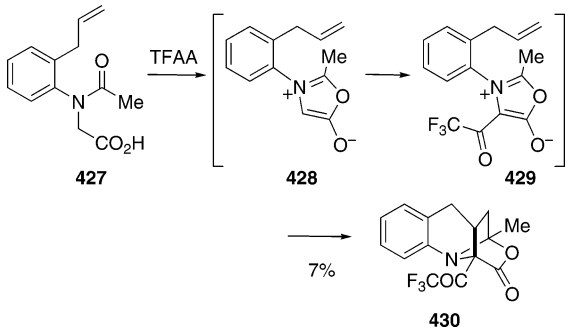
R^1	R^2	R^3	Yield (%)	Ratio **425** : **426**
H	H	Me	80	1 : 0
H	Me	Me	92	5.6 : 1
H	Ph	Me	77	1 : 0
Me	H	Me	75	1 : 0
Ph	H	Me	84	1 : 2.2
Ph	Ph	Ph	65	0 : 1

The results of these experiments showed that when the C-4 position is unsubstituted or substituted with a methyl group (R^1 = H or Me), the substituent at C-2 (R^2) has little effect on the regioselectivity of the cycloaddition and the regioisomer **425** predominates. When the substituent at C-4 is a phenyl group (R^1 = Ph), the C-2 substituent has a marked effect on the

regioselectivity and a general bias toward the regioisomer **426** is often displayed.

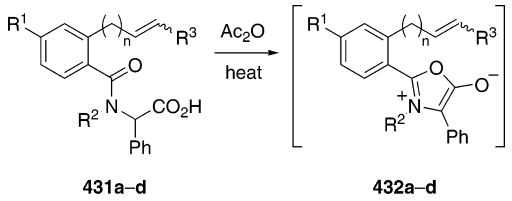
The use of trifluoroacetic anhydride (TFAA, $R^3 = CF_3$) as the cyclodehydrating agent gave the oxazoloquinolinine **430**, in which a trifluoroacetyl group had become attached at the C-2 (R^2) position (Scheme 109). To explain the formation of this product, it was proposed that the intermediate münchnone **428** underwent acylation at C-4 to give the münchnone **429**, which reacted with the internal double bond to give cycloadduct **430**. The rate of acylation was thought to be faster than the rate of cycloaddition thus giving rise to **430** exclusively (albeit in poor yield).

Scheme 109



To investigate the effect of spacial proximity between the dipole and the dipolarophile on the course of the cycloaddition reaction, the phenylglycine derivatives **431a** ($n = 1$) and **431b** ($n = 2$) were prepared and were heated with acetic anhydride to give the münchnones **432a** and **432b**, respectively (Scheme 110). The results of these experiments are summarized in Table 9.

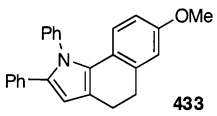
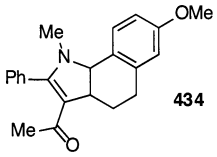
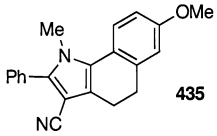
Scheme 110



Previous studies indicated that the p-orbitals of the dipolarophile should lie in a plane parallel to the plane of the 1,3-dipole to allow for an effective three-center overlap, thus promoting cycloaddition.[172] By examination of the molecular models of the münchnone **432a** ($n = 1$), it was believed that the planes of the azomethine ylide and the π-system of the alkene could not be arranged in parallel thus precluding cycloaddition of this substrate with the short alkene-containing tether. To verify that the münchnone was indeed being formed, dimethyl acetylenedicarboxylate (DMAD) was added to the reaction mixture and the products of the intermolecular cycloaddition reaction were isolated in modest yield.

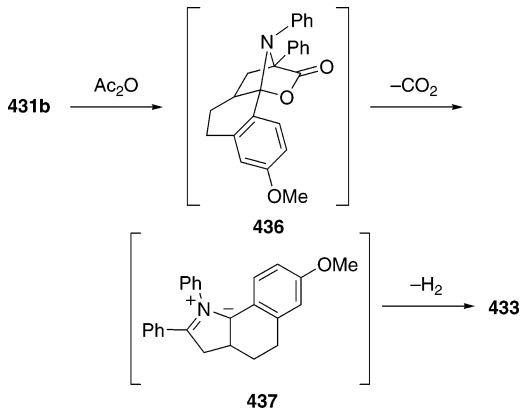
Upon extension of the alkene tether by one methylene unit, the münchnone **432b** underwent intramolecular 1,3-dipolar cycloaddition to form the cycloadduct **433** in 17% yield (Scheme 111). Although not a direct comparison (R^2 in this instance is phenyl, a substituent that may provide different electronic or steric effects from R^2 = Me), the outcome of the experiment allowed for a "parallel-plane approach" of dipole and dipolarophile and a successful cycloaddition resulted. Formation of the cycloadduct **433** was postulated to occur via the primary cycloadduct **436**. Under the reaction conditions, **436** is thought to lose carbon dioxide to form the ylide **437**, which subsequently undergoes tautomerization and oxidation to give the pyrrole **433**. In a separate experiment, DMAD was introduced into the reaction mixture, and the cycloadduct derived from intermolecular reaction of the münchnone **432b** with DMAD was the only product isolated (33% yield).

Table 9. An Investigation of Spacial Proximity and Substituent Effects Using Münchnones 432a–d

431	R^1	R^2	R^3	n	Product
a	H	Me	H	1	–
b	MeO	Ph	H	2	 **433**
c	MeO	Me	H	2	 **434**
d[a]	MeO	Me	CN	2	 **435**

[a] Mixture of *E*- and *Z*-isomers.

