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Asymmetric 1,3-Dipolar Cycloadditions of Acrylamides

Marie Kissane[a] and Anita R. Maguire[b]*

[a] *Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland.*

[b]*Department of Chemistry & School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland.*

**Corresponding author. Tel.: +353 21 4901693; fax: +353 21 4274097. E-mail: a.maguire@ucc.ie.*

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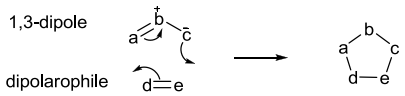
1.1 1,3-Dipolar cycloadditions

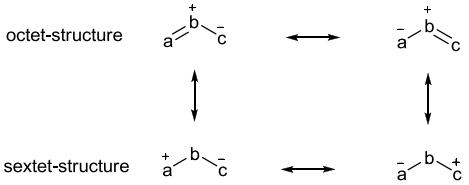
1,3-Dipolar cycloadditions offer a very useful method for the preparation of five-membered ring heterocycles.[1,2] This [4πs + 2πs] cycloaddition, thermally allowed by the Woodward-Hoffmann rules,[3] involves the reaction of a dipolarophile (*e.g.* alkenes, alkynes, carbonyls and nitriles) with a 1,3-dipolar compound (Scheme 1). The concept of 1,3-dipolar cycloadditions was initially suggested by Smith in 1938,[4] but it was only after the generalisation of the reaction by Huisgen in the 1960's that the reaction became widely applicable.[5] The research conducted in the area of 1,3-dipolar cycloadditions has been immense over the past 40 years,[6-45] and the reaction is now utilised in almost every area of chemistry, from materials chemistry[46] to drug discovery,[47] indicating its diversity.



Scheme 1

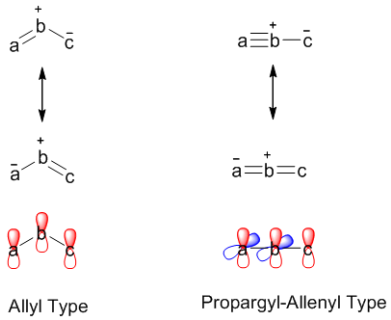
1.1.1 The 1,3-Dipole

The 1,3-dipole is a three-atom π-electron system, with four π-electrons delocalised over the three atoms. It can be represented by two octet-structures, in which the positive charge is located on the central atom and the negative charge is distributed over the two terminal atoms, and two sextet-structures, wherein two of the four π-electrons are localised at the central atom (Scheme 2). The sextet formulas contribute little to the electron distribution of the resonance hybrid but illustrate the ambivalence of the 1,3-dipole, which is key to understanding the mechanism, reactivity and regiochemistry of 1,3-dipolar cycloadditions.



Scheme 2

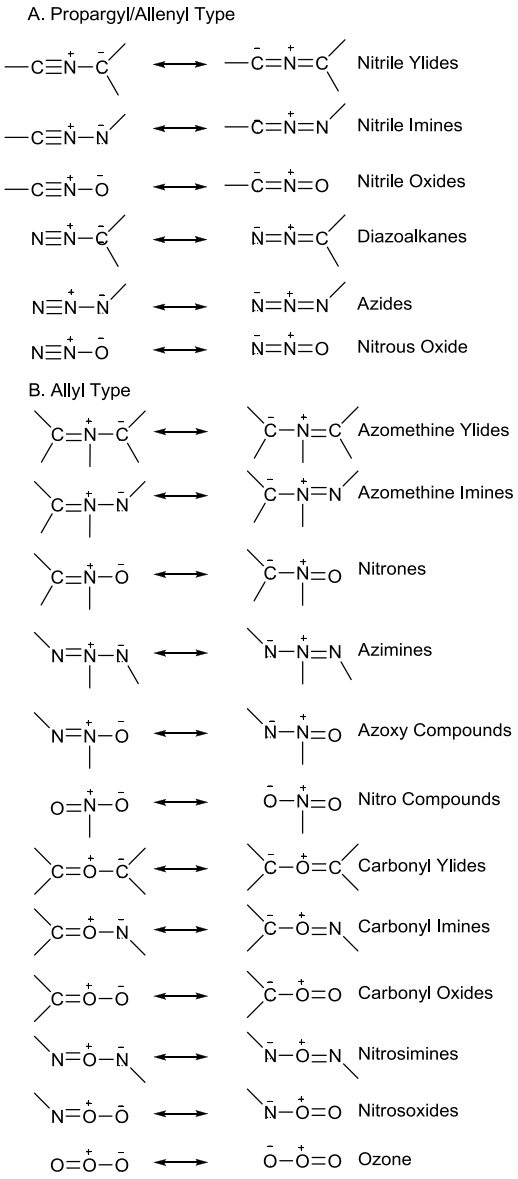
1,3-Dipoles can be classified into two types; the allyl anion type (so-called because it is isoelectronic with the allyl anion) and the propargyl/allenyl anion type. The allyl anion type is characterised by four electrons in three parallel p_Z orbitals perpendicular to the plane of the dipole. 1,3-Dipoles of the allyl type are bent, while the presence of a double bond orthogonal to the delocalized π-system in the propargyl/allenyl anion type confers linearity to the dipole (Scheme 3).



Scheme 3

For the allyl type dipoles, the central atom *b* may be a group V element (*e.g.* N or P) or a group VI element (*e.g.* O or S). For the propargyl/allenyl types, the role of *b* is restricted to group V elements, as only an atom of this group can bear a positive charge in the quartervalent state. By restricting *a* and *c* to second-row elements (C, N, O), six dipoles of the propargyl/allenyl type can be formed and twelve of the allyl type (Table 1).[5] The incorporation of higher-row elements such as sulfur and phosphorus into the 1,3-dipole is also possible, but such dipoles are much less widely used.

Table 1-Classification of 1,3-Dipoles Consisting of Carbon, Nitrogen and Oxygen Centres



1.1.2 The Dipolarophile

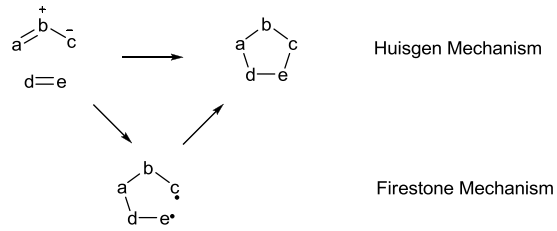
The 2π component of the 1,3-dipolar cycloaddition is commonly known as the dipolarophile. The dipolarophile can be almost any double or triple bond, containing functionality such as C≡C,[48] C=C,[49] C≡N,[50] C=N,[51] C=O,[5] and C=S.[52] The π-bond may be isolated, conjugated[53] or part of a cumulene[54] system. The structural variety of dipolarophiles makes 1,3-dipolar cycloadditions very valuable and versatile reactions in heterocyclic synthesis.

The presence of electron-withdrawing or electron-donating groups on the dipolarophile leads to enhanced reactivity with 1,3-dipoles (see Section 1.1.6), but a combination of both types of substituents in one molecule results in a dipolarophile of low reactivity. A second electron withdrawing substituent symmetrically added to the dipolarophile produces a

multiplicative effect on the rate, and the introduction of conjugation into the dipolarophile has a similar effect.[55]

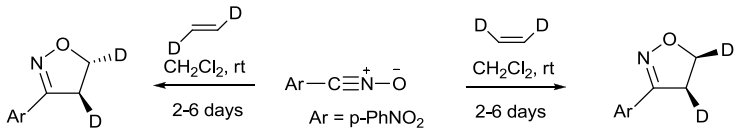
1.1.3 Mechanism of 1,3-Dipolar Cycloaddition

The mechanism of the 1,3-dipolar cycloaddition was subject to much debate during the 1960's. A synchronous, concerted mechanism was proposed by Huisgen, [5,56,57] whereas the stepwise, diradical pathway was favoured by Firestone (Scheme 4). [58-60]



Scheme 4

The strongest evidence in support of Huisgen's concerted mechanism is the strictly *cis*-nature of the additions, in that the geometrical relationships among the substituents on both the reactants are preserved in the product. Firestone, however, argued that in the intermediate diradical the energy barrier for rotation around the single bond is greater than the activation energy for ring closure, which would also explain the *cis*-stereospecificity. To aid in solving this debate, Houk and co-workers collaborated with Firestone in 1985[61] and studied the specificity of the 1,3-dipolar cycloaddition of *p*-nitrobenzonitrile oxide to *cis*- and *trans*-dideuterioethylene (Scheme 5). Reaction of the benzonitrile oxide **1** with *cis*-dideuterioethylene **2** yielded the *cis* adduct **3** exclusively. As rotation about single bonds to deuterated primary radical centres in diradicals is very fast relative to cyclisation, formation of both *cis*- and *trans*-adducts would be expected if a diradical intermediate were involved. Consistent results were obtained for *trans*-dideuterioethylene.



1 **3**

Scheme 5

At present, the most widely accepted view is of an asynchronous concerted process in which the formation of one of the new σ-bonds is more advanced than the other. The cycloadditions can be represented as going through a transition state in which the 4π-electron component of the dipole interacts with the 2π-electron component of the dipolarophile (Figure 1).

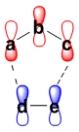


Figure 1

1.1.4 Regioselectivity of 1,3-Dipolar Cycloaddition

The regioselectivity of 1,3-dipolar cycloadditions can be rationalised by frontier orbital theory, since the transition state is controlled by the frontier orbital coefficients.[62] Sustmann has classified 1,3-dipolar cycloadditions into three types, designated Types I-III, depending on the nature of the substituents on the dipole and dipolarophile.[55] In Type I, the LUMO of the dipolarophile can interact with the HOMO of the dipole (common for electron-deficient dipolarophiles). In Type III, the HOMO of the dipolarophile can interact with the LUMO of the dipole (common for electron-rich dipolarophiles), and in Type II the frontier orbital energies of the dipole and dipolarophile are very similar and a combination of both modes of interaction can occur (Figure 2).

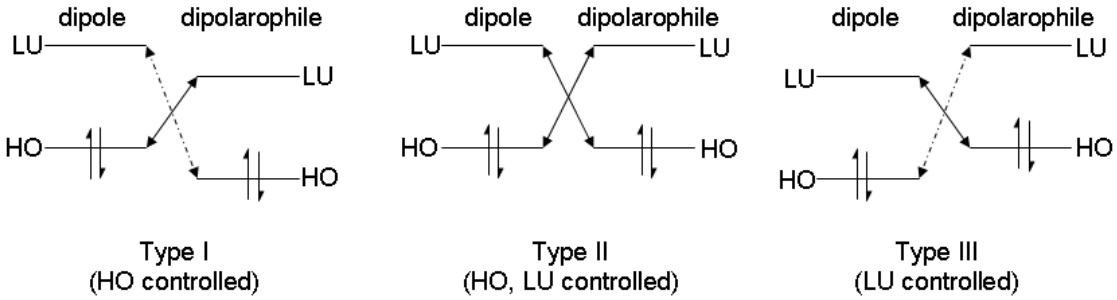


Figure 2-Sustmann's classification of 1,3-dipolar cycloadditions

Once the dominant frontier molecular orbital interaction has been identified, the most favourable direction of combination is then that in which the two terminal atoms with the largest orbital coefficients interact. This is depicted in Figure 3 in which transition state A is more stable than transition state B.

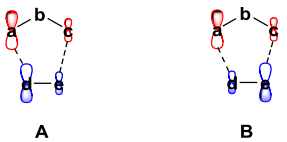


Figure 3

The frontier orbital coefficients for a large number of dipolarophiles and dipoles have been calculated, and these can be used to explain the observed regioselectivities for a range of

1,3-dipolar cycloadditions.[62,63] The effects of the substituents on the shapes of the frontier orbitals of dipolarophiles has been derived by Houk, and are depicted in Figure 4.[63]

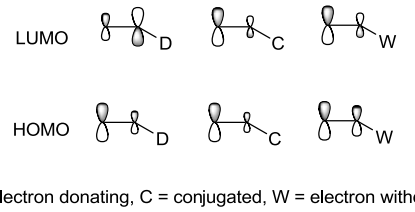
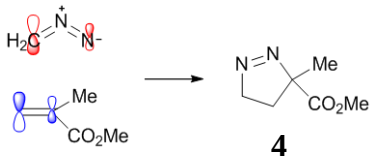


Figure 4

For example, in the addition of diazomethane to methyl methacrylate (a Type I interaction), the regioisomer **4** is predicted to form, which agrees with experimental data (Scheme 6).[64]



Scheme 6

1.1.5 Stereoselectivity

In addition to being regioselective, 1,3-dipolar cycloadditions are also highly stereoselective, with the stereochemistry of the original dipolarophile retained in the adduct. This is a consequence of the concerted mechanism of the reaction. Provided that the cycloaddition reaction is significantly faster than the isomerisation of the dipole by rotation, then the addition is also stereoselective with respect to the dipole. This is particularly important for azomethine ylides and carbonyl ylides, which are prone to isomerisation.[65]

When two chiral centres are formed during the cycloaddition, one arising from the dipole and one arising from the dipolarophile, diastereomeric products (*cis*- and *trans*-) may be produced *via endo* and *exo* transition states (Figure 5). Secondary orbital interactions have been used to explain the stereoselectivity of a large number of 1,3-dipolar cycloadditions. The extent to which each diastereomer forms depends on attractive π-orbital overlap of unsaturated substituents (favouring an *endo* transition state) and repulsive van der Waals steric interactions (favouring an *exo* transition state), with a mixture of diastereomers obtained in most instances. However, the *endo*/*exo* selectivity is more likely due to a combination of effects, including solvent effects, steric interactions, hydrogen bonds and electrostatic forces.[66]

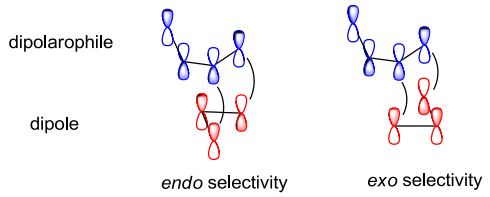
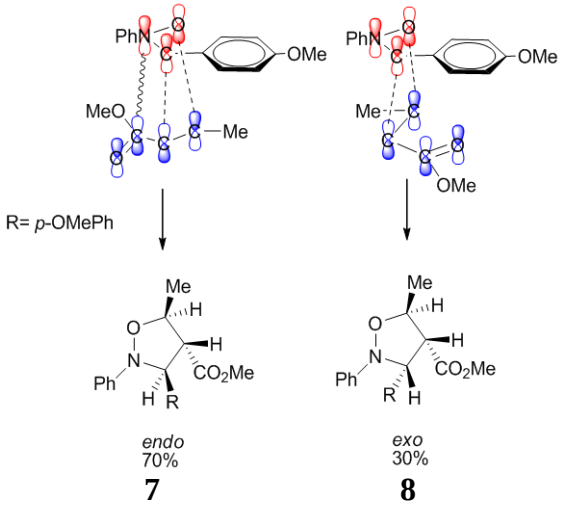


Figure 5

This was clearly demonstrated by Joucla *et al.* in his study of the reaction of *C*-*p*-methoxyphenyl-*N*-phenylnitrone **5** with methyl crotonate **6**.[67-69] A diastereomeric ratio of 70:30 (**7***endo*: **8***exo*) was observed, with the *endo*-isomer favoured due to the stabilising interaction of the nitrogen *p* orbital with the *p* orbital of the carbonyl carbon (Scheme 7).



Scheme 7

Furthermore, if the dipole or dipolarophile bears a chiral auxiliary or if a chiral catalyst is used, then non-racemic cycloadducts can be produced (see Section 1.2).[6,70]

1.1.6 Reactivity

The reactivity of 1,3-dipoles towards various dipolarophiles varies immensely. As mentioned previously, the cycloaddition is dominated by the HOMO and the LUMO of the two reactants, and the smaller the energy difference between the HOMO and LUMO, the stronger the interaction. Electron-withdrawing substituents on either the dipole or dipolarophile lower the level of both the HOMO and LUMO, electron-donating groups raise the energy of both while conjugating groups raise the energy of the HOMO but lower the LUMO energy.[38] The presence of substituents can thus lead to an acceleration or deceleration in the reaction rate depending on whether the FMO energy gap increases or decreases.

Reactions will be favoured if one component is strongly electrophilic and the other is strongly nucleophilic. The reactivity of 1,3-dipoles towards electron rich and electron poor

dipolarophiles differs greatly; for example, ozone is an electrophilic 1,3-dipole, diazoalkanes are nucleophilic whereas phenyl azide is not particularly nucleophilic or electrophilic, and the reactivity is influenced by the electronic nature of the dipolarophile.

The presence of Lewis acids in the 1,3-dipolar cycloaddition can have a pronounced effect on the reactivity; Lewis acids can alter the orbital coefficients of the reacting atoms and the frontier orbitals of the two reactants and overall, the coordination of a Lewis acid leads to a decrease in the energy difference between the HOMO and LUMO and thus to an increase in the reactivity (Figure 6).

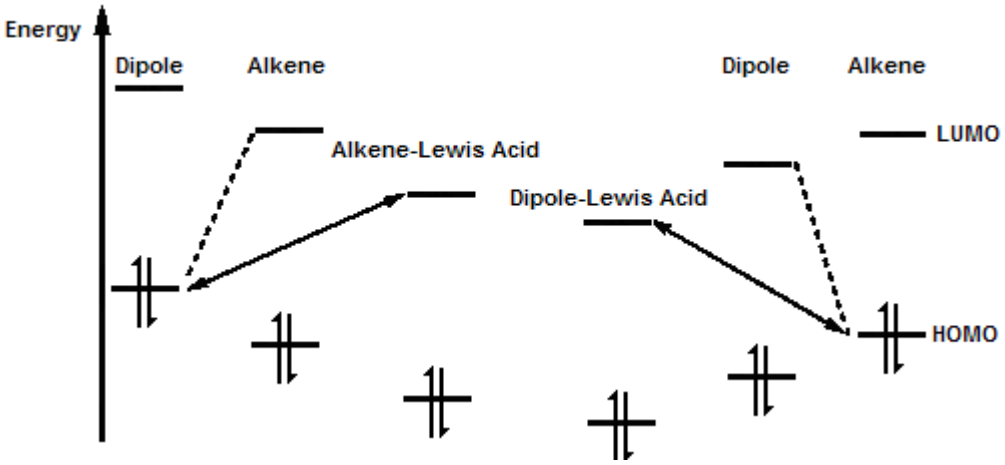
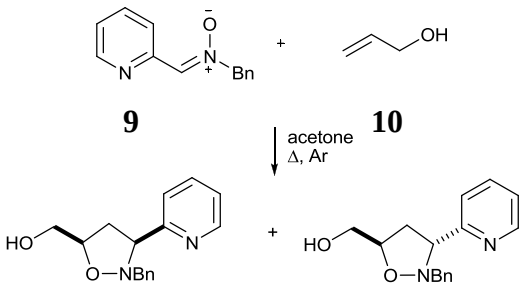


Figure 6

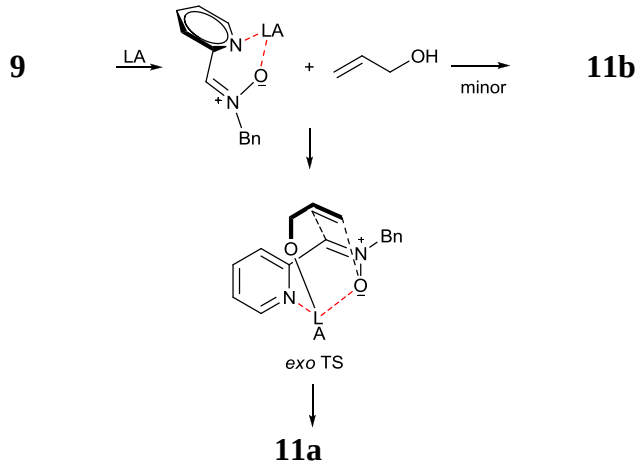
In 2003, Merino and co-workers examined the influence of Lewis acids on the cycloaddition between *N*-benzyl-*C*-(2-pyridyl)nitrone **9** and allylic alcohol **10**.[71] In the absence of catalyst, the reaction required heating at reflux for 7 days and the ratio of *cis*- and *trans*-isoxazolidine products **11a** and **11b** was 70:30. In the presence of one equivalent of AgOTf, [Ag($OClO_3$)(PPh_2Me)] or $Zn(OTf)_2$, the reaction rate approximately doubled and greatly improved *cis*-diastereoselectivity was observed (Scheme 8).



Lewis acid	time (days)	11a: 11b	yield (%)
None	7	70:30	90
AgOTf	3.5	>95:5	100
[Ag($OClO_3$)(PPh_2Me)]	5	>95:5	92
$Zn(OTf)_2$	3	>95:5	100

Scheme 8

The *endo* and *exo* transition states shown in Scheme 9 were proposed, and the preference for *cis*-diastereoselectivity was believed to be due to the substitution of one of the ligands of the Lewis acid by the alcohol group in the *exo* transition state. Such substitution is not feasible in the *endo* transition state.



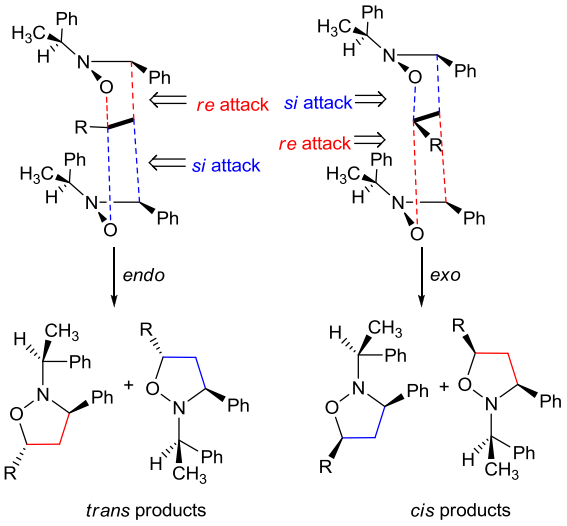
Scheme 9

Like the mechanistically related Diels Alder cycloaddition, the choice of solvent has very little influence on the rate of the 1,3-dipolar cycloaddition. According to quantum mechanical calculations, concerted cycloadditions have early transition states, and this is the primary reason why such a small solvent effect is usually observed.[7]

1.2 Asymmetric 1,3-Dipolar Cycloadditions

As up to four stereocentres can be introduced in a stereoselective manner in a single step, much attention has been devoted in recent years to the use of asymmetric 1,3-dipolar cycloadditions for the preparation of enantiomerically pure five-membered ring heterocycles.[6,10,14-16,19] Control of the diastereo- and enantioselectivity in the addition step is the major challenge in asymmetric 1,3-dipolar cycloadditions. It is possible to control the diastereoselectivity by choosing the appropriate substrates or using a metal complex acting as a catalyst, and the enantioselectivity can be controlled by either choosing a chiral 1,3-dipole, a chiral dipolarophile or a chiral catalyst.