Scheme 111



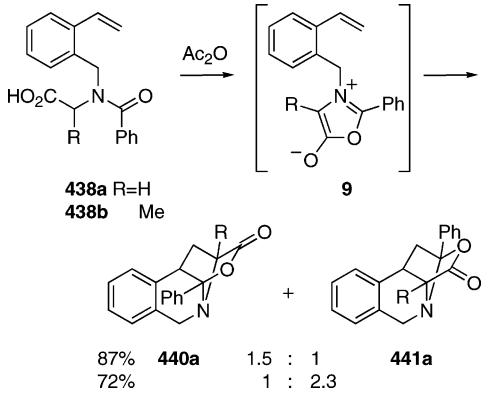
With the precursor **431c**, the major product from the reaction was found to be the unoxidized cycloadduct **434**, in which the acetate group was substituted at the 3-position of the dihydropyrrole ring. To aid structural assignment, the adduct **434** was oxidized with DDQ to provide the *N*-methyl-3-acetyl variant of the pyrrole **433** in 5% yield.

In an attempt to improve the yields of the 1,3-dipolar cycloaddition reactions, an electron-withdraw-

ing substituent was introduced at the terminus of the alkene (Table 9, **431d**). In theory, lowering the energy of the LUMO of the dipolarophile in this way should result in an increased HOMO−LUMO overlap and so enhance the cycloaddition process. In practice, the inclusion of a cyano-group had little effect on the yield (**435**, 11%). This observation led the authors to conclude that significant entropic factors were playing an important part in the rate-determining process.

A similar system comprising *N*-(2-vinylbenzyl)-glycine derivatives was investigated to probe further the spacial arrangements required for the münchnone and the alkene to undergo a successful cycloaddition reaction.[171] Substrates such as **438a** and **438b** were treated with an excess of acetic anhydride, and the ratio of the cycloadducts **440** and **441** was determined (Scheme 112).

Scheme 112

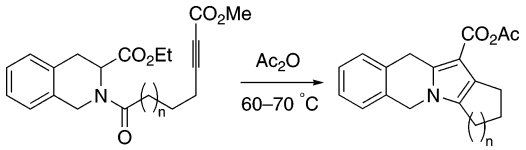


The main conclusion from the whole series of experiments was that the regioselectivity of *N*-(*o*-vinylbenzyl)-substituted münchnone cycloadditions was influenced more by the nature of the (R) substituent at the C-4 position of the münchnone ring than the substituent at the C-2 position (substituted in the examples of Scheme 112 by Ph). This observation could be explained if one assumes that the cycloadditions of mesoionic systems such as these are generally HOMO (dipole)−LUMO (dipolarophile)-controlled processes. The largest coefficient in the HOMO of the münchnone ring is located at the C-4 position and so substituent effects will be more noticeable at this position.

Treatment of the precursor **438a** with excess TFAA produced a single regioisomer corresponding to the cycloadduct **441** except that R = $COCF_3$ (82%). As before, the reaction was thought to proceed via a reactive trifluoroacetylated-münchnone intermediate (cf. Scheme 109).

As part of their studies into potential topoisomerase-1 inhibitors, Sainsbury and co-workers investigated münchnone cycloaddition reactions of the isoquinoline system **442**.[173] Treatment of **442a** with acetic anhydride at 60−70 °C produced an intermediate münchnone, which underwent cycloaddition onto the activated internal alkyne to form the tetracyclic anhydride **443a** in moderate yield. In the same way, the analogue **442b** ($n = 2$) was converted to the tetracycle **443b** in slightly better yield (Scheme 113).

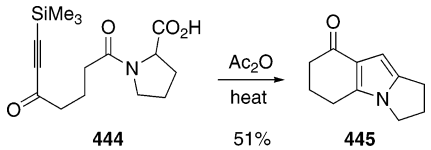
Scheme 113



The ^{1}H NMR spectroscopic data showed that the isoquinolinones **442a** and **442b** both exist as a 1:1 mixture of rotamers at low temperatures and free rotation about the amide bond occurs between 60 and 120 °C. Heating the reaction mixture at 80 °C or above resulted in discoloration of the solution.

In similar fashion, Martinelli and co-workers have described a method for preparing 4-oxygenated tetrahydroindoles and indoloquinones using intramolecular cycloaddition of münchnones.[174,175] A series of amino acid derivatives such as the proline derivative **444** were used to prepare substituted tetrahydroindoles (e.g., **445**) in modest to good yields (Scheme 114).

Scheme 114

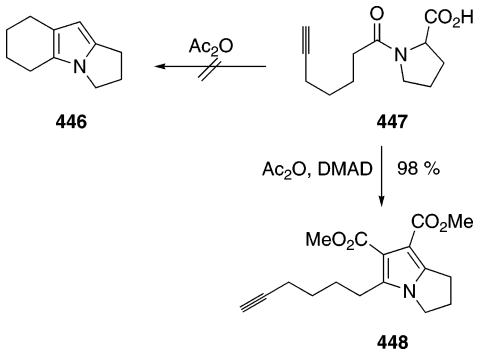


The intermediate münchnone was generated by heating the acid **444** in acetic anhydride at 70−80 °C. After 1 h, the temperature of the reaction mixture was raised to 125 °C, whereupon evolution of carbon dioxide occurred. As with all the examples documented, the cycloadduct **445** was found to be lacking the trimethylsilyl group present in the starting material. It was assumed that the trimethylsilyl group had facilitated the cycloaddition process by activating the alkynyl group to intramolecular 1,3-dipolar cycloaddition and was then cleaved from the molecule at higher temperature. The trimethylsilyl derivative of **445** was isolable when lower temperatures were used, but the reaction did not proceed to completion.

Further evidence that the trimethylsilyl group activated the alkyne toward internal cycloaddition of the münchnone came from the fact that the unsubstituted alkyne **447** was unable to undergo cycloaddition to the tricycle **446** under the same conditions (Scheme 115). Addition of DMAD to the reaction mixture gave the intermolecular cycloadduct **448**, thus showing that the münchnone intermediate was being formed.

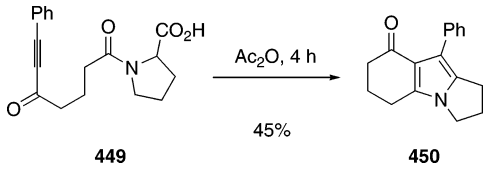
It could be argued that a carbonyl group at C-8, which is present in the trimethylsilyl-containing precursors **444**, may also activate the alkyne toward internal cycloaddition and therefore that the results shown in Scheme 115 do not demonstrate that the trimethylsilyl group alone is responsible for promoting the cycloaddition. A better comparison came from the fact that the precursor **449** (Scheme 116), in which a phenyl group is present at the alkyne

Scheme 115



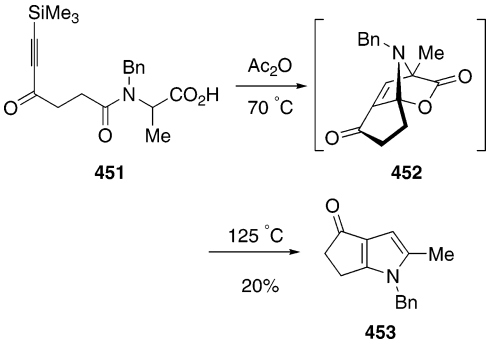
terminus, underwent cycloaddition with an extended reaction time to give the cycloadduct **450** in 45% yield (cf. Scheme 114; the precursor **444** gave the cycloadduct **445** in 51% yield and with a shorter reaction time of 2 h).

Scheme 116



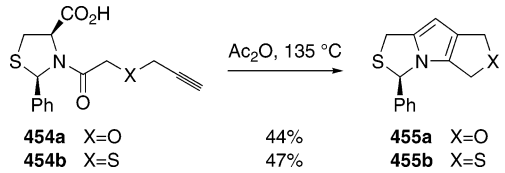
The effect of tether length on the cycloaddition process in these types of systems was also investigated. The precursor **451**, prepared from succinic anhydride, was heated in neat acetic anhydride to give the dihydropyrrolizine **453** in 20% yield (Scheme 117). In this case, the alkynyl tether is shorter by one methylene unit compared with the substrate **444**; this results in a large amount of molecular strain to bring the two reactive termini together to form the intermediate **452** and accounts for the low yield obtained for this cycloaddition reaction.

Scheme 117



From the examples shown, it is clear that intramolecular cycloaddition of a münchnone onto an alkyne tether proceeds well if the alkyne is "activated" by a terminal substituent. This substituent can take the form of an electron-withdrawing group such as a methyl ester or a trimethylsilyl group (e.g., Schemes 113 and 114).[173−175] The reaction of a münchnone with an unsubstituted alkyne in an intramolecular fashion is problematic (e.g., Scheme 115) but not precluded. Thus, heating the thiazolidine **454a** (Scheme 118) in acetic anhydride at 95−100 °C produced no reaction, but raising the temperature to

Scheme 118



135 °C gave the tricyclic product **455a** in 44% yield.[176] In the same way, the thiazolidine **454b** gave a similar yield of the tricyclic compound **455b**.

In this and a later publication, other thiazolidines **456** (Chart 18) were prepared to determine the effect of changing the substitution pattern of the thiazolidine ring and of changing the tether containing the dipolarophile.[177] The results of these experiments (Table 10) show that a variety of substitution patterns can be tolerated in the cycloaddition reaction and the products **457**−**463** were obtained in low to moderate yields.

Chart 18

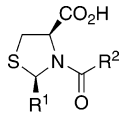
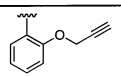
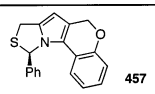
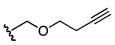
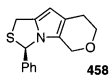
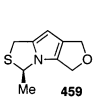
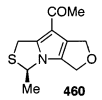
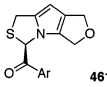
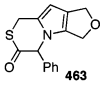


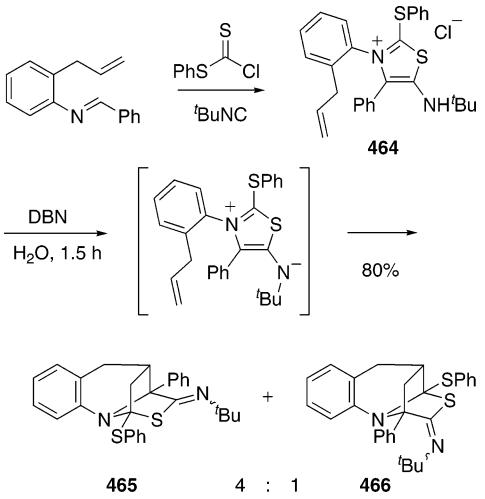
Table 10. Intramolecular Dipolar Cycloadditions of Bicyclic Münchnones

Entry	R^1	R^2	Cycloadduct(s)	Yield(s) (%)
1	Ph		 **457**	38
2	Ph		 **458**	18
3	Ph		–	–
4	Me		 **459**  **460**	26, 12
5	COAr[a]		 **461**	42
6	COPh		 **462**  **463**	17, 29

[a] Ar = C_6H_4-*p*-OMe.

Aminothiazolium salts, formed from a three-component reaction of an isocyanide, an aryl chlorothioformate, and an imine, can be converted to their corresponding azomethine ylides under basic conditions (Scheme 119). Subsequent reaction of these ylides with a dipolarophile has been shown to occur in an intermolecular fashion leading to five-membered heterocycles.[178] The intramolecular variation of this reaction has also been reported wherein a series of mesoionic thiazoles bearing an *o*-allylphenyl tether on the ylide nitrogen atom were found

Scheme 119

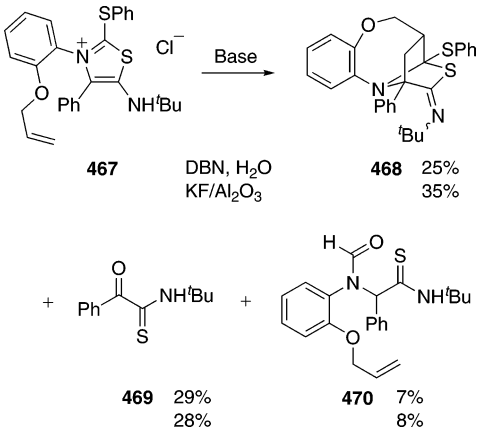


to undergo cycloaddition to the thiazoloquinolines in good to excellent yields.[179] An example of this process is shown in Scheme 119. The thiazolium salt **464** was treated with the base diazabicyclo[4.3.0]non-5-ene (DBN) in aqueous media thus prompting ylide formation and cycloaddition to the thiazoquinolines **465** (favored) and **466** in excellent yield.