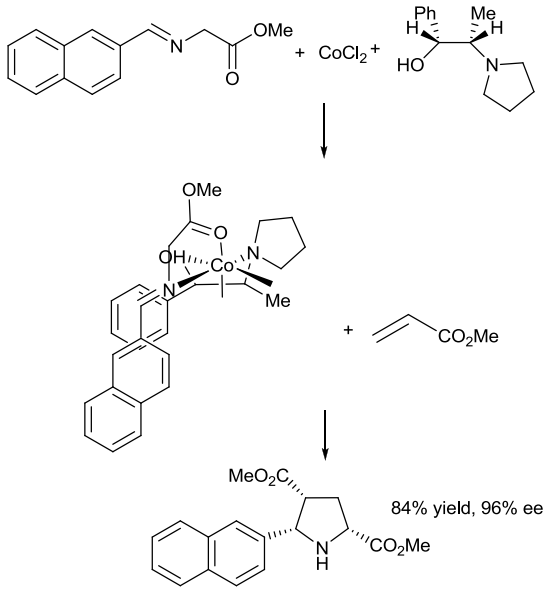
An early example of the use of chiral dipoles was described by Belzecki and Panfil in 1977.[72,73] The cycloaddition of chiral nitrones to monosubstituted and disubstituted alkenes led to four non-racemic isoxazolidines as two pairs of diastereomers arising from *endo* and *exo* addition to either the *re* or *si* face of the alkene, with preference for the formation of the *cis*-diastereomers resulting from *exo* attack (Scheme 10).



dipolarophile	*cis*	*trans*	*cis:trans*
$PhCH=CH_2$	76:11	8:5	87:13
$CH_2=CHCO_2Me$	40:24	29:7	64:36
$CH_2=C(CH_3)CO_2Me$	62:20	18:0	82:18

Scheme 10

One of the first examples of the employment of chiral catalysts in a 1,3-dipolar cycloaddition was reported by Grigg *et al.* in 1991.[74] In the cycloaddition of azomethine ylides to methyl acrylate, the use of Mn(II) or Co(II) salts in combination with a chiral ligand led to the attainment of enantiomeric excesses of up to 96% (Scheme 11). The pre-transition state chelate depicted in Scheme 11 provides effective shielding of one face of the dipole.



Scheme 11

Most of the reported studies on the control of the stereoselectivity by use of chiral dipolarophiles concern the use of α,β-unsaturated carbonyl compounds, and in particular acrylates.[75-82] However, in cycloadditions with chiral acrylates, in addition to controlling the direction of attack of the 1,3-dipole, the rotameric preference of the acrylate must be controlled to achieve high levels of diastereoselectivity – the acrylate can exist in the s-*cis* or s-*trans* conformation as depicted in Figure 7. This is often controlled by the addition of Lewis acids,[82] but is not always feasible [for example in 1,3-dipolar cycloadditions with nitrile oxides (see Section 1.2.1.3)].

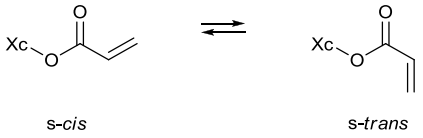


Figure 7

The use of chiral tertiary acrylamides provides a solution to the rotamer problem encountered with esters, as the planar s-*trans* conformation is disfavored.[83] However, rotation about the C-N bond is possible leading to two low-energy s-*cis* conformers (Figure 8).

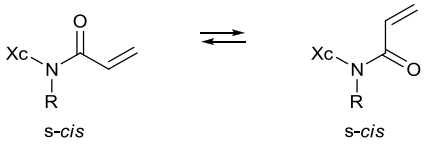
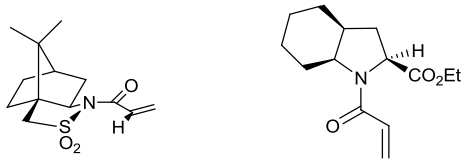


Figure 8

The development of chiral tertiary acrylamides containing nitrogen heterocycles such as **12** and **13** overcomes this problem.[83,84]

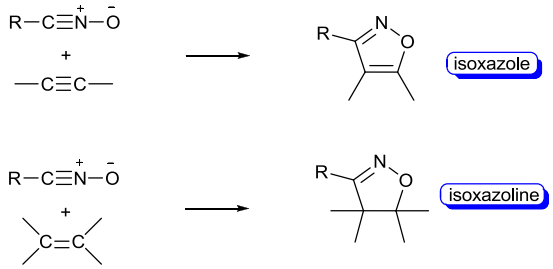


12 **13**

This review focuses on the asymmetric 1,3-dipolar cycloadditions of acrylamides, with particular emphasis on the rationale for the observed stereocontrol. The use of chiral acrylamides as dipolarophiles can lead to high levels of stereocontrol, due to conformational constraint in the acrylamides. Employment of chiral tertiary acrylamides containing nitrogen heterocycles is particularly effective at controlling the stereoselectivity of the process, as rotation around the C-N bond is disfavoured. The application of the cycloadducts derived from the 1,3-dipolar cycloadditions in natural product synthesis will also be highlighted. Several excellent reviews on asymmetric 1,3-dipolar cycloadditions have been published, however they have described cycloadditions with a range of dipolarophiles.[6,10,14-16]

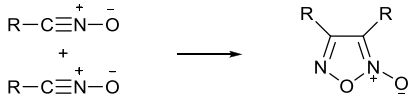
1.2.1 Cycloadditions with Nitrile Oxides

Nitrile oxides are highly reactive 1,3-dipoles of the propargyl/allenyl type which undergo cycloadditions with a variety of dipolarophiles to form isoxazole or isoxazoline cycloadducts (Scheme 12). As nitrile oxides have both nucleophilic and electrophilic character, their reactivity towards dipolarophiles is increased by either electron-withdrawing or electron-donating substituents on the dipolarophile.



Scheme 12

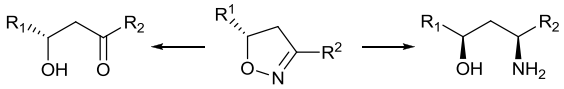
Nitrile oxides are extremely reactive, and readily undergo dimerisation to form the corresponding furoxan (Scheme 13). The rate of this dimerisation is exceptionally fast for lower aliphatic nitrile oxides, with acetonitrile oxide dimerising in less than one minute, whereas the half-life of most aromatic nitrile oxides at room temperature is several hours.[8,85]



Scheme 13

This dimerisation issue can be dealt with in two ways. The employment of sterically hindered nitrile oxides, such as 2,4,6-trimethylbenzonitrile oxide, blocks the dimerisation and nitrile oxides of this nature have unlimited stability.[86] The *in situ* generation of the nitrile oxide in the presence of the dipolarophile also overcomes this problem, provided the cycloaddition competes kinetically with the dimerisation. The nitrile oxide is generated very slowly so that a low stationary concentration is maintained.[5]

The 1,3-dipolar cycloaddition of nitrile oxides is a very versatile reaction for the construction of stereoselective compounds. The isoxazoline ring can be readily cleaved, allowing stereocontrolled access to a variety of acyclic compounds, including γ-hydroxyketones and γ-amino alcohols (Scheme 14).

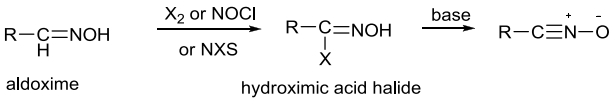


Scheme 14

1.2.1.1 Synthesis of Nitrile Oxides

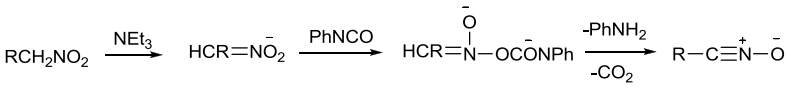
The most widely applicable methods for the preparation of nitrile oxides are the dehydrohalogenation of hydroximic acid halides and the dehydration of primary nitroparaffins.[8,87]

Hydroximic acid chlorides and bromides are most conveniently prepared from the corresponding aldoximes by reaction with halogens.[8] Use of milder reagents such as *N*-bromosuccinimide,[88] *N*-chlorosuccinimide[89] and nitrosyl chloride[90] have also been reported for this transformation, and these are particularly useful for aldoximes containing halogen sensitive groups. The use of the conventional halogenation reactions can be avoided by reaction of conjugated nitroalkenes with titanium tetrachloride.[91] Dehydrohalogenation is most commonly achieved by addition of one equivalent of a tertiary amine base (usually triethylamine) to a solution or suspension of the hydroximic acid halide in an inert organic solvent such as diethyl ether (Scheme 15). A range of aliphatic, aromatic and heterocyclic nitrile oxides have been prepared by this method.[8]



Scheme 15

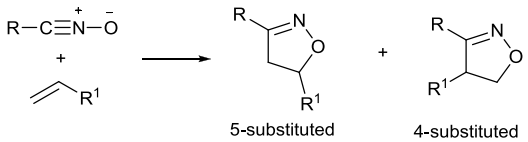
The dehydration of primary nitro compounds with phenylisocyanate in the presence of a catalytic amount of a tertiary base such as triethylamine, was first reported by Mukaiyama and Hoshino in 1960 (Scheme 16).[87] This method is particularly useful for the preparation of aliphatic nitrile oxides.[86]



Scheme 16

1.2.1.2 Regioselectivity

The 1,3-dipolar cycloaddition of a nitrile oxide and a monosubstituted alkene can yield two regioisomeric isoxazolines, either the 4-substituted or 5-substituted cycloadduct (Scheme 17), with the regioselectivity dependant upon electronic and steric effects.



Scheme 17

The cycloadditions of nitrile oxides with electron-rich and conjugated alkenes are dipole-LUMO controlled, with the carbon atom of the nitrile oxide attacking the terminal carbon of the alkene, resulting in exclusive formation of the 5-substituted isoxazolines (Figure 9).[37]

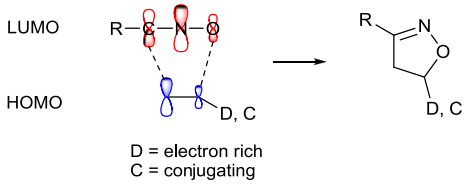


Figure 9

For electron-deficient dipolarophiles, both the dipole-HOMO and -LUMO interactions are significant and a mixture of regioisomers results (Figure 10). The 4-substituted isoxazoline is favoured when strongly electron-withdrawing substituents (such as the sulfono group) are present on the dipolarophile.

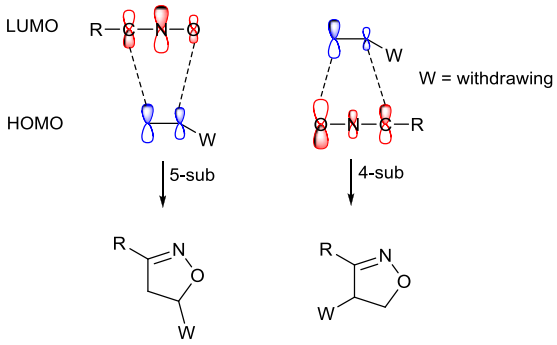


Figure 10

For 1,1-disubstituted or trisubstituted alkenes, there is a preference for the more substituted carbon to be located at the 5-position of the isoxazoline due to dipole-LUMO control of the cycloaddition, although the presence of strong electron-withdrawing groups give the 4-substituted product. Mixtures of regioisomers usually result from cycloaddition with 1,2-disubstituted alkenes.[9,86]

1.2.1.3 Asymmetric 1,3-Dipolar Cycloaddition of Nitrile Oxides

The employment of chiral nitrile oxides in the asymmetric 1,3-dipolar cycloaddition has not been widely reported; poor diastereoselectivity is achieved in most instances.[92,93] The linearity of the dipole and the distance between inducing and created stereocentres have been suggested as possible reasons for the low diastereoselectivity observed.[93] Asymmetric catalysis in the 1,3-dipolar cycloadditions of nitrile oxides by Lewis acids is also not commonly employed. The difficulties in controlling the stereoselectivity with metal complexes arise because the presence of base (such as triethylamine) used for the *in situ* generation of nitrile oxides may interfere with the metal catalyst. Also, nitrile oxides are strong Lewis bases (due to the high donor ability of the oxygen atom of the dipole) and their ready complexation with

Lewis acids leads to deactivation of the dipole.[94] As a result, in the asymmetric 1,3-dipolar cycloadditions of nitrile oxides, cycloaddition of achiral nitrile oxides to optically active dipolarophiles has attracted most interest. The chiral dipolarophiles include alkenes in which the centre of chirality is vicinal to the double bond - such as allylic alcohols[95] and chiral vinyl sulfoxides[96]- and alkenes in which the centre of chirality is two or more bonds away from the double bond. The latter include acrylates[97] and acrylamides.[83,84]

The employment of acrylamides, and in particular tertiary acrylamides with chiral auxiliaries incorporated, is a particularly attractive route (see Section 1.2), and the synthesis of isoxazolines with high optical purities has been achieved using this approach. The cycloadditions are dipole-LUMO controlled due to the conjugated functionality of the acrylamide (see Section 1.2.1.2) and thus highly regioselective cycloadducts are obtained. However, highly diastereoselective cycloadditions of nitrile oxides are extremely challenging; as the oxygen atom of the nitrile oxide attacks the substituted carbon of the alkene, the interaction between the incoming nitrile oxide and auxiliary is limited. The two atoms nearest the auxiliary (O and N) bear no substituents while the remote C bears a lone substituent that points away from the auxiliary (Figure 11).

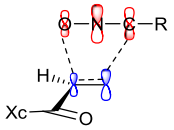
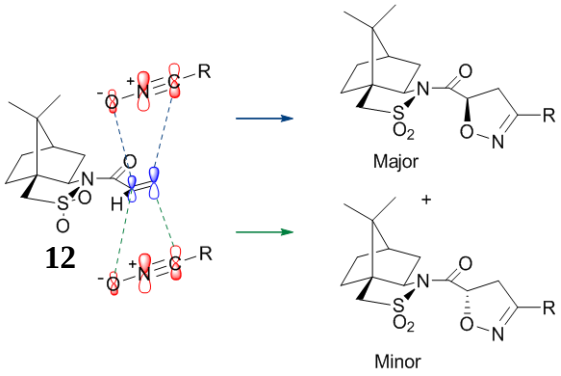
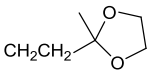


Figure 11

1.2.1.4 Asymmetric 1,3-Dipolar Cycloadditions of Nitrile Oxides and Acrylamides

The use of chiral acrylamide derivatives in cycloadditions with nitrile oxides was first explored by Curran in 1988.[83] Curran had earlier studied the cycloaddition of a range of chiral acrylates with nitrile oxides, with modest degrees of asymmetric induction (up to 56% de) achieved.[75] Using Oppolzer's chiral sultam derivative **12**, diastereoselectivities of up to 95:5 were obtained (Scheme 18). The preferred conformation of the acrylamide is s-*cis* in which the carbonyl group points away from the sultam oxygen. The major diastereomer then results from the preferential attack of the incoming dipole from the top-side of the dipolarophile. Curran hypothesised that this was due to the pseudoaxial S-O bond (which projects directly down from the plane of the acrylamide) sterically and electronically hindering attack of the dipole from the bottom-side of the dipolarophile.



R	Major:Minor
t-Bu	95:5
Ph	95:5
Me	90:10
Et	90:10
	88:12*

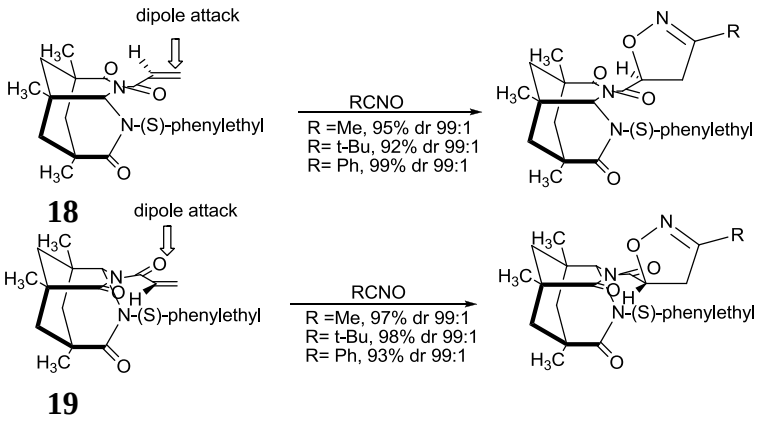
*This reaction was conducted in benzene; all others were conducted in hexane.

Scheme 18

The usefulness of this asymmetric nitrile oxide cycloaddition was illustrated by Curran in his total syntheses of (+)-hepialone **14**,[98] (–)-(1*R*,3*R*,5*S*)-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane **15** and (–)-(1*S*)-7,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane **16**.[99] These syntheses demonstrate that enantiomerically pure isoxazolines can be transformed to a variety of functional groups including β,γ-dihydroxy ketones, alcohols, 1,2 and 1,3-diols, 1,3,4-triols, 1,3-amino alcohols and 1,3,4-amino diols. The synthesis of (–)-pestalotin **17** from nitrile oxide cycloaddition with **12** was communicated in a later paper by Curran.[100]

14 **15** **16** **17**

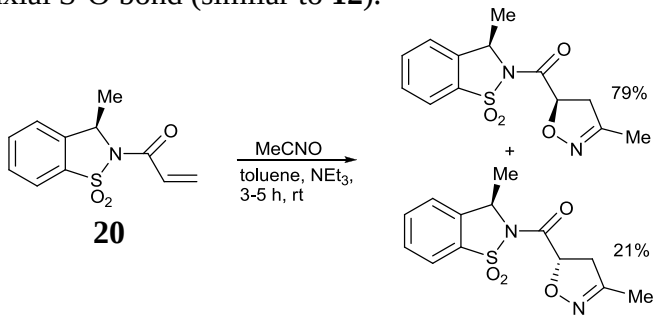
In 1989, Curran reported new *bis*-lactam chiral auxiliaries **18** and **19** based on Kemp's triacid,[101-103] with outstanding selectivities (99:1) achieved in the cycloadditions with nitrile oxides (Scheme 19).[104,105] The excellent face-shielding capabilities of **18** and **19** sterically shield attack of the dipole from the bottom-face of the alkene.



Scheme 19

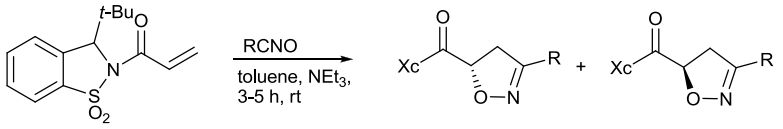
The diastereomeric acrylamides **18** and **19** were subjected to nitrile oxide cycloaddition with ethanenitrile oxide, 2,2-dimethylpropionitrile oxide and benzonitrile oxide and in each cycloaddition, the degree of asymmetric induction was sufficiently high that the quantity of the minor diastereomer was difficult to determine by spectroscopic methods.[104,105]

Oppolzer *et al.* have studied the addition of nitrile oxides to chiral *N*-acryloyl toluene-2,α-sultams.[106] The initial dipolarophile studied was the acryloyl derivative **20**. The degree of asymmetric induction was only moderate, with the isoxazoline cycloadducts isolated in a 79:21 diastereomeric ratio (Scheme 20). The major isomer resulted from preferential attack of the dipole to the top-face of the dipolarophile due to the electrostatic repulsion force between the dipole and the pseudoaxial S-O bond (similar to **12**).



Scheme 20

Replacement of the methyl group with a tertiary butyl group led to a dipolarophile which underwent highly selective nitrile oxide cycloadditions (Scheme 21). The resulting isoxazoline cycloadducts were easily cleaved with L-Selectride®.

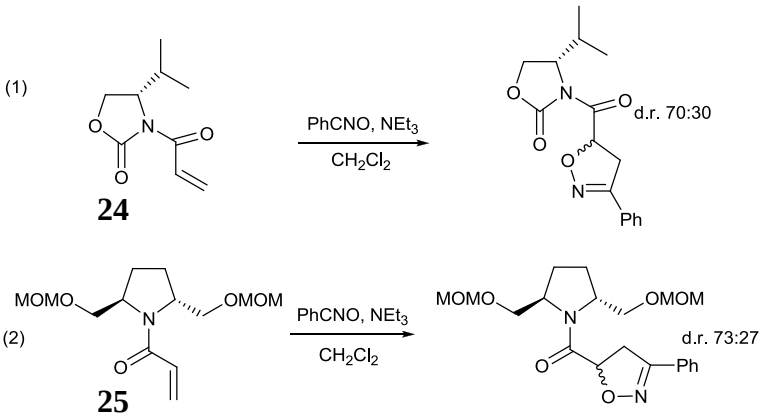


21 **22** **23**

N-acryloyl sultam	R	ratio 22: 23
(*R*)-**21**	*t*-Bu	98:2
(*R*)-**21**	Ph	95:5
(*R*)-**21**	Et	95:5
(*R*)-**21**	Me	96:4
(*S*)-**21**	*t*-Bu	2:98
(*S*)-**21**	Ph	3:97
(*S*)-**21**	CH_2Ot-Bu	4:96

Scheme 21

Kanemasa and co-workers have studied the reaction of Evans's chiral 2-oxazolidinone[107] **24** (eq. 1, Scheme 22) and the acrylamide derived from Katsuki's C_2-symmetric pyrrolidine[108] **25** (eq. 2, Scheme 22) with benzonitrile oxide. Moderate diastereoselectivity was achieved as the substituents on the auxiliaries are too far removed from the incoming dipole to cause significant face shielding.[109]



Scheme 22

As the asymmetric induction of **24** and **25** in the cycloadditions with nitrile oxides was not exceptional, Kanemasa *et al.* designed a series of oxazolidine and imidazolidine derived dipolarophiles based on conformationally controlled *N*-acryloyl derivatives of chiral heterocycles such as C_2-symmetric imidazolidine (X = NR, one of R_4 = R_5) and 4-chiral oxazolidines (X = O).[94,109,110] Considering the two conformations depicted in Figure 12, the *syn-E* conformer is much more stabilised than the *anti-E* conformer, in which there is steric congestion between the α-carbon of the vinyl substituent and the two alkyl substituents at the 2-position. The least hindered approach of the dipole will then occur from the side opposite to R_5 and such dipolarophiles were predicted to function as efficient chiral auxiliaries.

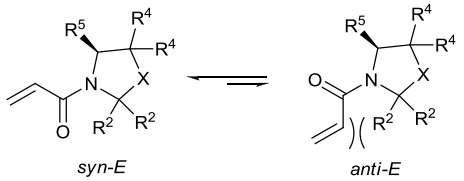
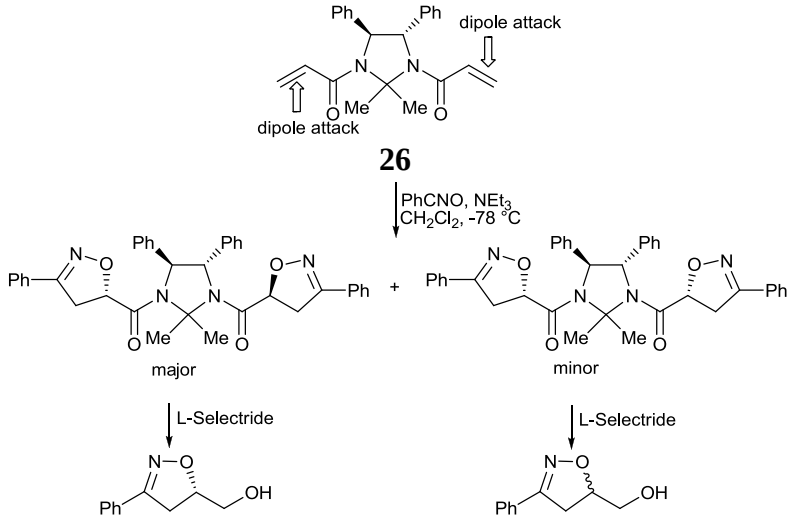


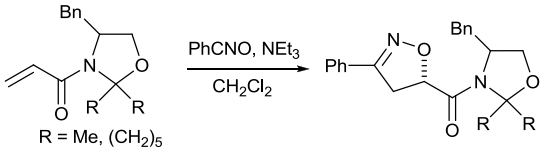
Figure 12

The optically pure imidazolidine bisacrylamide **26** was reacted with benzonitrile oxide at –78 °C to yield an 83:17 diastereomeric mixture of cycloadducts (Scheme 23). The major isomer was formed by benzonitrile attack of the alkene from the side opposite to the nearest phenyl substituent. Since the major diastereomer is symmetrical and the minor one is unsymmetrical, the total diastereoselectivity in this reaction was 91:9. Cleavage of the auxiliary was then accomplished by L-Selectride® reduction.[109]



Scheme 23

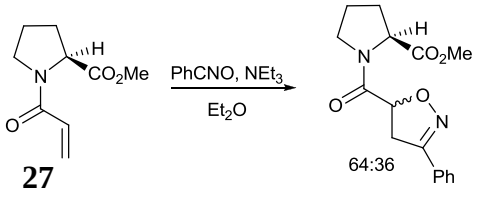
A range of 2,2-dialkyloxazolidines were also reacted with benzonitrile oxide, with effectively complete diastereoselectivities achieved when the oxazolidines outlined in Scheme 24 were employed. At the time of publication in 1992, these 2,2-dialkyloxazolidines were used as racemates and their optical resolution has not been subsequently reported.[110]



Scheme 24

Kim *et al.* have studied the nitrile oxide cycloaddition of chiral acrylamides derived from L-proline.[84] Employment of the auxiliary **27** led to disappointing diastereoselectivity (64:36)

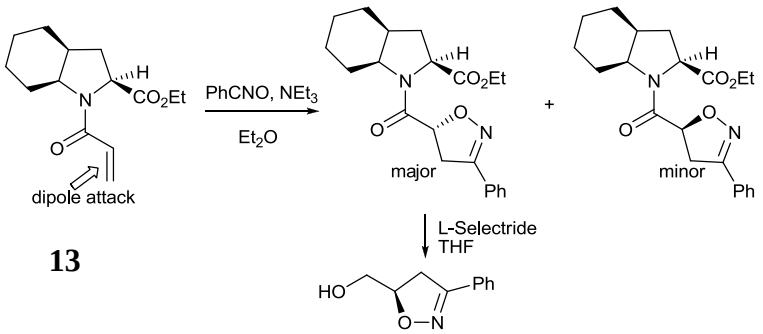
(Scheme 25), presumably due to insufficient face shielding of the alkene by the auxiliary and poor conformational control.



27

Scheme 25

Employment of acrylamides such as **13** with improved face-shielding substituents gave diastereoselectivities of up to 95:5 (Scheme 26). The major cycloadduct results from bottom-side (or *re*-face) attack of the incoming nitrile oxide, and was converted to isoxazoline **28** by reductive cleavage with L-Selectride®.[84]

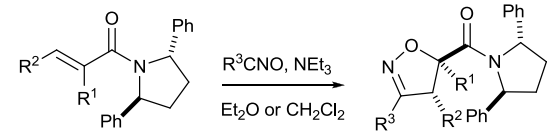


13

28

Scheme 26

In 2005, Lassaletta and co-workers reported the use of 2,5-*trans*-diphenylpyrrolidine as a suitable auxiliary in cycloadditions of acrylamides with nitrile oxides.[111] The cycloaddition of a number of diphenylpyrrolidine derivatives with a variety of nitrile oxides yielded cycloadducts with effectively complete regio- and diastereoselectivity (Scheme 27). Hydrolysis of the cycloadduct was then achieved by reaction with hydrochloric acid and acetic acid to yield the corresponding 4,5-dihydroisoxazole-5-carboxylic acids.



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

Scheme 27

The regioselectivity of the cycloaddition is believed to be due to the repulsive steric interactions between the R^3 group and the bulky 2,5-diphenylpyrrolidine substituent in the opposite regioisomer. The diastereoselectivity results from the shielding of the *Si* face of the alkene by the neighbouring phenyl group (Figure 13).[111]

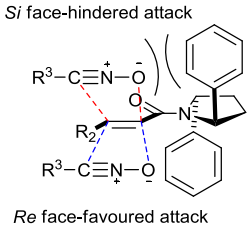
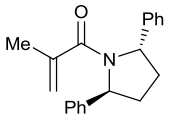


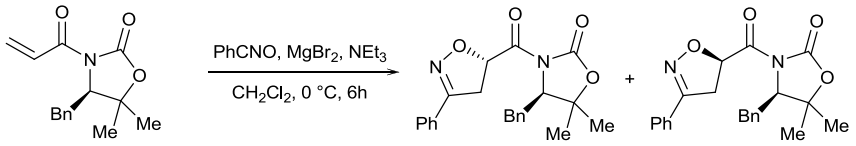
Figure 13

Lassaletta extended the scope of this methodology by investigating the cycloaddition of a range of nitrile oxides with the methylacrylamide **29**. Limited success was achieved; it was found that the cycloaddition is substrate-dependant, with complete regio- and stereoselectivity for aliphatic nitrile oxides, whereas complete loss of diastereoselectivity is observed for aromatic nitrile oxides. The high asymmetric induction in the cycloadditions of aliphatic nitrile oxides is believed to be due to the diastereofacial discrimination similar to that depicted in Figure 13.[111]



29

Though the activation of dipolarophiles by Lewis acids is very difficult in the presence of nitrile oxides, some catalytic approaches have been reported. The first successful Lewis acid mediated nitrile oxide cycloaddition employing acrylamide as dipolarophile was communicated by Yamamoto *et al.* in 2000.[112] The reaction of (*S*)-3-acryloyl-4-benzyl-5,5-dimethyl-2-oxazolidinone **30** with benzonitrile oxide was studied at 0 °C in a range of solvents in the absence and presence of Lewis acids. In dichloromethane, a 43:57 (**31:32**) mixture of diastereomeric cycloadducts was obtained without Lewis acid present (presumably due to insufficient conformational control), whereas a 96:4 (**31:32**) diastereomeric ratio was achieved when magnesium bromide was added (Scheme 28). The concentration was found to have a large effect on the outcome of the reaction, with much improved diastereoselectivities attained when the cycloaddition was performed at higher concentration.



30 **31** **32**

additive (equiv.)	concentration (M)	31: 32
None	0.17	43:57
ZnI_2 (1.2)	0.17	45:55
$MgBr_2$ (1.0)	0.083	71:29
$MgBr_2$ (0.5)	0.083	48:52
$Cu(OTf)_2$ (1.0)	0.083	51:49
$Ni(ClO)_4$ (1.0)	0.083	43:57
$Fe(ClO_4)_2$ (1.0)	0.083	45:55
Ti(*i*-OPr)$_4$ (1.0)	0.083	30:70
$MgBr_2$ (1.0)	0.25	96:4

Scheme 28

A dipolarophile-$MgBr_2$ complex is proposed, and the deactivation of the Lewis acid by coordination of the nitrile oxide is not believed to be important here. The acrylamide is thus held in the s-*cis* conformation as illustrated in Figure 14, and the benzyl group then shields the upper face from dipole attack. It is unclear why magnesium bromide is specifically favoured and why the concentration has such a large effect on the selectivity.

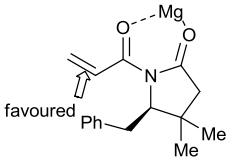
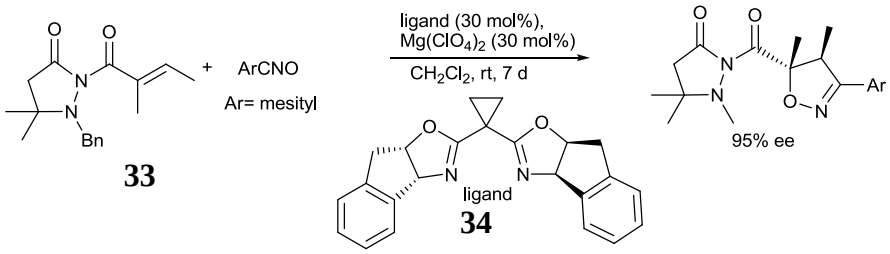


Figure 14

Sibi and co-workers have reported the Lewis acid catalysed enantioselective nitrile oxide cycloaddition with α,β-disubstituted acrylamides.[113,114] The best results were obtained by reacting the acrylamide **33** with 2,4,6-trimethylbenzonitrile oxide in the presence of $Mg(ClO_4)_2$ and the chiral bisoxazoline ligand **34** (Scheme 29).



33 **34**

Scheme 29

Sibi proposed the transition state depicted in Figure 15 to explain the absolute stereochemistry observed, with the ligand shielding the bottom face of the alkene from dipole attack.[113]

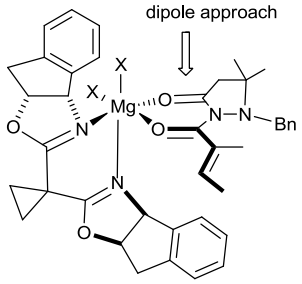
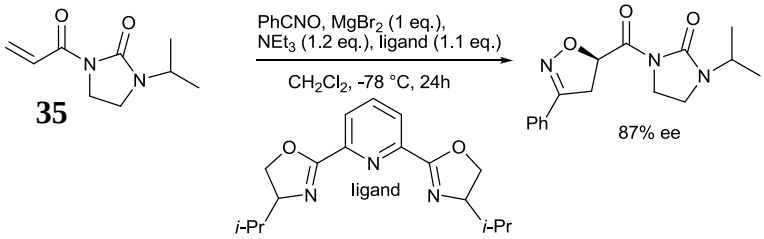


Figure 15

In 2007, Yamamoto *et al.* communicated the asymmetric 1,3-dipolar cycloaddition of benzonitrile oxide mediated by a chiral Lewis acid.[115] The cycloaddition of a number of acrylamide dipolarophiles bearing an oxazolidinone or imidazolidinone auxiliary with benzonitrile oxide in the presence of a pybox ligand and Mg^{2+} or Yb^{3+} salts were studied. Enantiomeric excesses of up to 87% were achieved when the acrylamide bearing the *N*-isopropylimidazolidinone moiety **35** was employed in the presence of the chiral Lewis acid derived from magnesium bromide and ip-pybox (Scheme 30).



Scheme 30

The geometry of the Mg(II)/ip-pybox complex was optimised by density functional theory calculations. The *si* face of the dipolarophile is less crowded than the *re* face due to the position of the isopropyl groups in the ip-pybox, and nitrile oxide attack from the *si* face is thus favoured (Figure 16).

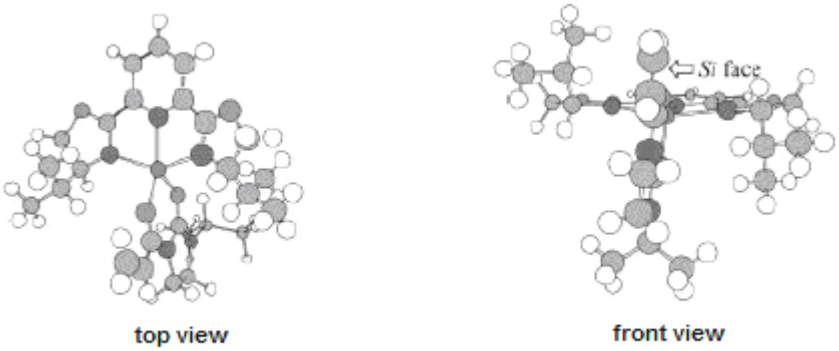
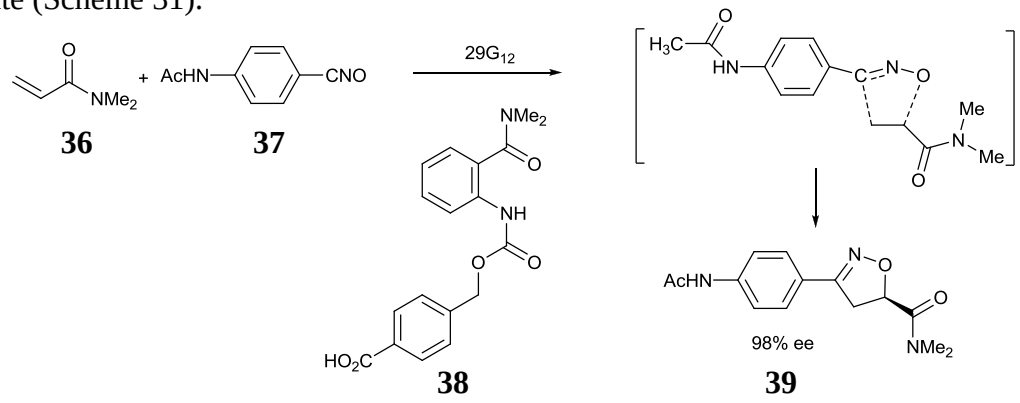


Figure 16-reproduced from reference [115]

The antibody-catalysed asymmetric 1,3-dipolar cycloaddition of nitrile oxides to simpler tertiary and secondary amides was reported by Wentworth and co-workers in 2000.[116] The 1,3-dipolar cycloaddition between *N*,*N*-dimethylacrylamide **36** and 4-acetamidobenzonitrile *N*-oxide **37** was catalysed by the murine monoclonal antibody 29G12 (which was elicited to hapten **38**) to generate the 5-acylisoxazoline **39** with excellent enantiomeric excess (98% ee) (Scheme 31).

Hapten **38** was designed upon the entropic trap theory; the translational entropy of the reaction is reduced by bringing the two substrates into the correct orientation for reaction within the antibody binding site. The planar aromatic core of **38** mimics the aromatic character of the transition state (Scheme 31).[116]



Scheme 31

The scope of the 29G12 antibody catalysed cycloaddition was communicated in 2005 by Wentworth *et al*.[117] Replacement of the *p*-acetamido group of the nitrile oxide with either a nitro group or hydrogen led to a loss of the catalytic activity, highlighting the specificity of the dipole substrate. However, a range of acrylamide derivatives can be tolerated, with enantiomeric excesses ranging from 71–98% ee (Table 2).

*Table 2-Enantioselectivity of 29G12 in reactions of 4-acetamidobenzonitrile N-oxide **36** with various acrylamides*

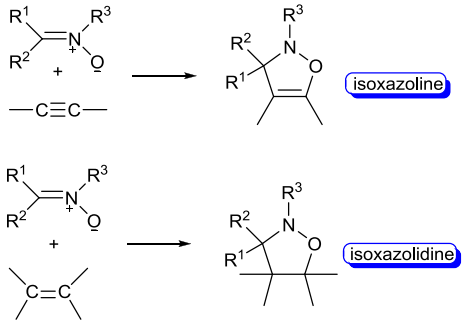
dipolarophile	**% ee**
N,*N*-dimethylacrylamide	98
N-*tert*-butylacrylamide	94
N-isopropylacrylamide	85
N-*sec*-butylacrylamide	97
N-phenylacrylamide	71

While excellent diastereomeric ratios were achieved with the chiral auxiliaries **18** and **19** based on Kemp's triacid (dr 99:1, Scheme 19) and the chiral auxiliaries derived from 2,5-trans-diphenylpyrrolidine (>99% de, Scheme 27), Oppolzer's chiral sultam derivative **12** is the most expedient dipolarophile; good to excellent diastereomeric ratios were achieved (up to 94:6) with

a wide range of nitrile oxides. In addition, the synthetic utility of **12** was demonstrated by its employment in the synthesis of a number of natural products.

1.2.2 Cycloadditions with Nitrones

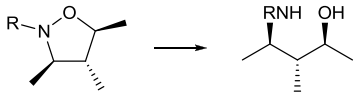
Nitrones are an important class of 1,3-dipole which undergo cycloadditions with alkenes and alkynes to yield isoxazolidines and isoxazolines respectively (Scheme 32). The presence of electron-withdrawing or electron-donating substituents on the dipolarophile or dipole leads to significant rate enhancement in the nitrone cycloaddition.



Scheme 32

In general, nitrones are rather stable compounds and thus do not require *in situ* generation, and are easy to handle in air at ambient temperature. Rearrangements can occur, however, under prolonged exposure to light.

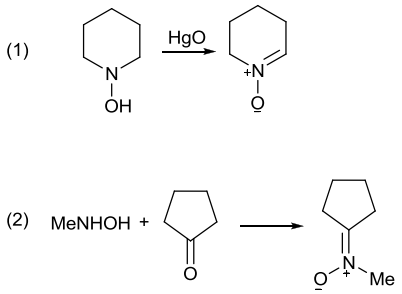
The isoxazolidines formed from the reaction of alkenes with nitrones have proven to be very useful building blocks.[7,9,118] Cleavage of the isoxazoline system allows access to a variety of attractive compounds such as β-amino alcohols, with the configuration at the chiral centres retained upon reduction (Scheme 33).



Scheme 33

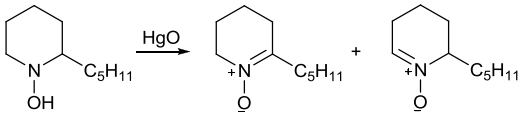
1.2.2.1 Synthesis of Nitrones

The two most commonly used methods for nitrone generation are oxidation of a disubstituted hydroxylamine with yellow mercuric oxide (eq. 1, Scheme 34), and reaction of an aldehyde or ketone with a monosubstituted hydroxylamine (eq. 2, Scheme 34).[118]



Scheme 34

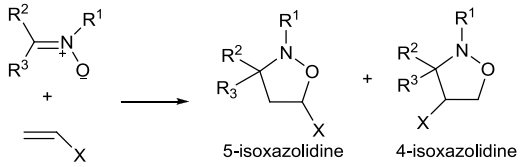
A major disadvantage of the first method is the lack of regiochemical control for unsymmetrical hydroxylamines; for example, the oxidation of 1-hydroxy-2-pentylpiperidine leads to the formation of a regioisomeric mixture of nitrones (Scheme 35).[119] The generation of nitrones from an aldehyde or ketone avoids this difficulty, and a single nitrone is obtained regiospecifically.



Scheme 35

1.2.2.2 Regioselectivity

The cycloaddition of nitrones and monosubstituted alkenes can lead to two regioisomeric cycloadducts (Scheme 36).