Further experiments showed that the effect of electron-donating substituents at C-4 of the thiazolium salt gave a slight reversion of the regiochemistry to that shown in Scheme 119. A variety of bases could also be tolerated (both organic and inorganic), which affected only the yields of the cycloadducts and not the ratios. When the substituent at C-2 was altered from a thiophenyl to a *p*-tolyloxy group, cycloaddition of the resultant mesoionic thiazole could be achieved only using KF on alumina (11%).

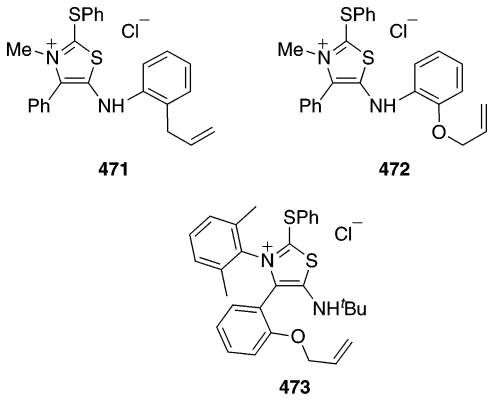
The effect of lengthening the alkene tether was also investigated using the *O*-allyl-containing aminothiazolium salt **467** (Scheme 120). When aqueous conditions with DBN as the base were used, the benzoxazepine **468** was obtained in moderate yield together with the reactive-intermediate decomposition products **469** and **470**. The benzoxazepine **468** was characterized by ^{1}H NMR NOE spectroscopy experiments. The alternative basic system KF on alumina, which was used with some success earlier, resulted in a slightly improved yield of this benzoxazepine **468**.

Scheme 120



Other experiments designed to investigate the effects of alkene tether position met with little success. The thiazolium salts **471**−**473** (Chart 19) produced none of the expected cycloadducts, giving instead a variety of hydrolysis or oxidation products. The apparent lack of reactivity was attributed to the inherent structural constraints preventing the alkenyl tether from adopting a parallel plane approach with the azomethine ylide (cf. ref 172).

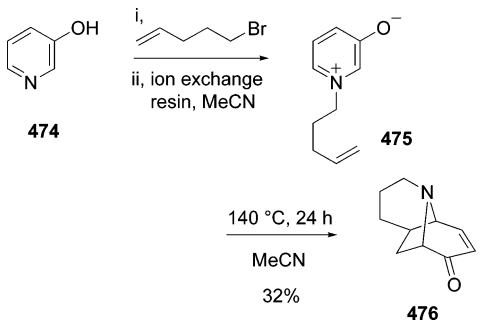
Chart 19



5.3. Ylides from Pyridines and Pyrazines

Azomethine ylides derived from *N*-substituted pyridinium or pyrazinium salts can be used to generate complex heterocyclic molecules via intramolecular [3+2] cycloaddition reactions.[180] Indeed, one of the earliest reported examples of an intramolecular dipolar cycloaddition reaction involved a pyridinium ylide. Quaternization of 3-hydroxypyridine (**474**) with 5-bromo-1-pentene followed by basification on an ion-exchange resin gave the ylide **475** (Scheme 121).[181] Subsequent thermolysis of **475** initiated cycloaddition of the ylide (aided by the 3-oxo substituent) with the pendant alkene and took place across the 2,6-positions of the pyridine ring. The yield of the cycloadduct **476** was low but was improved later (to 64%) by heating in an autoclave at 160 °C.[182]

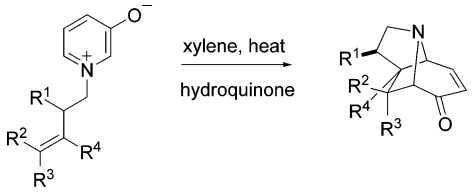
Scheme 121



A related cycloaddition was achieved using the pyridinium ylides **477a**−**c**, prepared in the same way as the ylide **475** (Scheme 122).[183] Thermolysis of the ylides **477a**−**c** in refluxing xylene gave the cycloadducts **478a**−**c** in poor to reasonable yields (Table 11). The yield was lowest for the unactivated alkene (R^4 = H) but was improved when an electron-withdrawing methyl ester group was present, thereby suggesting that the reaction is controlled by the

HOMO of the pyridinium ylide interacting with the LUMO of the dipolarophile.

Scheme 122



477a–c **478a–c**

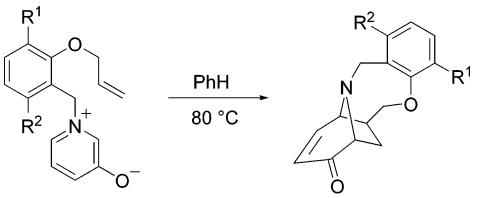
Table 11. Cycloaddition of the Pyridinium Ylides 477a–c

477	R^1	R^2	R^3	R^4	yield 478 (%)[a]
a	H	H	Me	H	20
b	H	H	H	CO_2Me	60
c		$-CH_2CH_2-$	H	CO_2Me	48

[a] Together with unreacted ylides **477a–c** (30–50%).

Sammes and co-workers investigated a similar 3-oxopyridinium system.[184] They sought to constrain the dipole and dipolarophile in close proximity to one another within the reactive intermediate, thus increasing the likelihood that a successful reactive encounter would occur. They also reasoned that it should be possible to use longer tethers and so form larger ring systems if the tether is restricted conformationally to force juxtaposition of the two reactive termini. In line with these expectations, several 3-oxopyridinium salts such as **479a** and **479b**, possessing conformationally restricted (2-allyloxy)benzyl linkers, were prepared and tested for their ability to undergo intramolecular cycloaddition (Scheme 123).[184]

Scheme 123

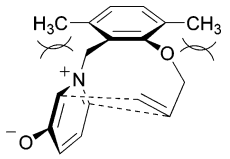


479a R^1=H, R^2=Me No reaction **480a**
479b R^1=Me, R^2=Me 80% **480b**

After being heated under reflux for 7 days in deuteriobenzene, the 3-oxopyridinium salt **479a** failed to give any of the cycloadduct **480a**. From this and the results of other experiments, it became apparent that the R^1 and R^2 positions of the phenoxy ring required substituents that restricted or "buttressed" the conformation of the tether containing the terminal dipolarophile sufficiently to enable (in part) cycloaddition to occur. The optimum buttressing effect occurred when R^1 and R^2 were substituted with methyl groups (**479b**, Chart 20), and the cycloadduct **480b** was then isolated in excellent yield.