Scheme 36

Nitrone cycloadditions are Type II processes by Sustmann's classification (see Section 1.1.4). For monosubstituted alkenes, cycloadditions with electron-rich alkenes are dipole-LUMO controlled. For the nitrone LUMO, the larger atomic orbital coefficient is at carbon and the larger coefficient of the alkene is at the unsubstituted carbon, leading to a transition state in which the carbon of the nitrone becomes bonded to the unsubstituted carbon of the alkene to yield the 5-substituted isoxazolidine (Figure 17).[9,118]

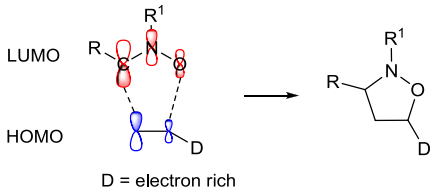


Figure 17

For nitrone cycloadditions with moderately electron-withdrawing groups such as methyl acrylate, the dominant interaction is HOMO (dipole)-LUMO (dipolarophile) and 4-substituted isoxazolidines should result. In practice, regioisomeric mixtures are obtained. Although the reactivity is dipole-HOMO controlled, the regiochemistry is dipole-LUMO controlled. This has been attributed to the much smaller difference in the terminal coefficients in the nitrone HOMO level compared to the nitrone LUMO (Figure 18).[9,118,120]

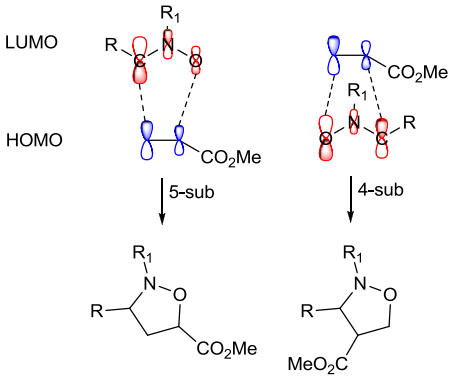


Figure 18

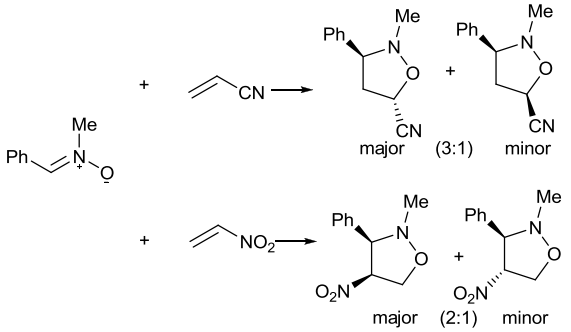
With very electron-deficient dipolarophiles such as nitroethene, dipole-HOMO control does predominate, and the 4-substituted isoxazolidine is obtained exclusively.[120]

The majority of 1,1-disubstituted alkenes undergo cycloaddition with nitrones to yield the 5,5-disubstituted isoxazolidine due to dipole-LUMO control, although the presence of strong electron-withdrawing groups give the 4,4-disubstituted product.[9,118] Mixtures of regioisomers usually result from cycloaddition with 1,2-disubstituted alkenes.[9,118]

1.2.2.3 Stereochemistry

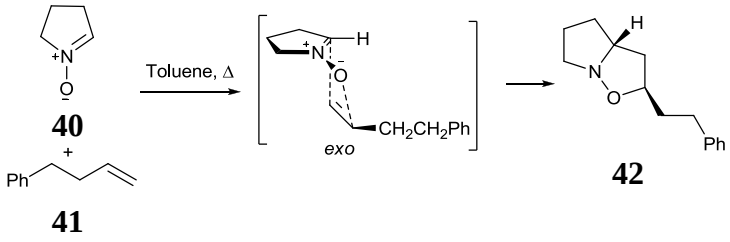
Nitrone cycloadditions are stereospecific as regards the alkene, with the stereochemistry of the original alkene preserved in the resulting isoxazolidine. However, with acyclic nitrones it is not always possible to predict the stereochemical outcome as both *endo* and *exo* transition states are possible, the former arising from favourable secondary orbital interactions (see Section 1.1.5). There is also the possibility of the nitrone undergoing *E*/*Z* isomerisation under the conditions of the reaction before cycloaddition takes place. For example, the cycloaddition of *N*-methyl-*C*-phenylnitrone with acrylonitrile gives the *trans* 5-substituted isomer as the major

product, whereas in the reaction with nitroethene the *cis* 4-substituted isomer predominates (Scheme 37).[121]



Scheme 37

Employment of cyclic nitrones leads to much higher stereoselectivities as the *E*/*Z* isomerisation is not possible. Also, the *exo* transition state is usually sterically favoured with cyclic nitrones, although when steric factors in the *endo* and *exo* transition states are similar, the existence of secondary orbital interactions can favour *endo* transition states.[122] In the cycloaddition of 1-pyrroline *N*-oxide **40** with 4-phenyl-1-butene **41**, the isoxazolidine **42**,which arises from the *exo* transition state, is obtained exclusively (Scheme 38).[122]



Scheme 38

1.2.2.4 Asymmetric 1,3-Dipolar Cycloadditions of Nitrones

The preparation of non-racemic isoxazolidines has attracted much attention in the past 30 years.[6,10,20] Chiral acyclic nitrones in which the chiral substituent is located at the nitrogen atom or the carbon atom are commonly employed.[123] Chiral cyclic nitrones have also been used for asymmetric induction in 1,3-dipolar cycloadditions.[124,125] The use of optically active alkenes in asymmetric nitrone cycloadditions has also been extensively studied. Alkenes in which the chiral centre is vicinal to the double bond such as chiral allylic ethers,[126-129] chiral allylic amines[130,131] and chiral vinyl sulfoxides[132,133] are most frequently used, and chiral α,β-unsaturated carbonyl compounds such as acrylates[77,134] and acrylamides[135,136] have also been successfully employed.

As most nitrones are stable compounds that do not require *in situ* preparation, a considerable amount of research has been conducted on the use of metal catalysts in the

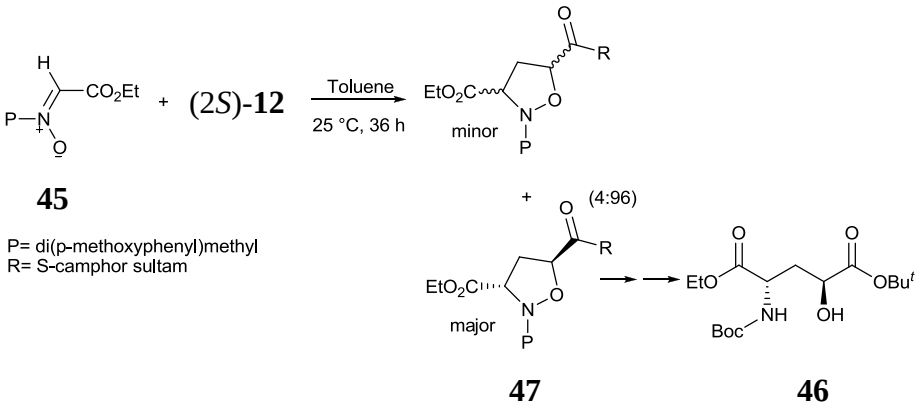
cycloadditions of nitrones.[6,16,20] Transition state energy calculations conducted by Gothelf *et al.* revealed that the coordination of a Lewis acid to a nitrone results in an increase in the transition state energy of the 1,3-dipolar cycloaddition to the alkene compared with the cycloaddition in the absence of a Lewis acid.[137] Hence, the application of metal catalysts in nitrone cycloadditions has focussed primarily on the activation of the dipolarophile, although the Lewis acid activation of nitrones containing α,β-unsaturated substitutents has been reported.[138] One of the major problems encountered in the Lewis acid activation of dipolarophiles such as α,β-unsaturated carbonyl systems, is competitive coordination of the nitrone and the α,β-unsaturated carbonyl compound to the Lewis acid. For example, when Tejero was studying the cycloaddition of thiazolyl nitrone **43** with Oppolzer's chiral sultam derivative **12** (Section 1.2.2.5.1), the presence of various Lewis acids was found to inhibit the reaction completely, and this was believed to be due to the preferential coordination of the metal to the nitrone leading to an inactive complex.[136] This problem can be overcome by using an alkene which is capable of bidentate coordination to the Lewis acid [for example acrylamides **24** (Scheme 22) and **44** (Scheme 48)]. Complexes of Ti(IV), Mg(II), Yb(II), Zn(II), Cu(II), Mn(II), Ni(II) and Pd(II) have now all been reported in the Lewis acid catalysis of nitrone cycloadditions,[6,139] and substantial increases in rate and levels of regio- and diastereoselectivity have been achieved. Furthermore, if a ligand-metal complex is present, non-racemic isoxazolidine cycloadducts can be produced.[139]

The asymmetric 1,3-dipolar cycloadditions of nitrones and acrylamides in the absence of Lewis acid metal catalysts will be discussed first. Metal catalysed reactions of nitrones and acrylamides will then be reviewed, with this section organised according to the nature of the metal catalyst.

1.2.2.5 Asymmetric 1,3-Dipolar Cycloadditions of Nitrones and Acrylamides

1.2.2.5.1 Non-Metal Catalysed Cycloadditions

There have been several reports of the use of chiral acrylamides to control the regio- and stereoselectivity in nitrone cycloadditions. In 1996, Koskinen *et al.* reported the asymmetric 1,3-dipolar cycloaddition of the Oppolzer chiral sultam derivative **12** with nitrone **45** as the key step in their asymmetric synthesis of *N*-protected (4*S*)-4-hydroxy L-glutamic acid diester **46**.[135] The cycloaddition of **12** with nitrone **45** led to the formation of the isoxazolidine cycloadducts in a distereomeric ratio of 96:4. These were separable by column chromatography and the sultam of the major cycloadduct **47** was subsequently transformed to the enantiopure diester **46** *via* a number of synthetic transformations (Scheme 39).[135]



Scheme 39

The major *trans* diastereomer **47** results from the cycloaddition of the *E*-isomer of **45** *via* an *exo* transition state and the cycloaddition of the *Z* isomer of **45** *via* an *endo* transition state (Figure 19). Coulombic repulsion between the dipolar oxygen and the sultam oxygen accounts for the diastereofacial selectivity.[83,135]

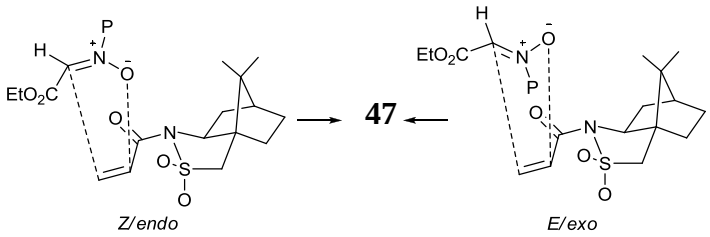
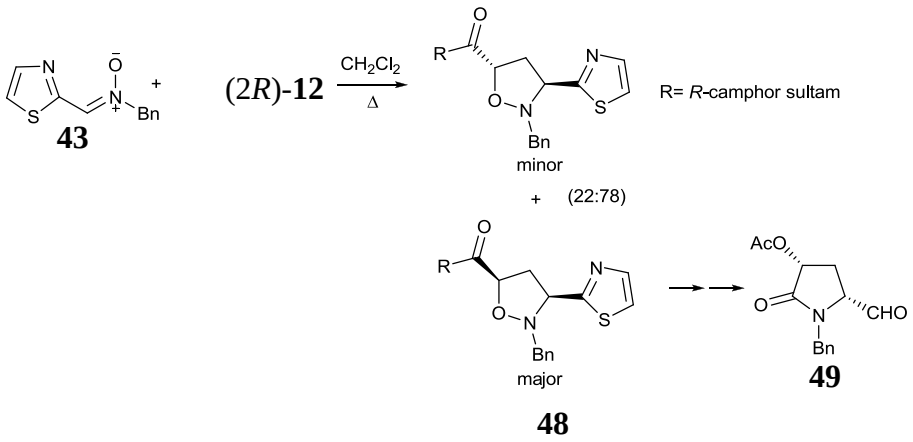


Figure 19

In 1997, Tejero *et al.* began a series of investigations into the cycloaddition of *N*-benzyl-*C*-arylnitrones to Oppolzer's chiral sultam derivative **12**.[136] The syntheses of enantiopure α-amino-2-alkylthiazoles and 5-formylpyrrolidin-2-ones were studied initially, and it was found that the thiazolyl nitrone **43** underwent cycloaddition with **12** in a completely regio- and stereoselective manner to yield exclusively the *trans*-isoxazolidines in a diastereomeric ratio of 78:22. These were separable by chromatography and the major isomer **48** was subsequently converted to **49**, which proved to be a very useful intermediate in synthesising functionalised chiral pyrrolidines (Scheme 40).[136]



Scheme 40

The proposed most favoured approach is *Z-endo* attack of the nitrone on the top face of the dipolarophile (Figure 20).

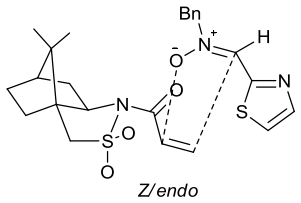
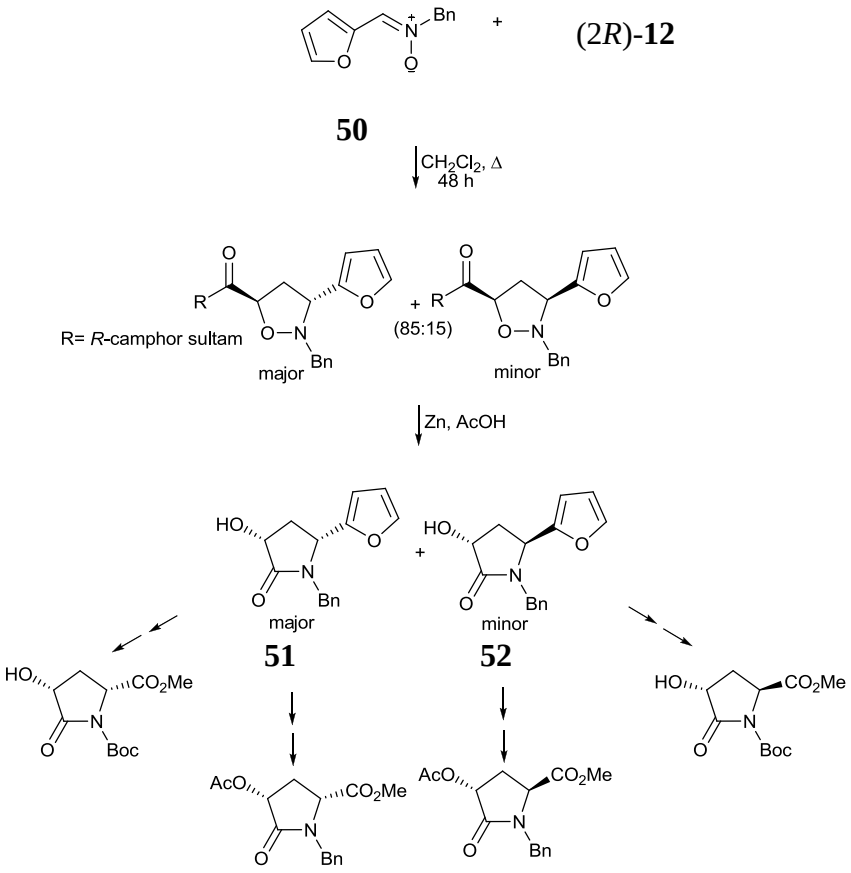


Figure 20

In 2000, Tejero and co-workers extended this synthetic strategy by using furfuryl nitrones such as **50** to construct the pyrrolidine ring.[78] In contrast to the cycloaddition with thiazolyl nitrones where cycloaddition to both faces of the alkene occurred, the addition of the furfuryl nitrone **50** led to complete stereofacial control to yield the *cis*- and *trans*-isomers in a diastereomeric ratio of 85:15. Subsequent transformation of the isoxazolidine cycloadducts to the corresponding pyrrolidin-2-ones **51** and **52** was achieved by reduction with zinc and acetic acid. The pyrrolidin-2-ones were easily separated by column chromatography and the preparation of protected derivatives of 4-hydroxy pyroglutamic acids demonstrated the synthetic utility of the isoxazolidines (Scheme 41).



Scheme 41

The four possible modes of addition of the nitrone **50** are depicted in Figure 21. Transition states A and B arising from *si* face attack are disfavoured due to coulombic repulsion between the dipolar oxygen and the sultam oxygen. Of the two transition states resulting from *re* face attack, *endo* approach leading to transition state D and ultimately the *trans*-diastereomer is predominant, presumably due to secondary orbital interactions between the nitrogen of the nitrone and the carbonyl group of the dipolarophile.

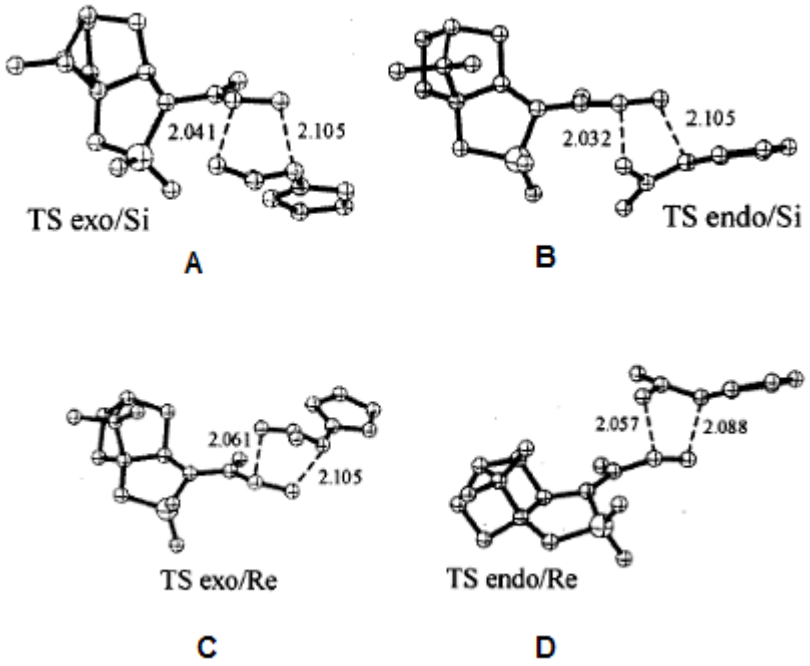
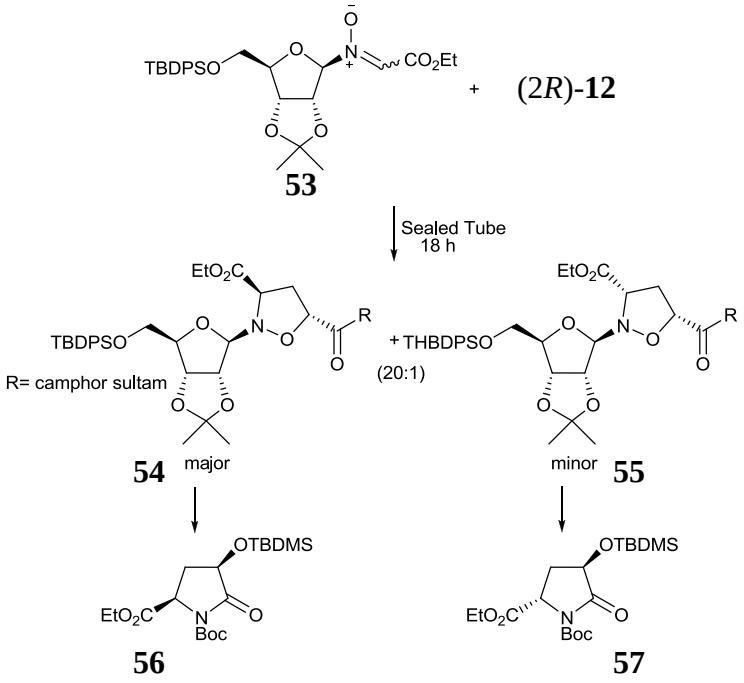


Figure 21-reproduced from reference [78]

The operation of double asymmetric induction was described by Tejero *et al.* in 2002 in their five-step asymmetric synthesis of protected 4-hydroxy-D-pyroglutamic acid using D-ribose and Oppolzer's chiral sultam derivative **12**.[140] The optically active nitrone **53** was reacted with **12** in a sealed tube for 18 hours to yield a 20:1 diastereomeric ratio of isoxazolidine cycloadducts **54** and **55**.[141] These were then converted to the 4-hydroxy-D-pyroglutamic acid derivatives **56** and **57** in a one pot procedure (Scheme 42). In a subsequent report by the same group, the scope of this cycloaddition was extended by studying the reaction of **12** with a range of D-glyceraldehyde nitrones.[142]



Scheme 42

The major *trans*-diastereomer **54** results from attack of the *E*-isomer of **53** *via* an *exo* transition state and attack of the *Z*-isomer of **53** *via* an *endo* transition state on the *re* face of the dipolarophile **12** (Figure 22). It is suggested that the *Z-endo* transition state is the preferred path due to secondary orbital interactions in the *endo* transition state.[140]

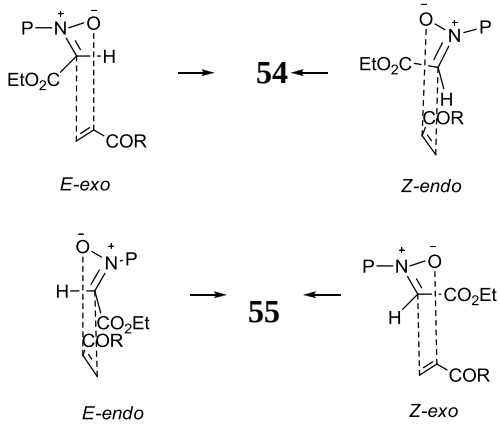
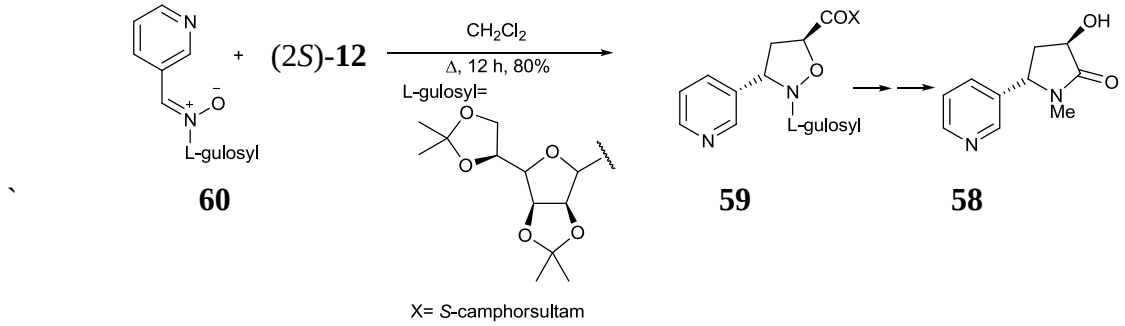


Figure 22

Inspired by the results achieved by Tejero *et al.*,[136] Tamura and co-workers examined the cycloaddition of *C*-(3-pyridyl)nitrones and Oppolzer's chiral sultam derivative (2*S*)-**12** as a route to (+)-(3′*R*,5′*R*)-3′-hydroxycotinine **58**, which is one of the main metabolites of nicotine (Scheme 43).[143]



Scheme 43

Treatment of the L-gulose derived nitrone **60** with (2*S*)-**12** yielded the *trans*-isoxazolidine **59** as the major product by double asymmetric induction (Scheme 43). When the nitrone **60** was reacted with the opposite enantiomer of Oppolzer's chiral sultam derivative (2*R*)-**12** a complex mixture of cycloadducts resulted, indicating that this combination of reagents is a mismatched pair. The Oppolzer's chiral sultam derivative (2*R*)-**12** reacts mainly from the *Re* face, whereas both **60** and (2*S*)-**12** react from the *Si* face, and hence high *endo* stereoselectivity results when **60** and (2*S*)-**12** are combined (Figure 23).[143]

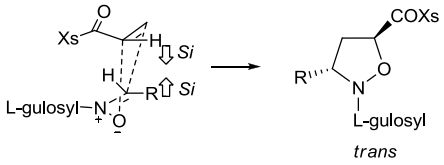
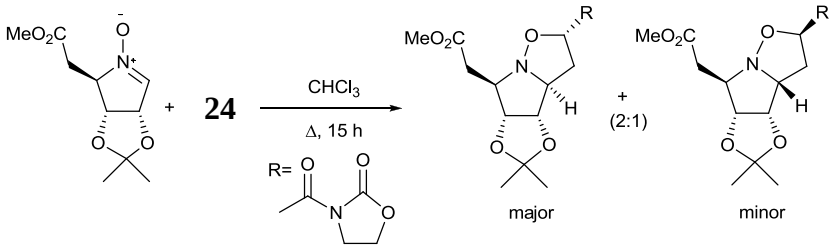


Figure 23

In 2007, Argyropoulos reported the cycloaddition of a pair of chiral pyrroline-*N*-oxides derived from D-ribose with Evans's chiral 2-oxazolidinone **24**.[144] The cycloadditions proceeded with complete regioselectivity to yield a 2:1 mixture of diastereomers (the cycloaddition of one of the enantiomeric nitrones is depicted in Scheme 44).



Scheme 44

The preferred stereochemical outcome arises from the *exo* approach of the dipolarophile **24** to the *anti* face of the nitrone (Figure 24).

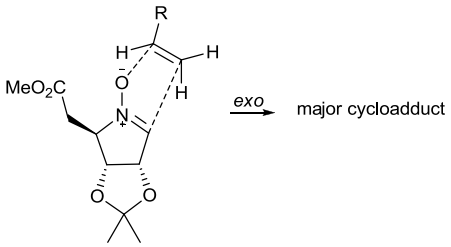


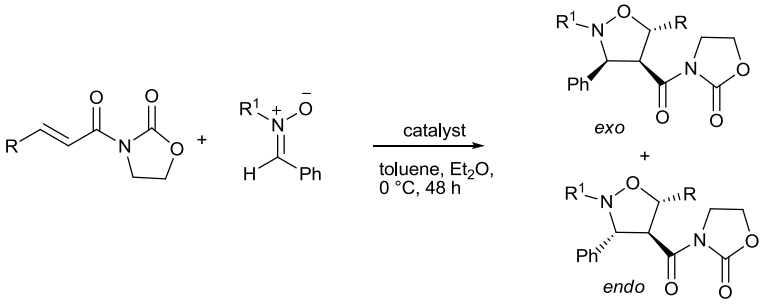
Figure 24

Similar to the 1,3-dipolar cycloadditions with nitrile oxides, the acrylamide **12** derived from Oppolzer's chiral sultam was again the most advantageous dipolarophile in non-metal catalysed cycloadditions with nitrones, in terms of synthetic utility and diastereoselectivity achieved (up to 96:4 dr).

1.2.2.5.2 Metal Catalysed Cycloadditions

The majority of studies on the metal-catalysed cycloadditions of nitrones and acrylamides have focussed on the reaction of Evan's 2-oxazolidinone with acyclic nitrones. Each reaction outlined in Table 3 will be discussed in the relevant metal catalyst section.

Table 3- Metal-catalysed cycloadditions of acyclic nitrones and 2-oxazolidinones



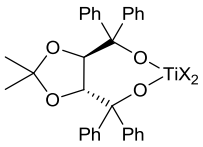
entry	R§	R1!	Catalyst*	*endo:exo*	%ee of major
1[137]	Me	Ph	$TiCl_2$-TADDOLate **61**	9:91	60
2[145]	Me	Ph	$Ti(OTos)_2$-TADDOLate **62**	95:5	93
3[145]	Pr	Ph	$Ti(OTos)_2$-TADDOLate **62**	95:5	93
4[146]	Me	Ph	Dendrimer-bound Ti-TADDOLate	14:86	44
5[146]	Me	Ph	Polymer-bound Ti-TADDOLate	10:90	56
6[147]	Me	Ph	Mg(II)-phenanthroline **63**	95:5	-
7[147]	Me	Bn	Mg(II)-phenanthroline **63**	95:5	-
8[147]	Pr	Ph	Mg(II)-phenanthroline **63**	95:5	-
9[147]	Pr	Bn	Mg(II)-phenanthroline **63**	95:5	-

10[147]	Pr	Ph	Mg(II)-bisoxazoline **64**	95:5	82
11[147]	Me	Ph	Mg(II)-bisoxazoline **64**	92:8	79
12[147]	Me	Bn	Mg(II)-bisoxazoline **64**	89:11	0
13[148,149]	Me	Ph	xabox-Bn-Mg(II) **65**	99:1	92
14[148,149]	H	Ph	xabox-Bn-Mg(II) **65**	96:4	96
15[148,149]	Me	Ph	xabox-Bn-Mn(II) **66**	96:4	95
16[148,149]	H	Ph	xabox-Bn-Mn(II) **66**	77:23	94
17[150]	H	Ph	Zn(II)-bisoxazoline **67**	27:73	84
18[151]	Me	Ph	Cu(II)-bisoxazoline **68**	70:30	99
19[151]	H	Ph	Cu(II)-bisoxazoline **68**	22:78	96
20[152]	Me	Ph	Cu(II)-bisimine **69**	91:9	90
21[152]	H	Ph	Cu(II)-bisimine **69**	56:44	90
22[153,154]	Me	Me	Pd(II)-TolBINAP **70**	60:40	91
23[153,154]	Me	Bn	Pd(II)-TolBINAP **70**	93:7	89
24[153,154]	Me	Ph	Pd(II)-TolBINAP **70**	28:72	48
25[155]	Me	Me	Ni(II)-DBFOX/Ph **71**	99:1	99
26[155]	Me	Bn	Ni(II)-DBFOX/Ph **71**	99:1	95
27[155]	Me	Ph	Ni(II)-DBFOX/Ph **71**	98:2	89
28[156,157]	H	Ph	Ni(II)-Pybox-*tipsom* **72**	99:1	99
29[156,157]	Me	Ph	Ni(II)-Pybox-*tipsom* **72**	99:1	97
30[158]	Me	Ph	$Yb(OTf)_3$	97:3	-
31[158]	Pr	Ph	$Yb(OTf)_3$	92:8	-
32[158]	Me	Ph	$Sc(OTf)_3$	93:7	-
33[158]	Pr	Ph	$Sc(OTf)_3$	82:18	-
34[158]	Me	Ph	Yb(III)-Pybox **73**	95:5	67
35[159]	Me	Bn	Yb(III)-[(*S*)-BINOL]-[(*R*)-MNEA] **74**	99:1	96

§ R = Me, **75**; R = H, **76**; R = Pr, **77**

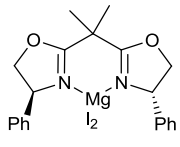
! R^1 = Ph, **78**; R^1 = Me, **79**; R^1 = Bn, **80**

*

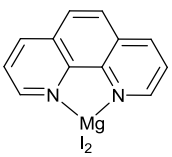


X=Cl, **61**

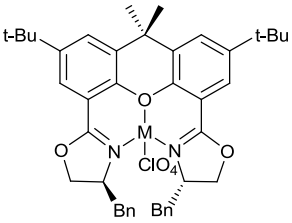
X=OTos, **62**



64

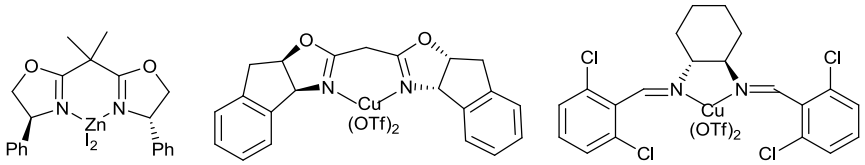


63

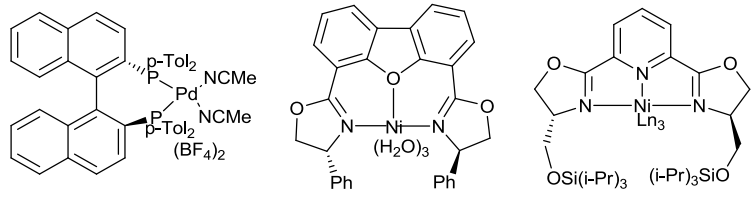


M=Mg, **65**

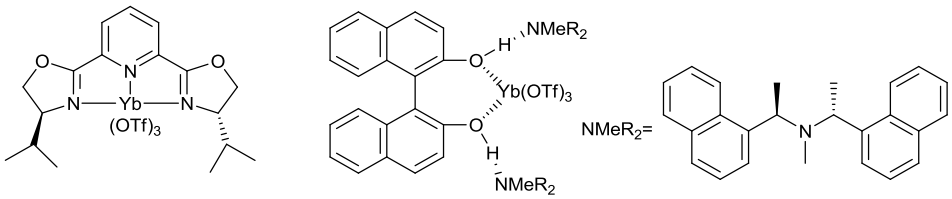
M=Mn, **66**



67 **68** **69**



70 **71** **72**



73 **74**

1.2.2.5.2.1 *Titanium Catalysts*

The first asymmetric 1,3-dipolar cycloaddition between an alkene and a nitrone in which the asymmetry was catalytically induced by a chiral ligand on the metal complex was reported by Gothelf and Jorgensen in 1994.[137] The presence of chiral dichlorotitanium alkoxides in the cycloaddition of acyclic nitrones with Evans's 2-oxazolidinones was investigated, with a diastereomeric ratio of 91:9 (*exo*:*endo*) and up to 60% ee achieved on employment of the chiral titanium complex **61** (entry 1, Table 3).

The catalytic effect is due to the bidentate coordination of the alkene to the Lewis acid lowering the energy of the HOMO and the LUMO of the alkene, leading to an activation for the addition of the nitrone (Figure 25), and *exo* attack of the nitrone to the *Re* face of the alkene leads to the major cycloadduct. The structure of the alkene-Lewis acid complex was subsequently confirmed by X-ray crystallography.[160] This reaction did not proceed at room temperature in the absence of a catalyst and only 39% conversion was observed after 20 hours at 50 °C.

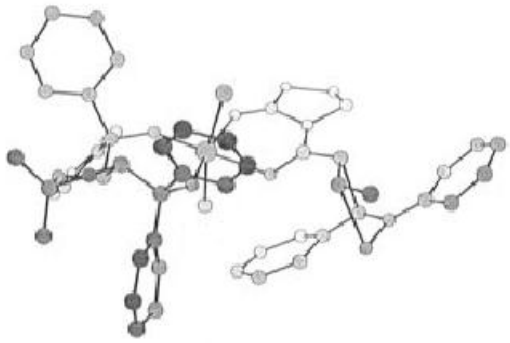


Figure 25-reproduced from reference [145]

Substitution of the chloride groups with the bulkier tosylate ligands in **62** led to the isolation of the *endo* cycloadduct as the major isomer in enantioselectivities of >90% ee (entries 2 and 3, Table 3).[145] The *exo* approach of the nitrone is unfavourable here due to the repulsion between the axial ligand on the titanium atom and the substituent on the α-carbon of the nitrone (Figure 26).

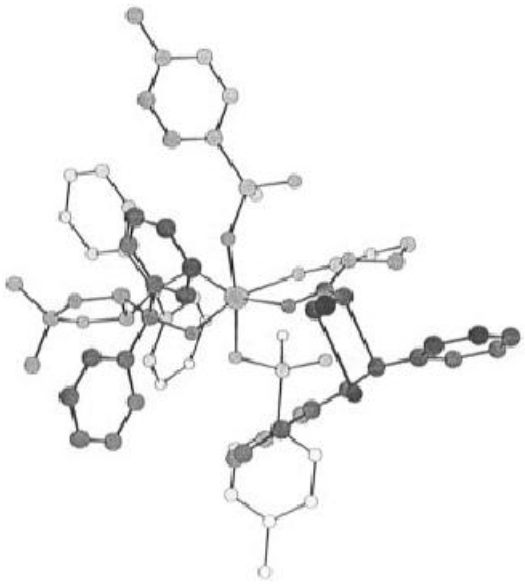
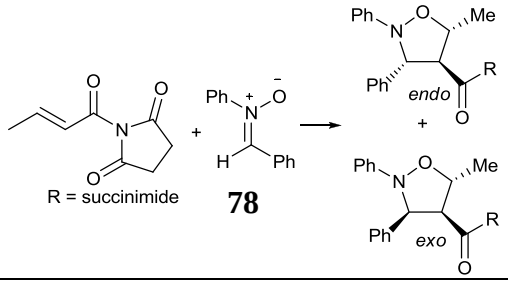


Figure 26-reproduced from reference [145]

Replacement of the oxazolidinone auxiliary of the acrylamide with succinimide resulted in greater reactivity, with 94% conversion in the absence of Lewis acid following stirring at room temperature for 71 hours and a 95:5 (*endo*:*exo*) mixture of diastereomers obtained (the corresponding oxazolidinone required elevated temperature to undergo cycloaddition with **78**).[161] In the presence of 5 mol% of **61**, a 6:94 (*endo*:*exo*) mixture of diastereomers was isolated in up to 73% ee for the *exo*-isomer (Scheme 45), with the transition state similar to that depicted in Figure 25.



catalyst	*endo:exo*
None	95:5
61 (5 mol%)	6:94

Scheme 45

Gothelf and co-workers have performed a series of *ab initio* calculations to account for the *endo*-selectivity observed in the absence of the Lewis acid catalyst and they found that steric repulsion between the *C*-phenyl substituent and one of the carbonyls of the succinimide group disfavours *exo* approach of the nitrone.[161]

Seebach *et al.* have developed a number of polymer- and dendrimer-bound chiral dichlorotitanium alkoxide catalysts and have studied the application of these catalysts in the cycloaddition of Evan's 2-oxazolidinone **75** and *C*,*N*-diphenylnitrone **78** (entries 4 and 5, Table 3).[146] Almost identical diastereoselectivities to Gothelf and Jorgensen's homogeneous catalysts were attained.

1.2.2.5.2.2 Magnesium Catalysts

In 1996, Gothelf and Jorgensen investigated the cycloaddition of acyclic nitrones with Evans's 2-oxazolidinones in the presence of achiral and chiral magnesium complexes. Application of 10 mol% of the achiral MgI_2-phenanthroline complex **63** led to the attainment of high *endo* selectivity (*endo*:*exo* 95:5) (entries 6-9, Table 3).[147]

When the chiral magnesium-bisoxazoline complex **64** was employed in cycloadditions with *C*,*N*-diphenylnitrone **78**, high *endo* selectivity was observed (ratio of *endo*:*exo* >95:5) and enantiomeric excesses of up to 82% were achieved for the *endo*-isomer (entries 10 and 11, Table 3).[147]

The diastereofacial discrimination in favour of the *endo*-diastereomer is due to the preferred *endo* attack of the nitrone **78** on the α-*Re* face of the alkene **75** from below the plane of the alkene (Figure 27).

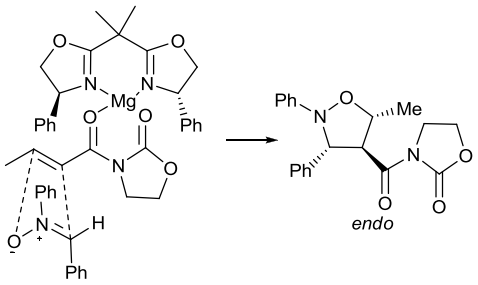
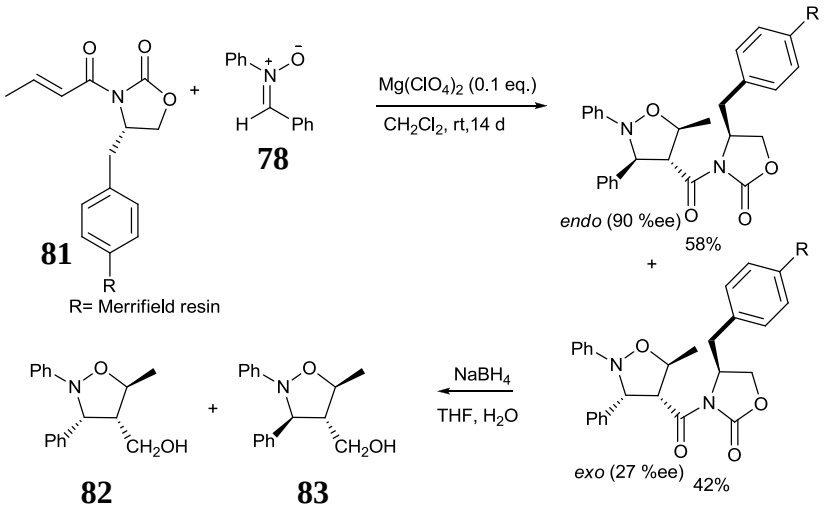


Figure 27

Interestingly, the reaction of the *N*-benzyl nitrone **80** with the 2-oxazolidinone **75** in the presence of **64** led to the attainment of good *endo*:*exo* diastereoselectivity (89:11) but the reaction was not enantioselective (entry 12, Table 3).

Later studies showed that in the absence of molecular sieves a reversal of the stereochemistry was observed; one enantiomer of the *endo*-isomer is obtained in the presence of molecular sieves and the mirror image enantiomer is isolated in the absence of molecular sieves.[162] It is postulated that the metal centre of the Lewis acid complex is attached to two oxygen atoms at the surface of the molecular sieve, resulting in a change in the transition state for the cycloaddition. However, due to the complexity of the structure of the molecular sieve, it is difficult to predict the exact nature of this binding.

The effect of the counterion was investigated by Desimoni and co-workers.[163] When perchlorate or triflate were used as the counterions in the presence of molecular sieves, the opposite enantiomer to that obtained from the iodide counterion catalyst was isolated. Desimoni has also studied the nitrone cycloaddition of a novel, soluble polymer-supported optically active oxazolidinone **81**. When reacted with the *C*,*N*-diphenylnitrone **78** in the presence of $Mg(ClO_4)_2$ catalyst, a diastereomeric ratio of 58:42 (*exo*:*endo*) was achieved in up to 90% ee.[164] Reductive cleavage with sodium borohydride yielded the diastereomeric isoxazolidines **82** and **83** (Scheme 46).



Scheme 46

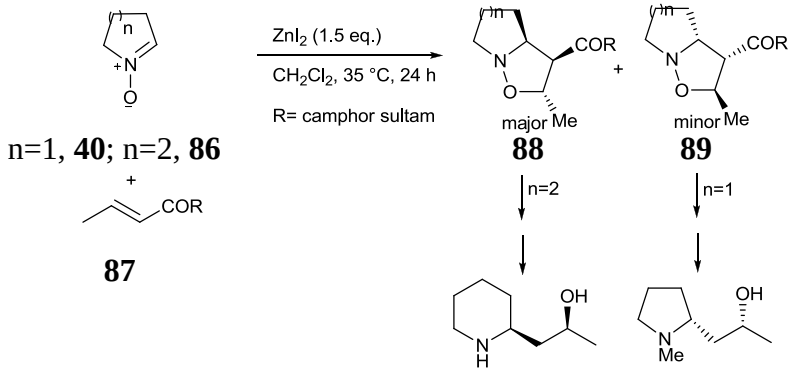
Nishiyama and co-workers have developed a series of tridentate oxazoline-derived chiral ligands having a xanthene backbone, and have studied the cycloaddition of nitrones such as **78** to the oxazolidinone **75** in the presence of these ligands.[148,149] The xabox-Bn-Mg(II) complex **65** yielded diastereoselectivities of up to >99:1 with % ee's of the *endo*-isomer ranging from 85–96% (entries 13 and 14, Table 3). A transition state similar to that outlined in Figure 27 can be envisioned, with the diastereofacial selectivity due to the *endo* attack of the nitrone **78** on the *Re* face of the alkene **75**.

1.2.2.5.2.3 Manganese Catalysts

In addition to Mg(II) complexes, Nishiyama and co-workers have also studied the behaviour of Mn(II)-xabox-Bn complexes in the cycloadditions of nitrones to the oxazolidinone **75** (entries 15 and 16, Table 3).[148,149] Diastereoselectivities of 96:4 to 98:2 were achieved with enantiomeric excesses of 91–95% ee.

1.2.2.5.2.4 Zinc Catalysts

In 1993, Murahashi reported the cycloaddition of cyclic nitrones to acrylamide derivatives in the presence of zinc iodide as a route to the optically active β-amino alcohols (+)-sedridine **84** and (+)-hygroline **85**.[165] When 2,3,4,5-tetrahydropyridine *N*-oxide **86** (n=2) was reacted with Oppolzer's sultam derivative **87** in the presence of zinc iodide, a diastereomeric ratio of **88a**:**89a** of 78:4 was achieved, along with 18% of other diastereomers. In the absence of the metal catalyst, the ratio was 54:27:19. Oppolzer's sultam derivative **87** also underwent cycloaddition with 1-pyrroline *N*-oxide **40** (n=1) in the presence of zinc iodide to yield the isoxazolidines **88b**:**89b** in the ratio 77:14, along with 9% of other diastereomers. When the Lewis acid was not present, a ratio of 35:52:13 resulted.



n	additive	88:89:others
1	none	35:52:13

1	1.5 eq ZnI_2	77:14:9
2	none	54:27:19
2	1.5 eq ZnI_2	78:4:18

Scheme 47

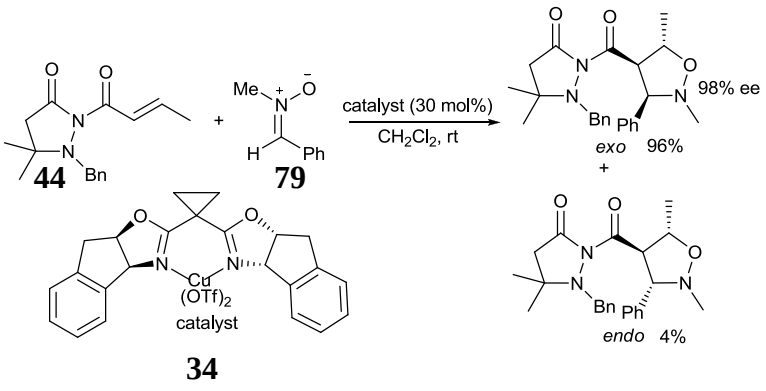
Desimoni has also studied the reaction outlined in Table 3 using Zn(II) as the cationic core of the bis-oxazoline catalyst, with some interesting results.[150] On changing the metal cation from Mg to Zn in **67**, a change in selectivity from *endo* to *exo* is observed (entry 17, Table 3). A strong chiral amplification is also seen for the Zn catalysed reaction; with 10% ee of the chiral bis-oxazoline ligand, cycloadducts with up to 62% ee were obtained.