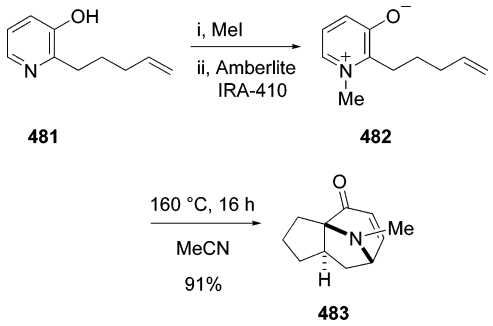
Methylation of the nitrogen atom of the pyridine **481** and formation of the ylide **482** provides an example of the use of this chemistry when the dipolarophile is tethered to the 2-position of the oxopyridinium ring (Scheme 124).[182,185] Intramolecular cycloaddition occurs on heating to give the cycloadduct **483**.

Chart 20



479b

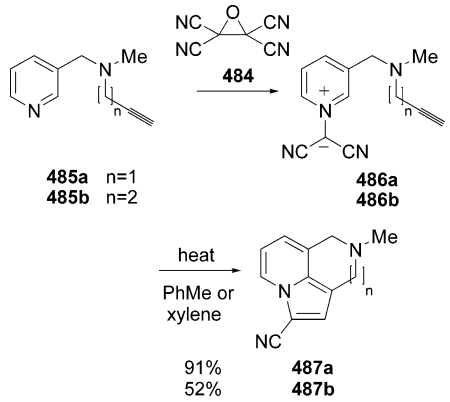
Scheme 124



481 **482** **483**

A common and effective method for generating *N*-pyridinium or *N*-pyrazinium ylides uses tetracyanoethylenoxide (TCNEO) **484** (Scheme 125). This interesting reagent acts by reacting with the nitrogen atom of the pyridine (or pyrazine) ring. Through loss of dicyanoketone, a dicyanomethylide salt is produced, which is able to undergo 1,3-dipolar cycloaddition reactions with dipolarophiles.

Scheme 125



485a n=1 **486a**
485b n=2 **486b**
487a
487b

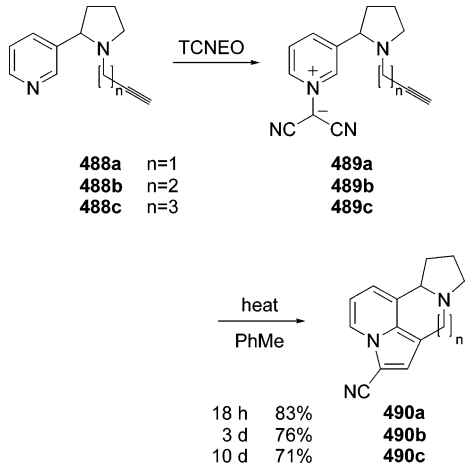
One of the first groups to use this reagent for intramolecular cycloaddition was that of Noguchi and co-workers.[186,187] The 3-substituted pyridine **485a** was treated with TCNEO to form the dicyanomethylide salt **486a**, which underwent thermolysis in toluene to provide the indolizine **487a** in excellent yield. The methyl group on the nitrogen atom present in the tether could also be substituted with other groups (e.g., SO_2CH_3, CH_2Ph) to give other indolizines in excellent yields. This chemistry therefore allows the preparation of tricyclic heterocyclic compounds with significant structural complexity and functionality from relatively simple starting materials.

In addition to substituent variations on the appendant nitrogen atom (and on the terminus of the alkyne **486**), the effect of different tether lengths was

investigated. The substrate **485b** ($n = 2$) was found to undergo thermolysis at an elevated temperature (by heating in xylene) to give the predicted cycloadduct **487b** in reasonable yield (Scheme 125).

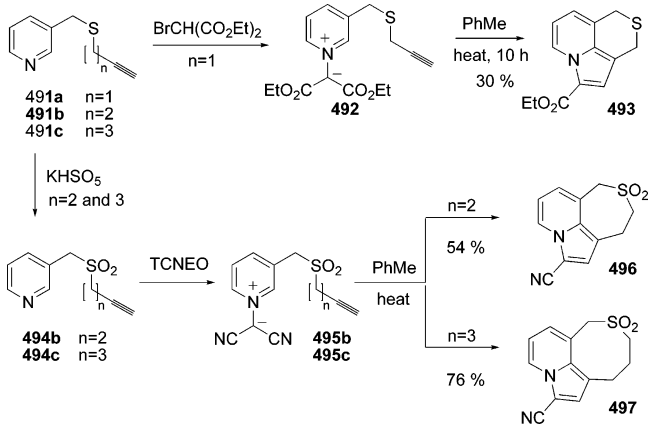
Using the same methodology, Seitz and Tegethoff were able to synthesize the more complex tetracyclic indolizines **490** simply by incorporating a pyrrolidine as part of the dipolarophile tether (Scheme 126).[188] Thus, the nicotinamide derivatives **488** were treated with TCNEO to give the dicyanomethylides **489**, which then underwent cycloaddition by thermolysis to form the annulated indolizines **490** in good yields. As was found earlier by Noguchi and co-workers, the length of the tether could be extended without detracting significantly from the yields of the larger-ringed cycloaddition products. However, as length of the tether increased, so did the time it took to complete the cycloaddition reaction. The synthesis of an indolizine containing an eight-membered ring ($n = 3$) by heating in toluene required 10 days for completion.