1.2.2.5.2.5 *Copper Catalysts*

In 2004, Saito and co-workers reported the catalytic enantioselective nitrone cycloaddition to the oxazolidinone **75** using an amino-indanol-derived bisoxazoline Cu(II) complex **68** as a bidentate chiral catalyst.[151] Employing $Cu(OTf)_2$ led to a diastereomeric ratio of 70:30 (*endo*:*exo*), with enantiomeric excesses of >99% achieved for each diastereomer (entry 18, Table 3). Employment of the oxazolidinone **76** led to high *exo* selectivity (*endo*:*exo* 22:78), along with high enantiopurity of 96% ee for the *exo*-diastereomer.

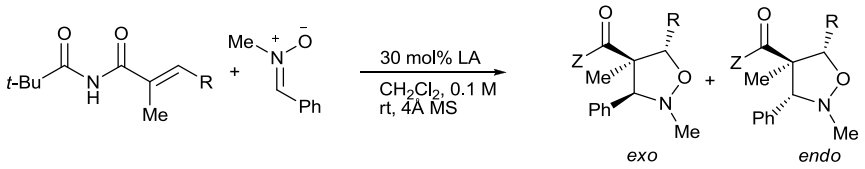
On changing the chiral ligand to the bis(imine) ligand **69**, an increase in the diastereomer ratio to 91:9 was observed for the cycloaddition of the oxazolidinone **75** to the *C*,*N*-diphenylnitrone **78**, whilst maintaining the high enantioselectivity (entry 20, Table 3).[152] Using the oxazolidinone **76** resulted in a dramatic decrease in the diastereoselectivity (*endo*:*exo* 56:44), but the high enantioselectivity was preserved (90% ee for the *endo*-isomer and 96% ee for the *exo*-isomer) (entry 21, Table 3).

In the same year, Sibi *et al.* communicated the cycloaddition of the pyrazolidinone **44** with the acyclic nitrone **79** in the presence of the chiral Lewis acid **34** derived from copper triflate and the amino-indanol ligand.[166] An *exo*:*endo* diastereoselectivity of 96:4 was observed, in 98% ee for the *exo* isomer (Scheme 48). It is postulated that the *exo* selectivity is due to the square planar complex formed by the Lewis acid ensuring that *exo* attack is not sterically restricted in the complex.[166]



Scheme 48

Sibi extended this work to include α,β-disubstituted acrylamide derivatives. On employment of the chiral Lewis acid **34** in cycloadditions with acyclic nitrones, diastereomeric ratios of up to 99:1 were achieved with enantiomeric excesses of up to 97% (Scheme 49).[114]



R	*exo:endo*	% ee *exo*
Me	99:1	94
H	81:19	89

Scheme 49

1.2.2.5.2.6 *Palladium Catalysts*

Furukawa has investigated the palladium(II) catalysed asymmetric cycloaddition of nitrones to oxazolidinone derivatives, with the palladium co-ordinated to a chiral phosphine ligand.[153,154] Late transition metal complexes such as palladium are advantageous as they do not require strictly anhydrous conditions. Employment of the (*S*)-TolBINAP ligand in the palladium complex **70** led to an *endo*:*exo* ratio of up to 93:7, with excellent enantioselectivity for both isomers (entries 22-24, Table 3). The diastereoselectivity was found to be dependant on the *N*-substituent of the nitrone, with poor diastereoselectivity for the *N*-methyl nitrone **79** (entry 22, Table 3), excellent *endo* diastereoselectivity for the *N*-benzyl nitrone **80** (entry 23, Table 3) and preferential formation of the *exo*-diastereomer for the *N*-phenyl nitrone **78** (entry 24, Table 3).

The selectivity differences are due to the steric effect in the transition state between the Lewis acid-alkene complex and the nitrones. Attack of the nitrone occurs from the *Si* face of the alkene, as the *Re*-face is sterically hindered by the aryl substituent of the Lewis acid. For the *N*-benzyl nitrone, *endo* approach to the *Si* face of the alkene is favoured (a, Figure 28) as *exo* approach leads to steric repulsion between the aryl substituent on the Lewis acid and the nitrone

(b, Figure 28). For the *N*-phenyl nitrone, the *N*-phenyl group prevents *endo* attack (c, Figure 28) and *exo* attack is favoured (d, Figure 28).

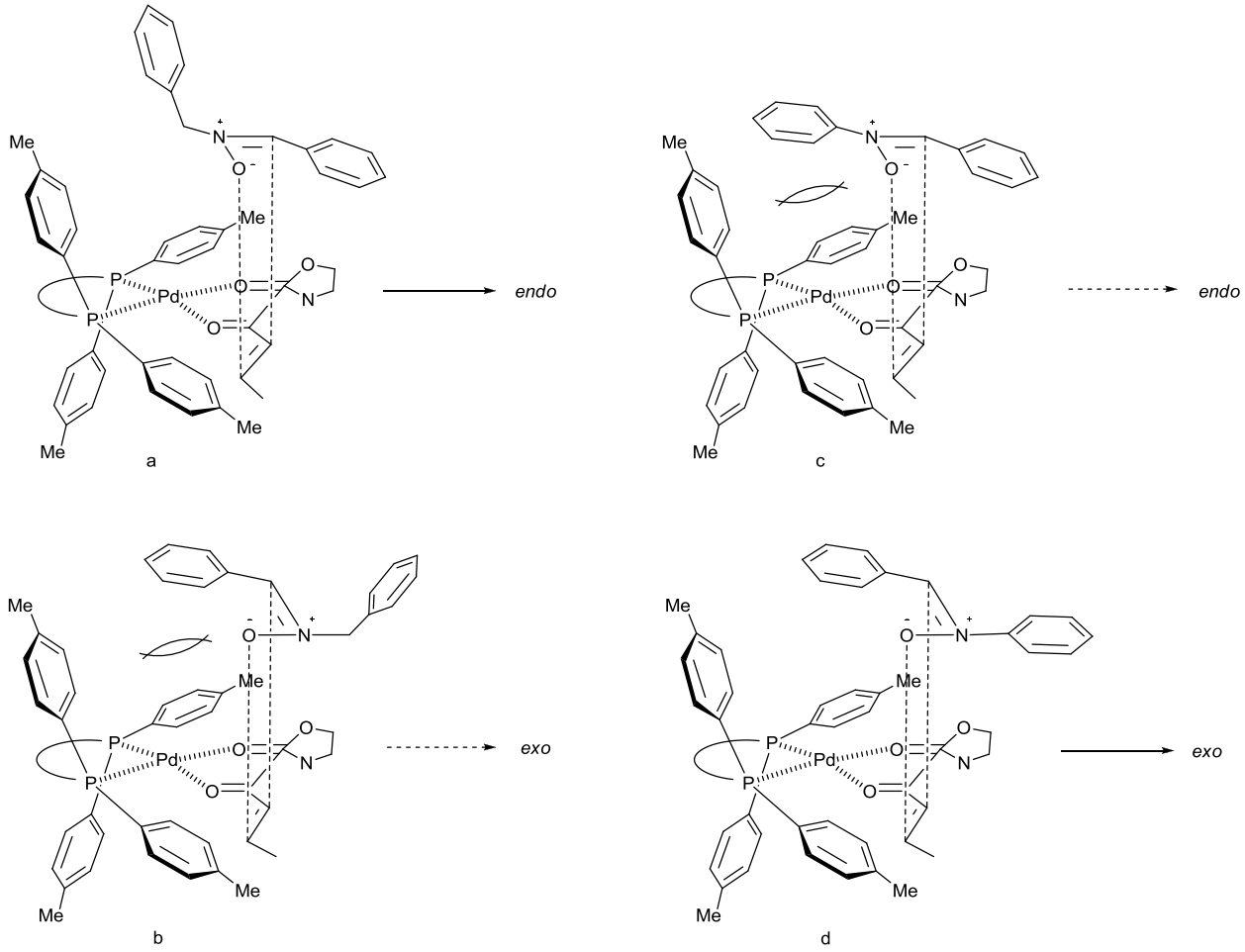


Figure 28

1.2.2.5.2.7 <u>*Nickel Catalysts*</u>

Kanemasa and co-workers have reported the asymmetric cycloaddition of a range of acyclic nitrones to the oxazolidinone **75** catalysed by the aqua complex **71** derived from (*R*,*R*)-4,6-dibenzo-furandiyl-2,2′-bis(4-phenyloxazoline) ligand (*R*,*R*-DBFOX/Ph) and $Ni(ClO_4)_2.6H_2O$.[155] Diastereomeric ratios of up to 99:1 (*endo*:*exo*) and enantioselectivities of >99% ee were obtained, with the presence of molecular sieves necessary to achieve high selectivities (entries 25-27, Table 3).

The bottom face of the alkene is shielded by one of the phenyl substituents of the DBFOX/Ph ligand, and the other phenyl group inhibits *exo* approach of the nitrone (Figure 29).

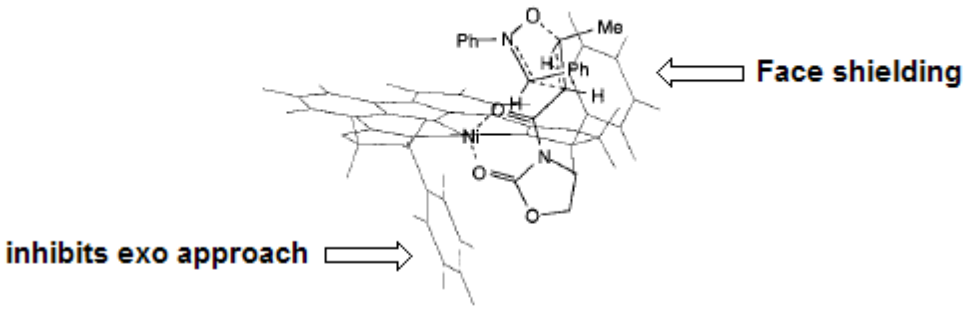


Figure 29-reproduced from reference [155]

Excellent stereocontrol and rate acceleration was observed by Iwasa on studying the cycloaddition of oxazolidinones with a range of nitrones in the presence of Ni(II) complexed to a sterically tuned bis(oxazolinyl)pyridine ligand, bearing a hydroxymethyl group on the oxazoline ring.[156,157] The introduction of trialkylsilyl groups onto the oxazoline ligand in complex **72** led to the attainment of excellent levels of regio-, diastereo- and enantioselectivities. The isoxazoline cycloadducts were obtained in ratios of up to >99:1 (*endo*:*exo*) and 97 to >99% ee (entries 28 and 29, Table 3).

The bulky trialkylsilyl groups block the approach of the nitrone from one face of the alkene (Figure 30) with *endo* approach of the nitrone to the alkene favoured as shown in Figure 30.

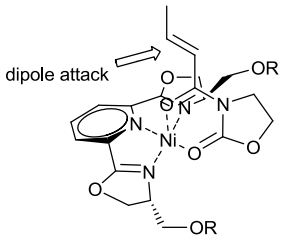


Figure 30

This was later extended to include pyrrolidinone derivatives and the excellent levels of diastereo- and enantioselectivities were maintained (Scheme 50). It was also discovered that changing the solvent to alcohols such as *t*-butanol and *s*-butanol significantly increased the rate of the cycloaddition compared to dichloromethane.[167]

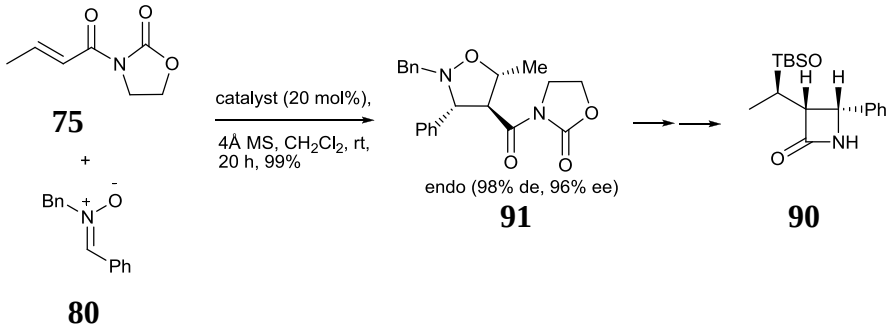
R	***endo:exo***	**% ee *endo***
H	97:3	98
Me	99:1	95

Scheme 50

1.2.2.5.2.8 *Lanthanide Catalysts*

As part of their development programme of new metal catalysts for the asymmetric 1,3-dipolar cycloaddition of nitrones with alkenes, Jorgensen *et al.* communicated the use of $Yb(OTf)_3$ and $Sc(OTf)_3$ as catalysts in the cycloaddition of a range of nitrones and oxazolidinones in 1997.[158] In the presence of $Yb(OTf)_3$, diastereoselectivities of 92:8 to 97:3 (*endo*:*exo*) were obtained (entries 30 and 31, Table 3). These were slightly lower when $Sc(OTf)_3$ was used (82:18 to 93:7) (entries 32 and 33, Table 3), but a significant rate increase was observed; in one instance the reaction time decreased from 48 hours to 5 hours. The introduction of the chiral ligand 2,6-bis[4-(*S*)-isopropyl-2-oxazolidin-2-yl]pyridine (PyBOX) **73** led to high *endo* selectivity (93:7) with up to 67% ee for the *endo*-diastereomer (entry 34, Table 3).

Much higher enantiomeric excesses (up to 96% ee) were achieved by Kobayashi on employment of a chiral Yb(III) catalyst **74** prepared from $Yb(OTf)_3$, (*S*)-1,1′-binaphthol [(*S*)-BINOL] and *N*-methyl-bis[(*R*)-1-(1-naphthyl)ethyl]amine [(*R*)-MNEA] (entry 35, Table 3).[159] The synthetic utility of the resulting cycloadduct was demonstrated by the synthesis of the β-lactam derivative **90** (Scheme 51).



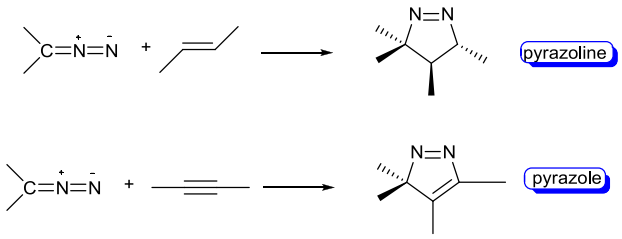
Scheme 51

Kobayashi later discovered that the opposite enantiomer of the *endo*-diastereomer could be isolated in the absence of molecular sieves.[168]

Thus, in terms of conversion, isolated yield, diastereomeric ratio and enantiomeric excess, the most expedient catalysts for the asymmetric 1,3-dipolar cycloaddition of Evan's 2-oxazolidinone with acyclic nitrones are xabox-Bn-Mg(II) **65** and xabox-Bn-Mn(II) **66** (entries 13-15, Table 3), Ni(II)-DBFOX/Ph **71** and Ni(II)-Pybox-*tipsom* **72** (entries 25-29, Table 3), and Yb(III)-[(*S*)-BINOL]-[(*R*)-MNEA] **74** (entry 35, Table 3).

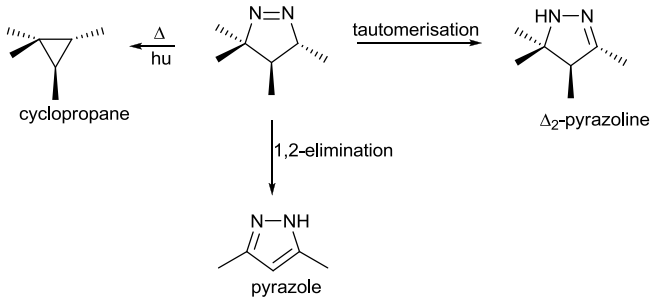
1.2.3 Cycloadditions with Diazoalkanes

Diazoalkanes undergo 1,3-dipolar cycloadditions with alkenes and alkynes to yield pyrazolines and pyrazoles respectively (Scheme 52).[169]



Scheme 52

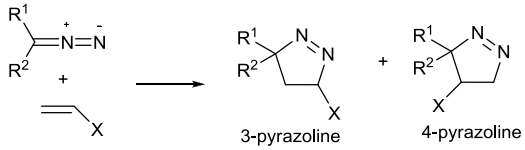
The pyrazoline cycloadducts are frequently too unstable to isolate and readily tautomerise to yield Δ^2-pyrazolines. Pyrazolines may also be transformed to pyrazoles by a 1,2-elimination reaction, and they can eliminate nitrogen on thermolysis or photolysis to yield cyclopropanes (Scheme 53). This method has been utilised in the synthesis of a number of cyclopropane natural products.[170]



Scheme 53

1.2.3.1 Regioselectivity and Reactivity

The addition of diazoalkanes to alkenes can lead to the formation of two regioisomeric cycloadducts (Scheme 54).



Scheme 54

The cycloadditions of simple diazoalkanes with electron-deficient and conjugated alkenes are dipole-HOMO controlled, with the carbon atom of the diazoalkane attacking the terminal carbon of the alkene resulting in exclusive formation of the 3-substituted pyrazolines (Figure 31).[37,62]

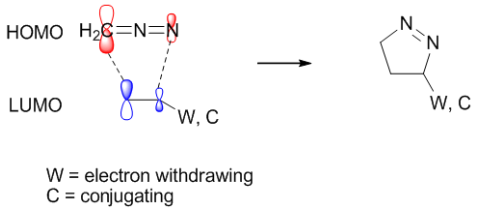


Figure 31

For electron-rich alkenes, both the dipole HOMO – dipolarophile LUMO and dipole LUMO – dipolarophile HOMO interactions are comparable. However, since the coefficients of the dipole-LUMO are almost equal, the regioselectivity is controlled by the dipole-HOMO leading to 4-substituted pyrazolines (Figure 32).[37]

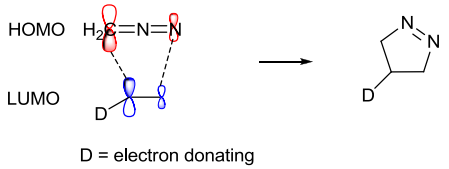


Figure 32

The presence of electron-rich substituents on the diazoalkane raise both the HOMO and LUMO energies and the rate of cycloadditions with electron-deficient alkenes is increased as the energy separation between the frontier orbitals decreases. This is confirmed by the greater reactivity of alkyl diazomethanes in cycloadditions.[171] The introduction of electron-withdrawing groups on the diazoalkane, such as the keto group in diazoketones, lowers the HOMO and LUMO energies, leading to an increase in the rate of reaction with electron-rich alkenes (Figure 33).[62]

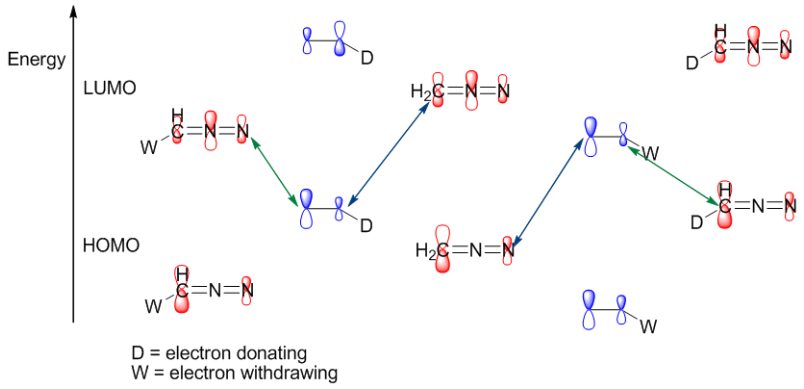


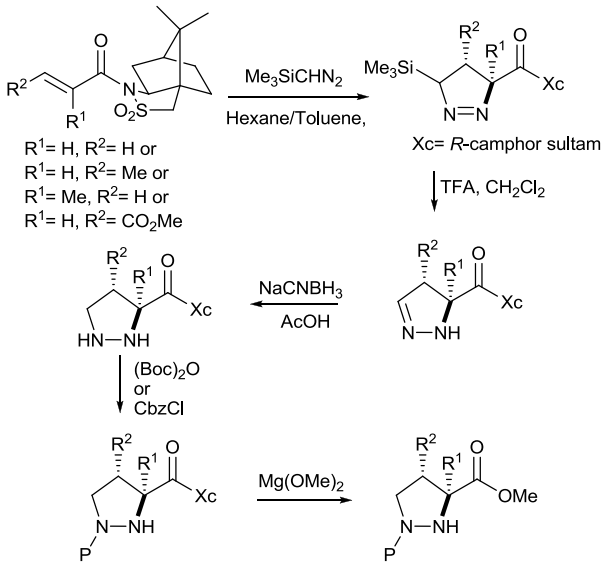
Figure 33

1.2.3.2 Asymmetric 1,3-Dipolar Cycloadditions of Diazoalkanes and Acrylamides

Synthetic applications of the pyrazoline cycloadducts obtained from the 1,3-dipolar cycloaddition of diazoalkanes to alkenes have not been extensively studied, and have usually

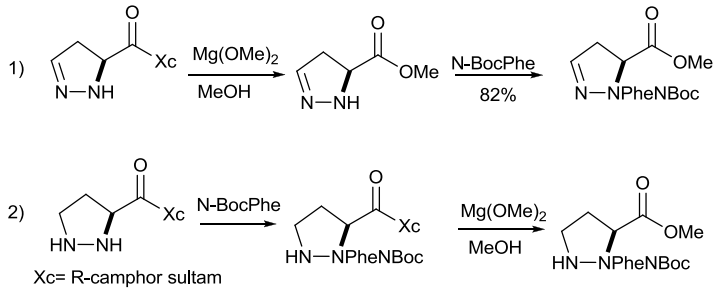
been restricted to the preparation of the resulting cyclopropanes or pyrazoles. The difficulties associated with employing diazoalkanes in asymmetric dipolar cycloadditions arise because the diazoalkanes are generally not readily available, they cannot be stored for long periods and they may also be thermally unstable. Studies on the synthetic utility of diazoalkanes with acrylamides have therefore been mainly concentrated on the commercially available trimethylsilyldiazomethane.