Scheme 126



Heteroannulated indolizines containing heteroatoms other than nitrogen may also be prepared using this chemistry. Treating the sulfide **491a** with diethyl bromomalonate gave the pyridinium ylide **492**, which underwent cycloaddition on heating under reflux in toluene to form the indolizine **493** in 30% yield (Scheme 127).[189] The homologous sulfides **491b** and **491c** were oxidized to their corresponding sulfones

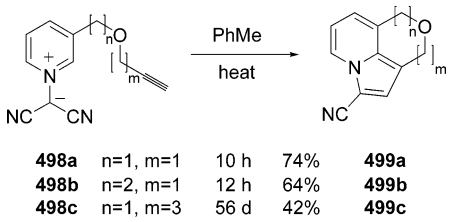
Scheme 127



494b and **494c**, which were then converted to the pyridinium dicyanomethylides **495b** and **495c** with TCNEO. Once again, cycloaddition was instigated on heating at reflux in toluene to give the cyclic sulfone-containing indolizines **496** and **497** in good yields.

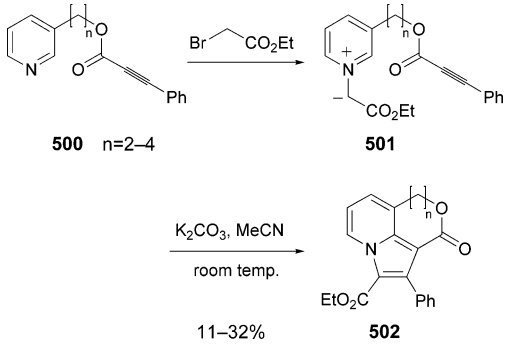
The pyridinium dicyanomethylides **498**, which contain various alkynyl-containing side chains, undergo intramolecular 1,3-dipolar cycloaddition on heating in toluene to form novel annulated indolizines **499**.[190] Indolizines containing six-, seven-, or eight-membered rings were synthesized in moderate to excellent yields, the eight-membered variant **499c** requiring 8 weeks to achieve 42% conversion (Scheme 128).

Scheme 128



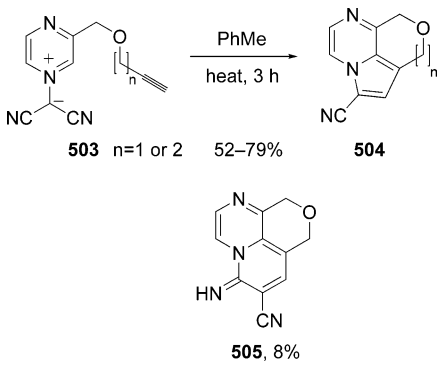
Indolizines annulated with lactones have been synthesized by Miki and co-workers in a fashion similar to that shown above.[191] *N*-Quaternization of the pyridines **500** with ethyl bromoacetate gave the pyridinium ylides **501** in almost quantitative yields (Scheme 129). Intramolecular cycloaddition of these ylides using potassium carbonate in acetonitrile at room temperature gave the annulated indolizines **502** in low yields. Nevertheless, it is worth mentioning that this chemistry provides seven-, eight-, or nine-membered lactones, formed by intramolecular cycloaddition onto appropriate substituted alkynes, using relatively mild reaction conditions.

Scheme 129



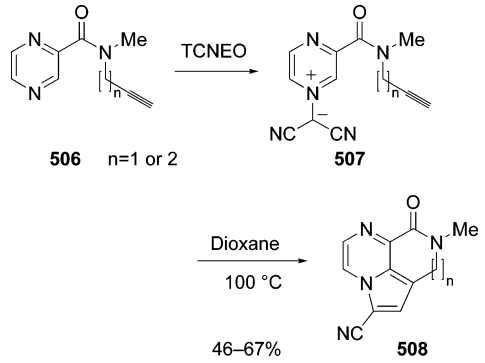
Later, the scope of this work was extended by Seitz and co-workers to include intramolecular cycloaddition reactions of alkynyl-substituted pyrazines to form 7-aza-indolizines.[192] In the same way as the 3-substituted pyridines, the pyrazinium dicyanomethylide salts **503** were prepared by reaction of TCNEO with the corresponding 3-substituted pyrazines (Scheme 130). The 7-aza-indolizine **504** ($n = 1$) was isolated as colorless crystals in 52% yield together with a red byproduct found to be the azaquinolizine **505**. The indolizine containing the seven-membered ring **504** ($n = 2$) was formed in 79% yield.

Scheme 130



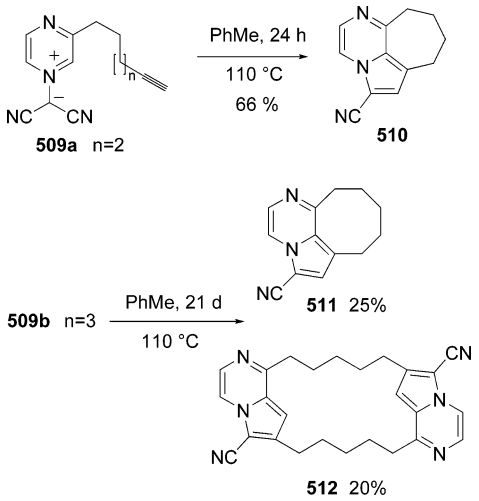
Azaindolizines annulated with other tethers have also been prepared in a similar way. Treatment of the 3-substituted pyrazines **506** with TCNEO gave the dicyanomethylides **507**, which then underwent cycloaddition in dioxane at 100 °C to give the aza-indolizines **508** in moderate to good yields (Scheme 131).

Scheme 131



Two examples of aza-indolizines annulated with carbocycles were prepared using this methodology. The pyrazinium dicyanomethylide **509a** reacted in an intramolecular fashion over a 24 h period on heating under reflux in toluene to give the aza-indolizine **510**, containing a seven-membered ring, in good yield (Scheme 132). When the pyrazinium precursor **509b** was subjected to the same reaction conditions, the corresponding aza-indolizine **511** was

Scheme 132

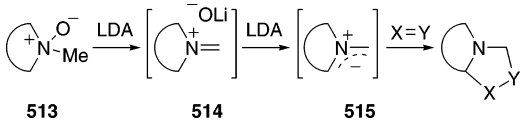


formed in only 25% yield, even after 3 weeks at reflux. A second product was isolated from the reaction mixture, and its analytical data indicated that the dimeric azaindolizine **512** had been formed, presumably by an end-to-end intermolecular 1,3-dipolar cycloaddition reaction. A five-atom tether was thus adjudged to be the limit at which a completely intramolecular cycloaddition takes place for these types of systems.

6. Other Methods of Ylide Formation

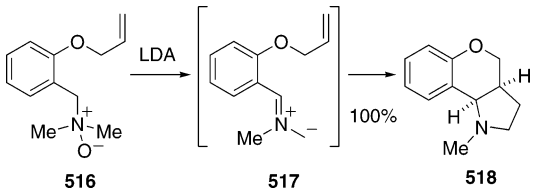
The examples described in sections 2−5 above represent the most common methods to generate the required azomethine ylide. There are, however some limitations to the variety of substitution patterns that can be used in these transformations and a selection of other methods have been reported that expand the scope of this intramolecular cycloaddition chemistry. One such method involves the treatment of a tertiary amine *N*-oxide with a strong base such as lithium diisopropylamide (LDA). The mechanism of ylide generation is thought to proceed by deoxygenation of the *N*-oxide **513** to form the iminium salt **514**, which then reacts with a second equivalent of base to form the azomethine ylide **515** and lithium oxide (Scheme 133). The ylide is then able to react with dipolarophiles in the usual way.[193]

Scheme 133



Although intermolecular reactions of azomethine ylides derived from tertiary amine *N*-oxides with dipolarophiles are reasonably well-known, relatively few examples of the intramolecular process have been described. Roussi has shown that the ylide **517**, prepared by slow addition of the *N*-oxide **516** to LDA at low temperature, underwent intramolecular cycloaddition onto the double bond in quantitative yield and in a stereoselective manner to give the cis-fused tricyclic compound **518** (Scheme 134).[193]

Scheme 134



The scope of the reaction was investigated by introducing a methyl substituent on the double bond and by increasing the chain length of the tether. The results of these investigations are shown in Scheme 135 and Table 12.

The effect of substitution on the alkene (R = Me) resulted in a reduced yield of the cycloadduct **520a** compared with the yield of the unsubstituted analogue **518** (Scheme 134). In addition to the desired product **520a**, the dimer **521a** was isolated in low yield as a mixture of cis and trans isomers (cis/trans

Scheme 135

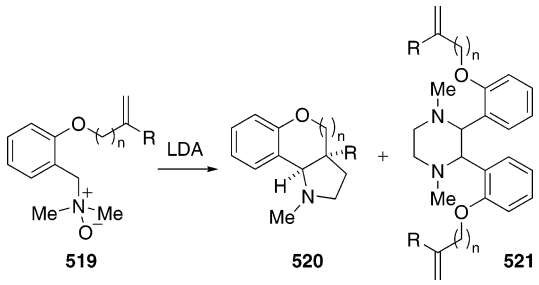


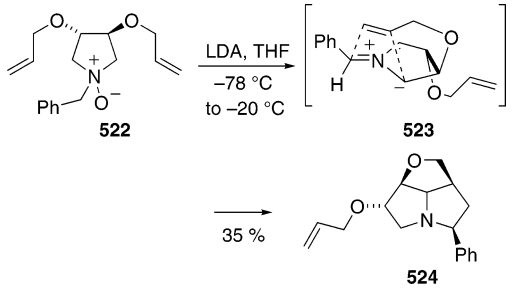
Table 12. Cycloaddition from the *N*-Oxides 519a−c

n	R	519	temp (°C)	yield 520 (%)	yield 521 (%)
1	Me	**a**	−78	13	11
1	Me	**a**	0	44	30
2	H	**b**	−78	6	28
2	H	**b**	0	48	
2	H	**b**	25	30	
3	H	**c**	0		10

ratio 1:1.6). Raising the temperature at which the *N*-oxide **519a** reacted with LDA enhanced the yield of the cycloadduct **520a** (and the yield of the dimer **521a**). Increasing the chain length of the dipolarophile tether served to slow the rate of cycloaddition to the extent that only 6% of the cycloadduct **520b** was obtained at −78 °C (cis/trans ratio 1:16), the dimer **521b** being the major product of the reaction. However, raising the temperature of the reaction increased the yield of the cycloadduct **520b** (cis/trans ratios at 0 and at 25 °C were 1:7 and 1:5, respectively) while suppressing formation of the dimer **521c**. Extending the chain length beyond $n = 2$ gave only dimeric products.

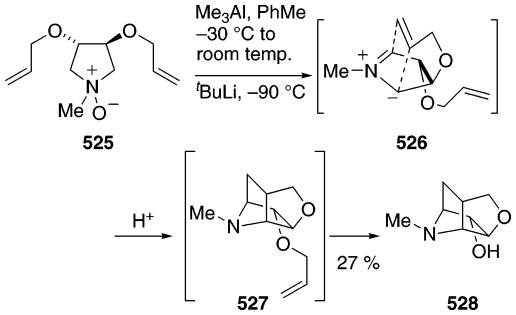
In a later publication, Takano and co-workers described how the C_2-symmetric pyrrolidine **522** underwent ylide formation and intramolecular cycloaddition to give the tricyclic amine **524** in 35% yield as a single stereoisomer (Scheme 136).[194] The ylide **523** was thought to adopt the conformation shown, in which maximum separation of the phenyl group and the incoming dipolarophile was possible, thus minimizing steric interactions of the two groups.

Scheme 136



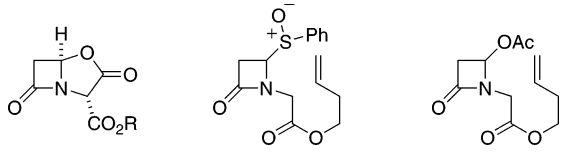
The related methylamine *N*-oxide **525** was subjected to the same conditions as the benzylamine analogue **522**, but no cycloadducts were detected in the reaction mixture. Other, more forcing reaction conditions were assayed, including stronger bases and elevated reaction temperatures, but without success. Only when trimethylaluminum was added to the reaction mixture prior to treatment with base were any cycloaddition products observed (Scheme 137). The construction of the cycloadduct **528** (as confirmed by ^{1}H NMR spectroscopic analysis) inferred that the ylide **526** was formed and underwent cycloaddition to form the tricyclic compound **527**. Subsequent loss of the *O*-allyl group gave the alcohol **528** as the only isolable product.