Carreira has investigated the cycloaddition of trimethylsilyldiazomethane to a range of Oppolzer's chiral sultam derivatives.[172] 3-Trimethylsilyl-substituted pyrazolines were isolated in quantitative yield following treatment with a 2 M solution of trimethylsilyldiazomethane in hexane. Tautomerisation with loss of the trimethylsilyl group on exposure to trifluoroacetic acid in dichloromethane yielded optically active Δ^2-pyrazolines as single regioisomers with 90-94% diastereoselectivity. These were subsequently transformed to synthetically useful pyrazolidines by C=N reduction with sodium cyanoborohydride in acetic acid, chemoselective protection as the *N*-Cbz or *N*-Boc carbamates and auxiliary removal by treatment with dimethoxymagnesium in methanol (Scheme 55).



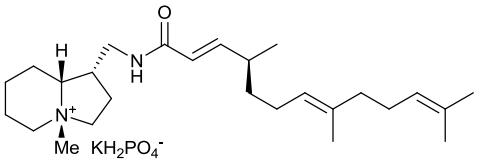
Scheme 55

Azaproline analogues of the Δ^2-pyrazolines and the pyrazolidines were synthesised by chemoselective coupling reactions (Scheme 56).[172]



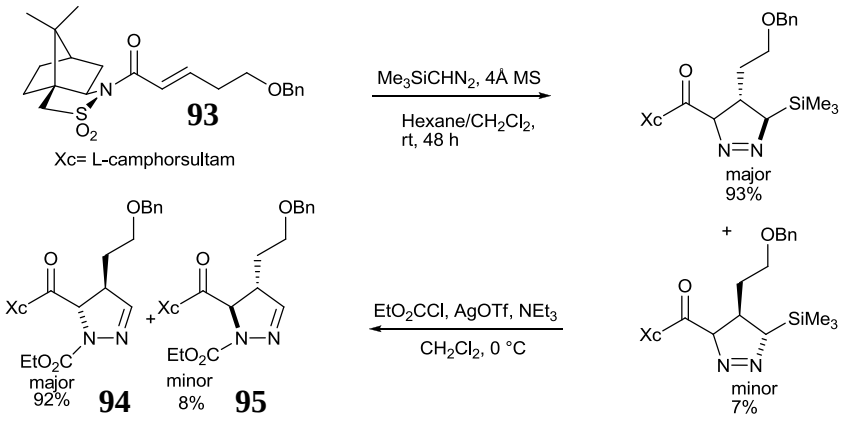
Scheme 56

In the same year, Carreira *et al.* demonstrated the versatility of this cycloaddition in the efficient synthesis of the marine metabolite stellettamide A **92**, which possesses anti-fungal activity and displays cytotoxicity against K562 epithelium cell lines.[173,174]



92

Cycloaddition of the Oppolzer sultam derivative **93** with a solution of trimethylsilyldiazomethane led to the isolation of the pyrazoline cycloadducts in quantitative yield as a 93:7 mixture of diastereomers. Desilylation was achieved on exposure to ethyl chloroformate and silver triflate to yield the diastereomeric Δ^2-pyrazolines **94** and **95** in a 92:8 ratio (Scheme 57).



Scheme 57

The major diastereomer results from the preferential attack of the incoming dipole from the top-side of the dipolarophile (Figure 34).

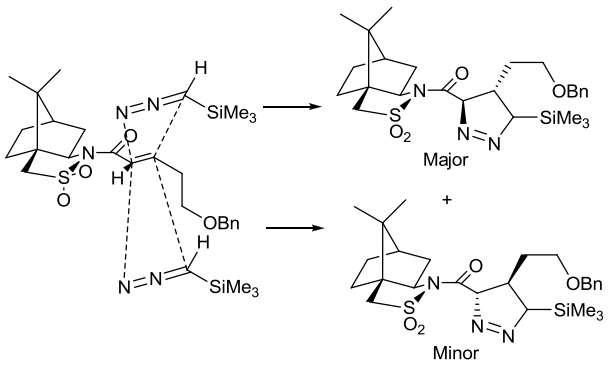
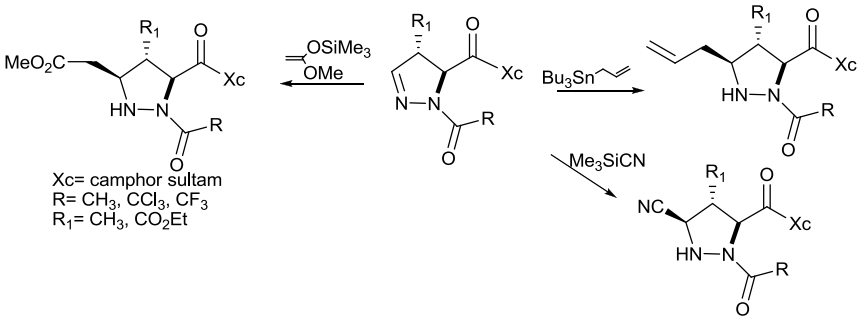


Figure 34

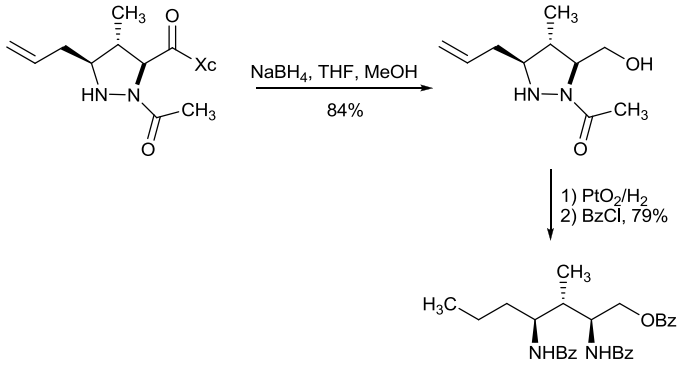
The diastereomeric Δ^2-pyrazolines **94** and **95** were separable by column chromatography and the major diastereomer **94** was transformed to stellettamide A **92** *via* a number of synthetic steps.[173,174]

The synthetic utility of this cycloaddition was further demonstrated in a communication by Carreira in 2000, in which the Lewis acid facilitated diastereoselective nucleophilic addition to *N*-acyl protected pyrazolines was reported (Scheme 58).[175] This allows access to a variety of useful highly functionalized building blocks for asymmetric synthesis.



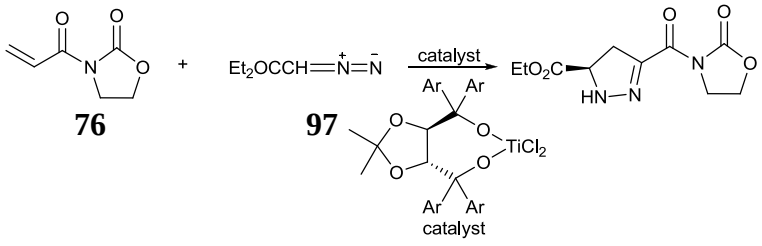
Scheme 58

Optically active acyclic products can be easily formed by auxiliary removal and reductive N-N bond cleavage (Scheme 59).[175]



Scheme 59

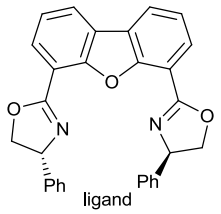
The enantioselective 1,3-dipolar cycloaddition of diazoalkanes in the presence of Lewis acid catalysts has also been reported. In Jorgensen's review on asymmetric 1,3-dipolar cycloadditions in 1998,[10] he described his unpublished findings on the affect of the Ti-TADDOLate catalyst **96** in the cycloaddition of ethyl diazoacetate **97** to the oxazolidinone **76**, with enantiomeric excesses of 30-40% achieved (Scheme 60).



76 **97** **96**

Scheme 60

The first effective Lewis acid catalysed enantioselective cycloaddition of diazoalkanes was reported by Kanemasa in 2000.[176] The cycloadditions of trimethylsilyldiazomethane and a range of oxazolidinones were studied in the presence of metal complexes of (*R*,*R*)-DBFOX/Ph **98**, with enantiomeric excesses of up to 99% achieved for the resulting desilylated Δ^2-pyrazolines.



98

On treatment of the oxazolidinone **75** with the (*R*,*R*)-DBFOX/Ph **98**-$Zn(ClO_4)_2.3H_2O$ complex, the corresponding desilylated Δ^2-pyrazoline was obtained in 99% ee. The introduction of an isopropyl or propyl group at the β-position of the oxazolidinone led to a decrease in the enantioselectivity of the cycloaddition (Scheme 61).[176]

R	%ee
Me	99
n-Pr	47
i-Pr	71

Scheme 61

The observed stereochemistry in the cycloaddition of the oxazolidinone **75** is due to attack at the top face of the dipolarophile by trimethylsilyldiazomethane as the bottom face is shielded by the lower 4-phenyl group of the ligand (Figure 35). As the isopropyl and propyl groups are more flexible than the methyl group, steric hindrance between the shielding phenyl group and the R substituent exists and the reaction site departs from the shielding zone of the 4-phenyl group, leading to decreased chiral shielding efficiency and hence lower enantioselectivities.[176]

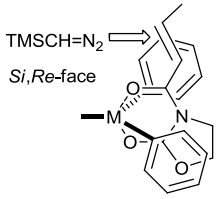
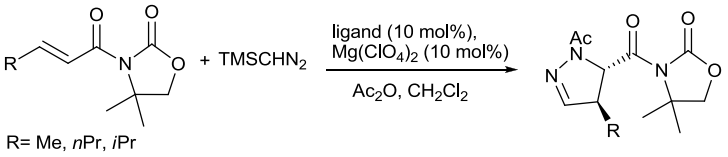


Figure 35

Interestingly, the introduction of an isopropyl or propyl group at the β-position of 4,4-dimethyl-2-oxazolidinone had no detrimental effect on the enantioselectivity of the magnesium catalysed cycloaddition with trimethylsilyldiazomethane, and % ee's ranging from 97–98 were achieved in the presence of $Mg(ClO_4)_2$ complexed to **98** (Scheme 62).[176]



R	% ee
Me	97
n-Pr	98
i-Pr	98

Scheme 62

In this instance, the top face of the alkene is shielded by the top 4-phenyl group on the ligand and trimethylsilyldiazomethane attack occurs exclusively from the bottom face (Figure 36). For the cycloadditions described in Scheme 61 and Scheme 62, *endo* approach of the dipole is favoured as the *exo* transition state is expected to be less stable due to steric repulsion between the bulky trimethylsilyl group and the β-substituent.

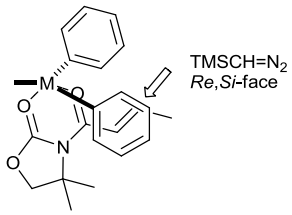
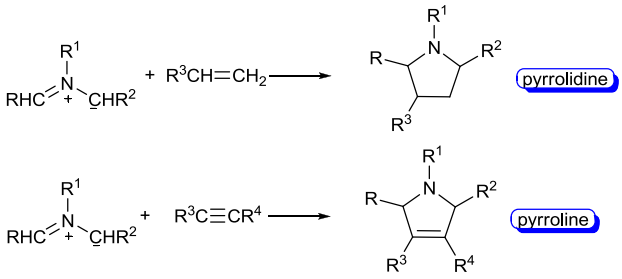


Figure 36

While reports of 1,3-dipolar cycloadditions of acrylamides with diazoalkanes are limited, very good diastereomeric ratios of up to 93:7 have been obtained, and in the Lewis acid catalysed enantioselective cycloadditions, excellent enantiomeric excesses of up to 99% ee were achieved. The resulting cycloadducts have also been transformed to a variety of useful building blocks for asymmetric synthesis.

1.2.4 Cycloadditions with Azomethine Ylides

The 1,3-dipolar cycloaddition of azomethine ylides to alkenes and alkynes leads to the formation of pyrrolidines and pyrrolines respectively (Scheme 63).



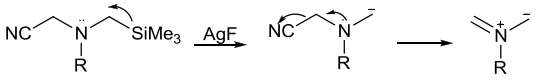
Scheme 63

Azomethine ylides are allyl anion-type 1,3-dipoles that are bent even in the ground state. The 1,3-dipolar cycloadditions of azomethine ylides are generally stereospecific, with the stereochemistry of the dipole and dipolarophile retained in the cycloadduct. Cycloadditions with azomethine ylides have been extensively investigated in recent years and these have been applied in asymmetric and natural product synthesis, as well as the syntheses of biologically interesting compounds.[1,6]

1.2.4.1 Synthesis of Azomethine Ylides

Azomethine ylides are unstable species that must be generated *in situ* and are subsequently trapped by the added dipolarophile. A number of methods have been developed for their generation, including deprotonation of imminium salts,[177] thermal isomerisation of imines of α-amino acids[178] and decarboxylation of imminium ions derived from primary and secondary α-amino acids.[179] The most commonly employed methods nowadays involve the thermolysis or photolysis of suitably-substituted aziridines[180] and the desilylation of cyanoaminosilanes.[181]

The fluorine-mediated desilylation of cyanoaminosilanes was developed by Padwa in 1985.[181] Treatment of α-cyanoaminosilanes with silver fluoride results in fluoride-assisted desilylation to give the intermediate anion, and subsequent loss of cyanide yields the azomethine ylide (Scheme 64).



Scheme 64

The stereospecific thermal and photolytic conversion of aziridines to acyclic azomethine ylides was reported by Huisgen in 1967.[180] As the aziridine ring system is isoelectronic with the cyclopropyl anion, the thermal isomerisation of aziridines to azomethine ylides involves a conrotatory ring opening by the Woodward and Hoffmann rules, and the photochemically induced process involves a disrotatory ring opening.[182] Thus, the *cis*-dicarboxylic acid ester **99** will undergo conrotatory ring opening under thermal conditions to give the *trans*-azomethine

ylide and disrotatory ring opening under photochemical conditions to yield the *cis*-azomethine ylide (Figure 37). The *trans*-dicarboxylic acid ester **100** behaves in a similar manner.

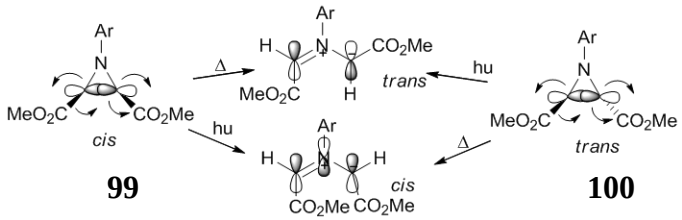


Figure 37

The ring-opening of the aziridines and the cycloaddition are stereospecific if the cycloaddition occurs before bond rotation in the intermediate azomethine ylide. For example, the *trans*-azomethine ylide thermally derived from the *cis*-dicarboxylic acid ester **99** combines stereospecifically even with weak dipolarophiles whereas for the *cis*-azomethine ylide thermally derived from the *trans*-dicarboxylic acid ester **100**, isomerisation to the *trans*-isomer competes with the cycloaddition except for reactions with highly reactive dipolarophiles such as tetracyanoethylene.[183,184]

1.2.4.2 Reactivity and Regioselectivity

The cycloaddition of azomethine ylides to alkenes can lead to the formation of two regioisomeric pyrrolidines. In general, the reactions exhibit marked regioselectivity, with almost exclusive or predominant formation of one regioisomer. The cycloadditions of azomethine ylides occur most readily with electron-deficient dipolarophiles through a HOMO-dipole controlled interaction (Figure 38). The presence of electron-rich or conjugating groups on the dipole raise the energy of the HOMO and hence the energy gap between the HOMO-dipole and LUMO-dipolarophile is reduced leading to a more efficient reaction.

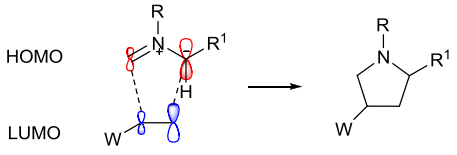


Figure 38

The cycloaddition of electron-rich dipolarophiles to azomethine ylides is also possible through a LUMO (dipole) – HOMO (dipolarophile) interaction, but cycloadditions of this type are less common.[185]

1.2.4.3 Asymmetric 1,3-Dipolar Cycloadditions of Azomethine Ylides

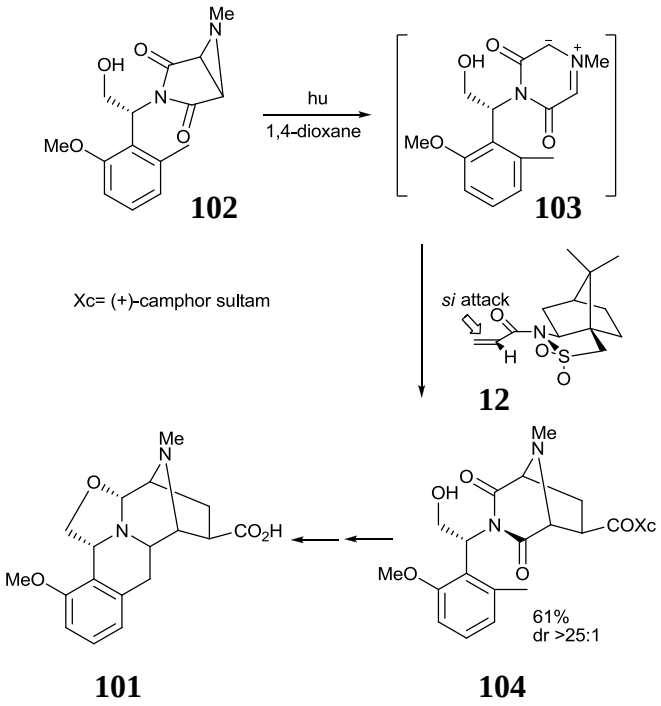
As chiral pyrrolidines are common building blocks for many natural and unnatural compounds which possess important biological activity, the asymmetric 1,3-dipolar cycloaddition of azomethine ylides has attracted much attention.[34] Chiral azomethine ylides (both cyclic and acyclic),[186-190] chiral dipolarophiles[191-193] and chiral catalysts[74,191] have all been successfully implemented for asymmetric induction in azomethine ylide 1,3-dipolar cycloadditions.

Most of the reported studies on the control of the stereoselectivity by use of chiral dipolarophiles concern the use of acrylates.[192,194,195] However, excellent results have also been achieved with chiral acrylamides, and the synthesis of a number of biologically active compounds has been accomplished through their use.

1.2.4.4 Asymmetric 1,3-Dipolar Cycloadditions of Azomethine Ylides and Acrylamides

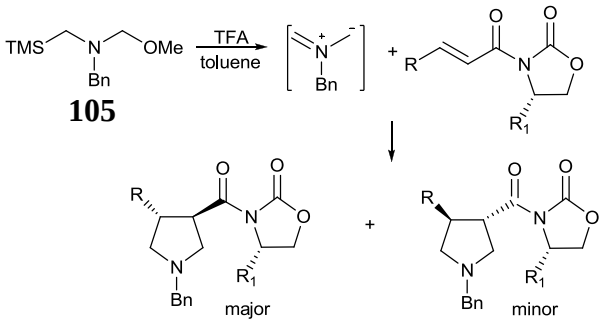
Encouraged by Curran's work on the 1,3-dipolar cycloaddition of Oppolzer's chiral sultam derivative **12** to nitrile oxides,[83] Garner investigated the cycloaddition of **12** to photochemically generated azomethine ylides as a route to the asymmetric synthesis of quinocarcin **101**, a potential antitumor antibiotic isolated from *Streptomyces* broths.[196-200]

Irradiation of the aziridine **102** yielded the azomethine ylide **103**, which subsequently underwent selective *exo* attack at the *si* face of Oppolzer's chiral sultam **12** to give the *exo*-substituted pyrrolidine **104** (diastereomeric ratio >25:1). As **12** is photochemically unstable, portionwise addition to the azomethine ylide **103** was necessary. The cycloaddition of chiral acrylates derived from menthol and 10-[dicyclohexyl(sulfonylamido)]isoborneol to a number of photochemically generated azomethine ylides was also conducted, however no facial selectivity was observed.[197] With four of the six stereogenic centres present in quinocarcin **101** now in place, the pyrrolidine **104** was transformed to **101** *via* a number of synthetic steps (Scheme 65).[199]



Scheme 65

In 1997, Ma and co-workers utilised the asymmetric 1,3-dipolar cycloaddition of the azomethine ylide derived from *N*-benzyl-*N*-(methoxymethyl)-trimethylsilylmethylamine **105** with a range of chiral oxazolidinones as a route to a series of optically active *trans*-3-amino-4-alkylpyrrolidines, which is present at the *C*-8 position of 2-pyridones, novel DNA gyrase inhibitors that exhibit antibacterial activity (Scheme 66).[201]



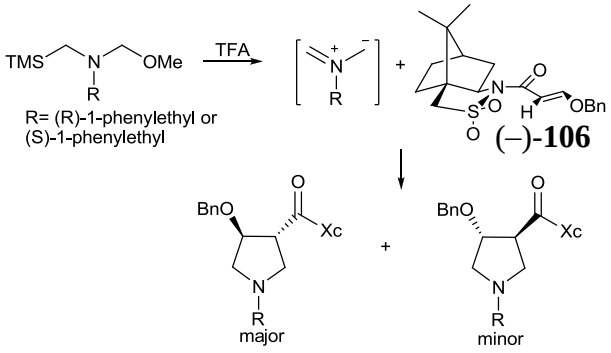
R	R^1	major:minor
Me	*i*-Pr	60:40
Me	Bn	58:42
Me	Ph	73:27
Et	Ph	77:33
c-Pr*	Ph	80:20
Ph	Ph	67:33

*c-Pr = cyclopropyl

Scheme 66

The pyrrolidines were obtained in high yield and moderate diastereoselectivity, with the diastereoselectivity dependant on the structure of the oxazolidinone; diastereomeric ratios of up to 80:20 achieved when R = cyclopropyl and R^1 = phenyl. The major diastereomer resulted from the favoured dipole attack on the alkene from the face opposite to the R^1 substituent. Although the selectivity was moderate, the desired major diastereomer was easily separated by recrystallisation or chromatography, and this was subsequently transformed to the chiral pyrrolidine.[201]

In 2001, Karlsson reported the doubly diastereoselective cycloaddition of chiral azomethine ylides to a range of chiral acrylamides.[202,203] On employment of oxazolidinone and camphorsultam derivatives, the camphorsultam derivatives furnished the greater diastereoselectivities, with diastereomeric ratios of up to 88:12 achieved. The diastereoselectivity was found to be solvent-dependant, with the employment of more polar solvents furnishing higher diastereoselectivities. The optimum diastereoselectivity was achieved by reacting the camphorsultam derivative (–)-**106** with the (*R*)-1-phenylethyl-derived azomethine ylide (Scheme 67).



solvent	R	major:minor
toluene	(*R*)-1-phenylethyl	70:30
toluene	(*S*)-1-phenylethyl	52:48
acetonitrile	(*R*)-1-phenylethyl	88:12
acetonitrile	(*S*)-1-phenylethyl	75:25

Scheme 67

The major diastereomer results from attack of the azomethine ylide to the *re-re* face of the dipolarophile (Figure 39). The enhanced selectivity in more polar solvents is believed to be due to dipole-dipole interactions caused by the polar solvent stabilising the transition state.