Scheme 137



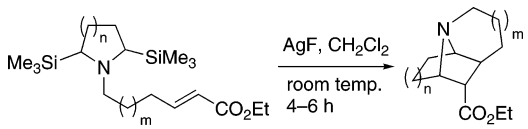
Azomethine ylides have been generated from oxazolidinones, typically formed by addition of an α-amino acid to an aldehyde (see section 2.2). The fused bicyclic oxazolidinones **529** (Chart 21) can be prepared from clavulanic acid and are known to provide an intermediate azomethine ylide on heating, which can be trapped intermolecularly.[195] Attempts to promote the intramolecular cycloaddition reaction using the related β-lactam **530** were unsuccessful.[196] The β-lactam **530** was heated in acetic anhydride to allow *O*-acylation and formation of the required iminium ion; however, only the acetate **531** was isolated from the reaction mixture.

Chart 21



A useful method that allows the formation of "nonstabilized" ylides involves desilylation of an α-amino organosilane.[197,198] Some examples of this approach have been given earlier (see Schemes 63, 68, and 69). An azomethine ylide was proposed as the intermediate in the formation of the cycloadducts **533** by double desilylation of the bis(trimethylsilyl)-pyrrolidines **532** (Scheme 138).[199,200] The pyrrolidines **532** were added to a suspension of dried silver(I) fluoride in CH_2Cl_2 at room temperature, and on reaction, a silver mirror was formed on the surface of the reaction flask. After purification, the products **533** were characterized, and the stereochemistry was

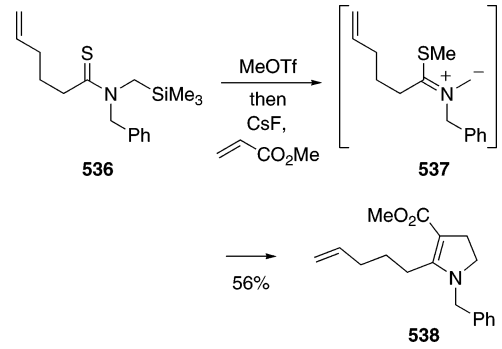
Scheme 138



assigned on the basis of ^{1}H NMR spectroscopy experiments. The chemistry was also amenable to a related aryl-fused substrate.

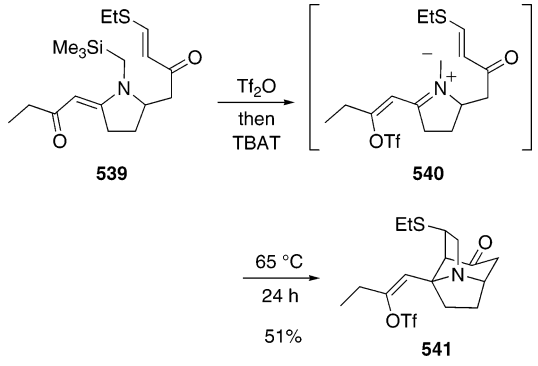
An alternative method to generate an azomethine ylide involves alkylation of an amide or thioamide followed by desilylation.[201,202] For example, treatment of the thioamide **536** with methyl trifluoromethane sulfonate and then addition of cesium fluoride and methyl acrylate gave the cycloadduct **538** via the intermediate azomethine ylide **537** (Scheme 139).[202] Notice that only the intermolecular cycloadduct **538** was isolated from this reaction, indicating that methyl acrylate is a better dipolarophile than the internal unactivated alkene. In the absence of methyl acrylate, no cycloadducts from intramolecular reaction were isolated.

Scheme 139



This type of methodology has significant potential as a useful, general method for ylide formation and has been applied successfully in an intramolecular cycloaddition reaction toward the synthesis of the core ring system of asparagamine A.[203] The vinylogous amide **539** was treated with triflic anhydride, followed by desilylation with tetrabutylammonium triphenyldifluorosilicate (TBAT), to give the intermediate azomethine ylide **540** (Scheme 140). Heating the azomethine ylide gave the cycloadduct **541** as a single regio- and stereoisomer. The structure of the cycloadduct **541** was confirmed by single-crystal X-ray diffraction and is consistent with the formation of the intermediate *Z*-enol triflate.

Scheme 140



7. Summary and Outlook

The dipolar cycloaddition reaction of azomethine ylides is one of the most important methods for the formation of pyrrolidines and pyrroles. By conducting the reaction in an intramolecular sense, one can produce two rings and up to four new chiral centers, making it a powerful method for organic synthesis. The regioselectivity in such reactions is almost always perfect due to constraints on the conformation of the molecule required for effective orbital overlap. The stereoselectivity is often high, typically with a preference for the endo transition state. The stereoselectivity is also dictated by the configuration of the azomethine ylide because the cycloaddition reaction occurs by a concerted process. The different methods for azomethine ylide generation and the substitution pattern can influence which ylide (S-, W- or U-shaped) is formed and hence which stereoisomer of the product is produced. However, interconversion of the ylides may occur at a rate that is faster than cycloaddition. Hence high levels of selectivity can be achieved in many cases even from mixtures of stereoisomeric starting materials with cycloaddition taking place via the lowest-energy transition state. Excellent levels of asymmetric induction have also been achieved in some cases, although the number of examples of asymmetric intramolecular cycloaddition is few at present.

The intramolecular dipolar cycloaddition reaction of azomethine ylides has progressed significantly since the first report nearly 30 years ago. The reaction has found use for the synthesis of a number of natural products, of core ring systems of natural products, and of potential medicinal compounds. The reaction is amenable to the solid phase and has allowed the production of libraries of compounds. A number of different methods exist for the formation of the azomethine ylide and hence a variety of functional groups can be installed in the bicyclic or polycyclic product. In general an anion-stabilizing group (often a carbonyl group) is used to help formation of the ylide, and there is scope for further development of methods that allow the formation of nonstabilized ylides. The reaction is often successful with unactivated alkenes or alkynes, and this is one of the advantages of this chemistry. As a result of the variety of substitution patterns, the good yields, and the high regio- and stereoselectivities, the reaction is likely to continue to attract widespread interest and use in synthetic organic chemistry.

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