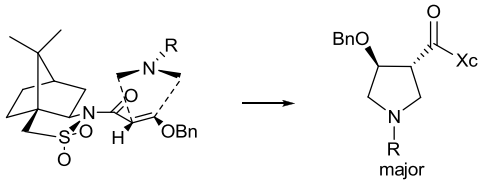
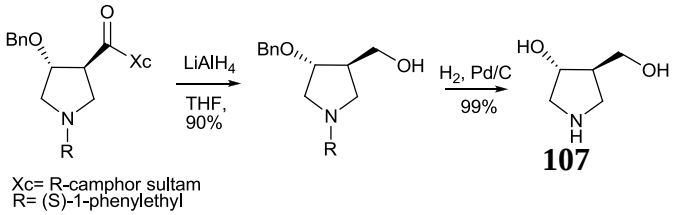


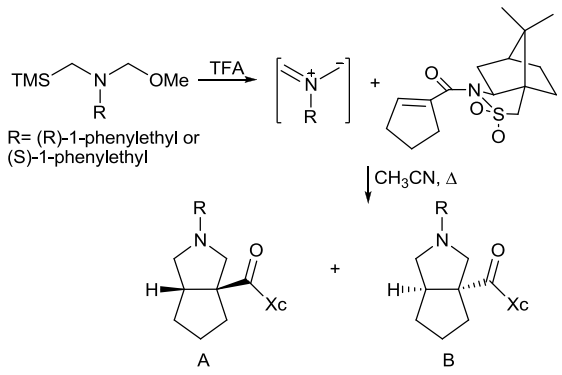
Figure 39

The resulting pyrrolidines can act as chiral building blocks for the synthesis of enantiopure bioactive pyrrolidines, and Karlsson demonstrated this in his short synthesis of (3*R*,4*R*)-4-(hydroxylmethyl)pyrrolidin-3-ol **107**, a known glycosidase inhibitor (Scheme 68).[202]



Scheme 68

When Karlsson extended this work to include monocyclic five-membered α,β-unsaturated acrylamides, reduced diastereoselectivity was observed.[204] Interestingly, changing the absolute configuration of the starting ylide reversed the diastereoselectivity of the cycloaddition (Scheme 69).



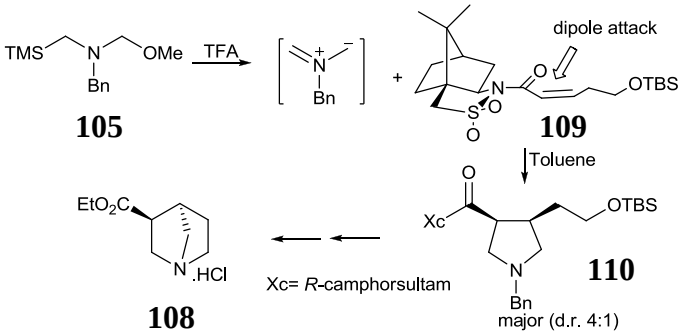
R	A:B
(*R*)-1-phenylethyl	74:26
(*S*)-1-phenylethyl	32:68

Scheme 69

More recently, the large-scale synthesis of **107** has been reported by Chand *et al.*, in which an achiral ylide was employed using an *N*-benzyl substituent in place of the *N*-phenylethyl substituent. Kilogram quantities of **107** have been prepared using this synthesis.[205]

In 2001, Carey reported an efficient synthesis of (3*S*,4*R*)-ethyl 1-azabicyclo[2.2.1]heptane-3-carboxylate **108** in which the key step was the cycloaddition of an azomethine ylide with a camphorsultam derivative (Scheme 70).[206] Cycloaddition of the camphorsultam derivative **109** with the azomethine ylide derived from **105** yielded a diastereomeric mixture of pyrrolidines in a 4:1 ratio, which were readily separated by column chromatography. The stereochemistry of the major pyrrolidine **110** was consistent with the

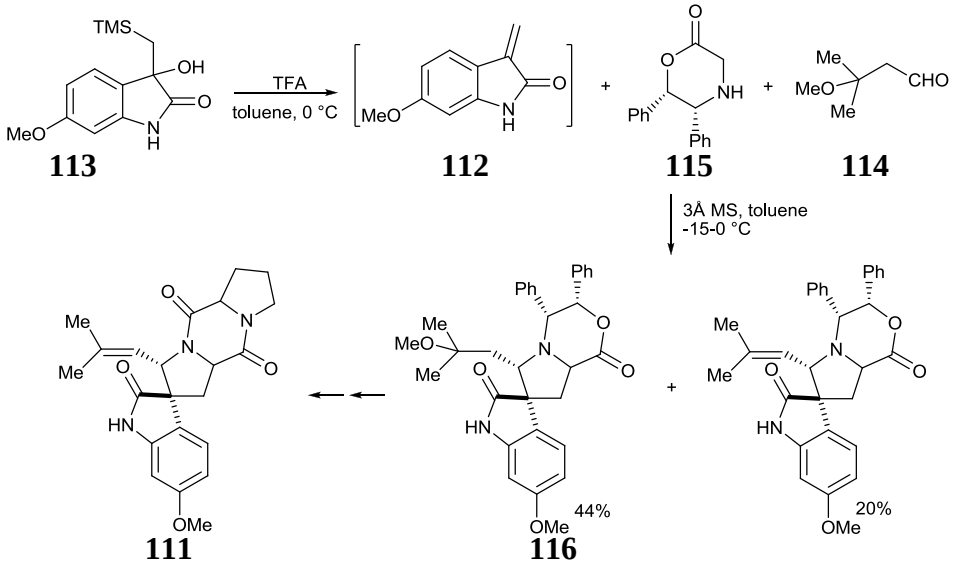
cycloaddition proceeding *via* the normal transition state structure for reactions of camphorsultam derivatives.



Scheme 70

The cycloaddition of an azomethine ylide to an acrylamide derivative was also the key step in the Williams report of the asymmetric total synthesis of spirotryprostatin A **111**, which is a member of a promising class of antimitotic agents.[207,208]

The unstable acrylamide dipolarophile **112** was prepared *in situ* by treatment of **113** with trifluoroacetic acid in toluene. This was then added to the azomethine ylide generated from morpholinone **114** and aldehyde **115** to yield an approximately 2:1 mixture of cycloadducts. The major cycloadduct **116** was then subjected to further synthetic transformations to yield spirotryprostatin A **111** (Scheme 71).



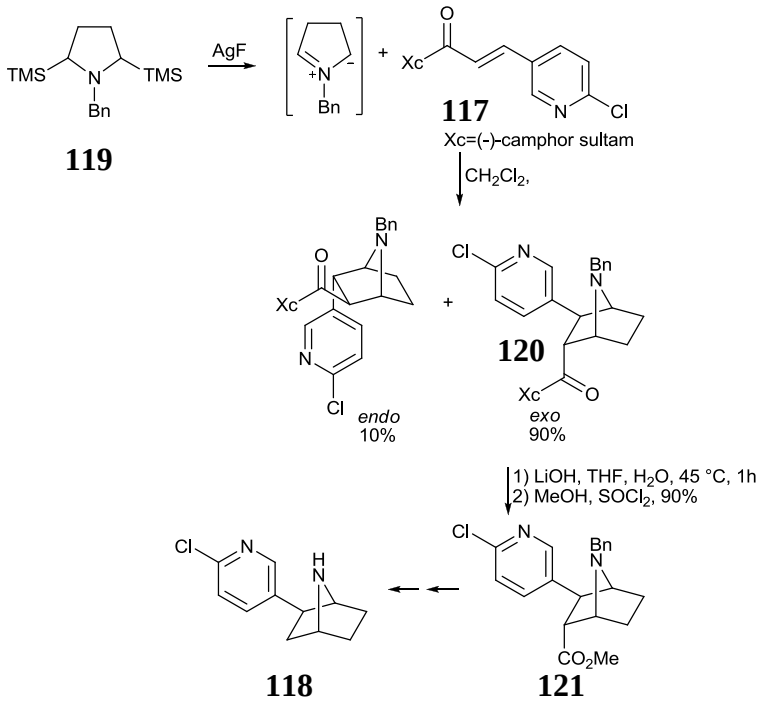
Scheme 71

The use of Lewis acid catalysts has also been reported to promote asymmetric 1,3-dipolar cycloadditions of azomethine ylides, with silver catalysts the most commonly employed.[6]

Diastereomeric ratios of up to 98:2 (*exo:endo*) were achieved by Pandey and co-workers on employment of cyclic azomethine ylides in silver fluoride catalysed cycloadditions with the

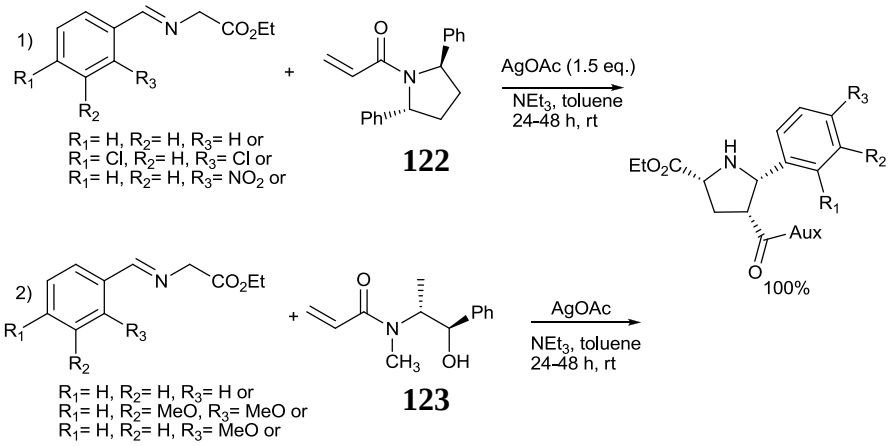
Oppolzer chiral sultam derivative **117**.[209] This route was then utilised towards a formal synthesis of optically active *ent*-epibatidine **118**.

The chiral dipolarophile **117**, which was synthesised by a Heck reaction, reacted with the cyclic azomethine ylide derived from **119** to give the pyrrolidine diastereomers in a 9:1 mixture. These were separable by chromatography, and the chiral auxiliary was cleaved from the major diastereomer **120** by exposure to lithium hydroxide in tetrahydrofuran and water, followed by reaction with thionyl chloride in methanol to yield **121** (Scheme 72). The conversion of **121** to *ent*-epibatidine **118** was reported earlier by the same group.[210]



Scheme 72

In 2005, Nyerges *et al.* reported the silver acetate catalyzed asymmetric cycloaddition of azomethine ylides derived from arylidene glycine imides and chiral acrylamides.[211] A range of chiral acrylamides were studied, with single pyrrolidine diastereomers obtained when the cyclic pyrrolidine derived and the (1*R*,2*S*)-(–)-ephedrine derived acrylamides **122** and **123** were employed (Scheme 73).



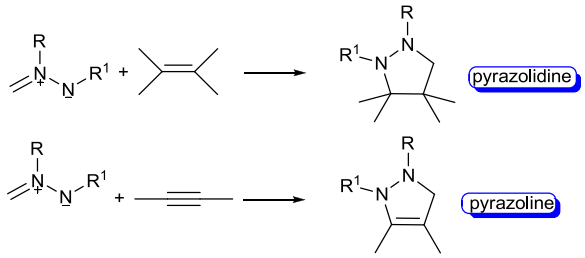
Scheme 73

The employment of acrylamides derived from Oppolzer's sultam again led to good diastereoselectivites in 1,3-dipolar cycloadditions with azomethine ylides. In the absence of metal catalysis diastereomeric ratios of up to 90:10 were obtained, while addition of silver fluoride led to an improved ratio of 98:2.

1.2.5 Cycloadditions with other 1,3-Dipoles

1.2.5.1 Allyl Anion Type Dipoles

Azomethine imines are a class of allyl anion type dipoles that undergo 1,3-dipolar cycloadditions with alkenes and alkynes to furnish pyrazolidines and pyrazolines respectively (Scheme 74).[212]

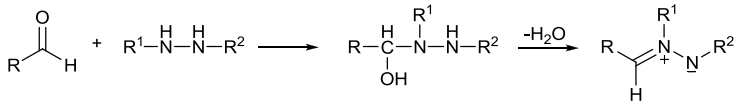


Scheme 74

The resonance form **A** in Figure 40 is expected to be more important as a result of the higher electronegativity of nitrogen relative to carbon.[212]

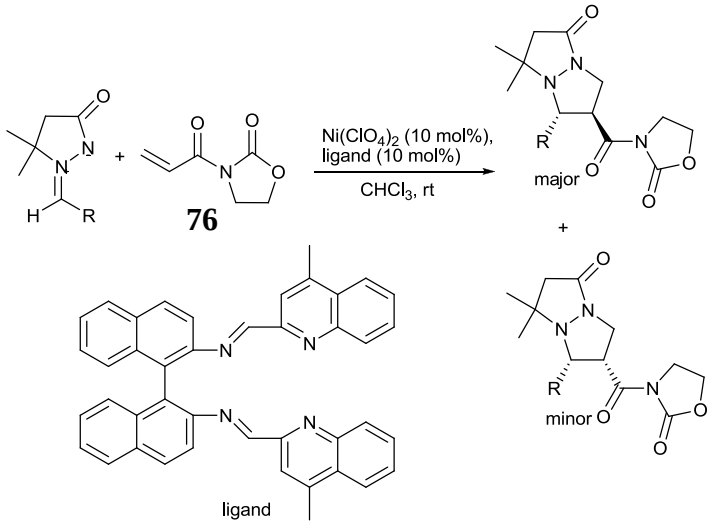
Figure 40

These dipoles are too reactive to be isolated and are normally generated *in situ*, most commonly by reaction of *N*,*N*′-disubstituted hydrazines with an aldehyde (Scheme 75).[212]



Scheme 75

Asymmetric 1,3-dipolar cycloadditions of azomethine imines have not been extensively studied.[6] The first report of an asymmetric reaction between an azomethine imine and an acrylamide was communicated in 2007 by Suga, who described the highly enantioselective and diastereoselective Lewis acid catalysed 1,3-dipolar cycloaddition between azomethine imines (derived from the reaction of pyrazolidin-3-one with an aldehyde)[213] and the oxazolidinone **76**.[214] Employing a chiral Ni(II)-binaphthyldiimine complex as the catalyst, diastereomeric ratios of 64:36 to >99:1 were achieved in enantiomeric excesses of 74-97% (Scheme 76).[214]



R	major:minor	% ee major
p-$MeOC_6H_4$	80:20	90
p-MeC_6H_4	91:9	93
p-CNC_6H_4	97:3	92
p-ClC_6H_4	91:9	95
o-ClC_6H_4	>99:1	93
p-BrC_6H_4	93:7	94
2-naphthyl	93:7	96
2-furyl	64:36	95
cyclohexyl	82:18	74

Scheme 76

The *re* face of the oxazolidinone is shielded from dipole attack by the 4-methyl-quinoline moiety of the Ni(II) complex, and the *trans* selectivity is believed to be due to favourable secondary orbital interactions between the empty nitrogen orbital of the azomethine imine and the oxazolidinone (Figure 41).

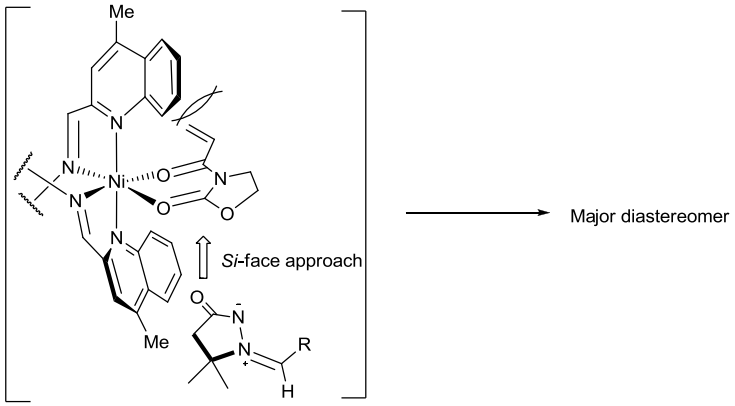
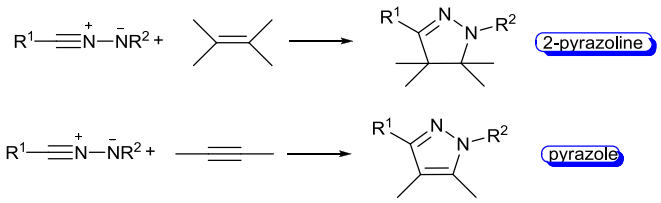


Figure 41

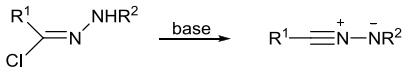
1.2.5.2 Allenyl/Propargyl Anion Type

The 1,3-dipolar cycloaddition of nitrilimines to alkenes and alkynes is a very useful method for the preparation of 2-pyrazolines and pyrazoles (Scheme 77).[86]



Scheme 77

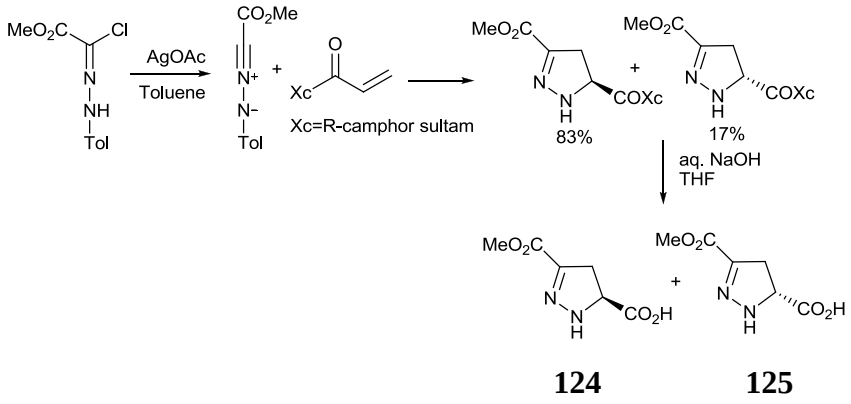
Nitrilimines are prepared *in situ*, generally from hydrazonoyl halides (Scheme 78).[86]



Scheme 78

Despite the utility of enantiopure pyrazolines and pyrazoles, the asymmetric 1,3-dipolar cycloaddition of nitrilimines has only become useful in recent years.[25] Molteni and co-workers communicated the cycloadditions of nitrilimines with a range of enantiopure acrylamides as a route to enantiopure 4,5-dihydropyrazoles in 2002.[215] Diastereoselectivities of up to 83:17 were obtained on employment of the Oppolzer chiral sultam derivative **12** (Scheme 79). Cleavage of

the auxiliaries was easily achieved by sodium hydroxide hydrolysis to yield the dicarboxy pyrazoles **124** and **125**, potentially interesting new chiral building blocks.



124 **125**

Scheme 79

1.3 Conclusion

As up to four stereocentres can be introduced in a stereoselective manner in a single step, the asymmetric 1,3-dipolar cycloaddition is one of the most useful methods for the preparation of chiral five-membered ring heterocycles. This review focused on the employment of acrylamides as dipolarophiles in asymmetric 1,3-dipolar cycloadditions, with particular emphasis on the rationale for the observed stereocontrol; the conformational properties of the acrylamides, relative to the more conformationally mobile acrylates for example, are critical to their use as chiral auxiliaries in these processes. Thus, the use of chiral acrylamides has led to the attainment of high levels of regioselectivity, *endo*/*exo* selectivity, diastereofacial selectivity and stereocontrol in cycloadditions with a range of 1,3-dipoles. The synthetic utility of the resulting cycloadducts was demonstrated in a number of natural product syntheses. For each of the dipoles discussed, acrylamides derived from Oppolzer's sultam proved to be the most advantageous; excellent diastereoselectivities could be achieved in each case. The majority of studies on metal-catalysed cycloadditions have focussed on nitrones, with excellent enantioselectivities and diastereoselectivites obtained. Acrylamides bearing a wide variety of chiral auxiliaries have been explored in 1,3-dipolar cycloadditions with nitrile oxides, as these reactions are not amenable to Lewis acid catalysis.

The employment of chiral acrylamides as dipolarophiles, particularly in 1,3-dipolar cycloadditions with nitrile oxides in which the use of chiral catalysts and chiral 1,3-dipoles is not an attractive option, will continue to be exploited in asymmetric 1,3-dipolar cycloadditions.

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